Clinical Study Report Synopsis	
Drug Substance	Tozorakimab (MEDI3506)
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A Phase II, Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of MEDI3506 in Adult Participants with Uncontrolled Moderate-to-severe Asthma

Study dates: First subject enrolled: 05 November 2020
Last subject last visit: 06 February 2023
The analyses presented in this report are based on a clinical data lock date of 03 April 2023

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator: PPD

Sponsor's Responsible Medical Officer: PPD

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

Study Centre(s)

The study was conducted by 68 investigators who screened patients at 68 centres in 7 countries (Argentina: 13 centres; United States: 10 centres; Germany: 12 centres; Poland: 12 centres; Hungary: 5 centres; South Africa: 12 centres; United Kingdom: 4 centres).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of tozorakimab compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	• As measured in clinic, change from baseline to Week 16 in pre-BD FEV_1 (L).
Secondary	
• To further assess the effect of tozorakimab compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	• As measured in clinic, change from baseline to Weeks 8 and 16 in post-BD FEV_1 (L).
• To assess the PK of tozorakimab in adult participants with uncontrolled moderate-to-severe asthma.	• Serum tozorakimab concentration-time profiles during the intervention and follow-up periods.
• To assess the immunogenicity of tozorakimab in adult participants with uncontrolled moderate-to-severe asthma.	• ADA during the intervention and follow-up periods.
• To assess the effect of tozorakimab compared with placebo on asthma control in adult participants with uncontrolled moderate-to-severe asthma.	• Change from baseline to Week 16 in ACQ-6 score. • Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16. • Proportion of participants achieving ACQ-6 well controlled status (defined as ACQ-6 score ≤ 0.75 at Week 16).
• To assess the effect of tozorakimab compared with placebo on health status in adult participants with uncontrolled moderate-to-severe asthma.	• Change from baseline to Week 16 in SGRQ score. • Proportion of participants with a decrease in SGRQ total score of ≥ 4 points from baseline to Week 16.
• To assess the effect of tozorakimab compared with placebo on CompEx in adult participants with uncontrolled moderate-to-severe asthma.	• Time to first CompEx event based on the period from baseline to Week 16. • CompEx annualised event rate.
• To assess the effect of tozorakimab compared with placebo on concentration of FeNO in adult participants with uncontrolled moderate-to-severe asthma.	• Percent change from baseline to Week 16 in concentration of FeNO in exhaled breath.

Objectives	Endpoints
Safety	
• To assess the safety and tolerability of tozorakimab compared with placebo, in adult participants with uncontrolled moderate-to-severe asthma.	During the intervention and follow-up periods: • AEs, SAEs, AESIs • Vital signs • Clinical chemistry, haematology, and urinalysis • ECGs • LVEF as measured by echocardiogram • NT-proBNP • Number of participants seropositive for SARS-CoV-2 at end of study who were seronegative at randomisation visit • For participants testing positive for SARS-CoV-2 (by PCR or serology test), during the intervention and follow-up periods, the number and proportion of participants with COVID-19 AEs/SAEs and the proportion asymptomatic.

ACQ-6 = asthma control questionnaire-6; ADA = anti-drug antibody(ies); AE = adverse event; AESI = adverse event of special interest; BD = bronchodilator; CompEx = composite endpoint for severe exacerbations of asthma; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in the first second; L = litres; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PCR = polymerase chain reaction; PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St George's respiratory questionnaire; tozorakimab = MEDI3506.

Study Design

This was a Phase II, randomised, double-blind, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, pharmacokinetics (PK) and immunogenicity of MEDI3506 (hereafter referred to as tozorakimab) in adult participants with uncontrolled moderate-to-severe asthma on top of standard of care (SoC). Participants who failed screening could be re-screened.

Participants were centrally assigned to randomised intervention using a randomisation and trial supply management system in a 1:1:1 ratio to receive either CCI or CCI mg tozorakimab, or placebo, CCI by subcutaneous (SC) injection for a total of CCI. The randomisation was stratified according to participation in the cough sub-study. As tozorakimab and placebo are not identical, study intervention was handled by an unblinded study intervention manager at the site and was administered by an unblinded study team member who was not involved in the management of study participants. Participants were required to take their asthma controller therapy regularly throughout the screening, intervention and follow-up periods.

Target Population and Sample Size

Eligible participants were adults (18 to < 65 years of age inclusive) with documented physician-diagnosed asthma of early onset, defined as development of asthma before the age of 25 years. Asthma was to have been diagnosed > 12 months prior to Study Visit 1 (SV1). Participants were to have been treated with medium to high dose inhaled corticosteroids (ICS) defined as total daily dose of > 250 µg fluticasone dry powder or equivalent, for at least 12 months prior to SV1 and on a stable dose for ≥ 3 months prior to SV1 and receiving stable long-acting beta agonist therapy for ≥ 3 months prior to SV1 (this may be as a fixed-dose combination product, or a separate inhaler). Treatment with additional asthma controller therapies eg, long acting muscarinic antagonists, leukotriene receptor antagonists, theophylline (≥ 1 month at a stable dose) prior to SV1 was also allowed. Participants were to have an asthma control questionnaire-6 (ACQ-6) score of ≥ 1.5 at each of SV1, SV2, and SV4 (randomisation) and morning pre-bronchodilator (BD) forced expiratory volume in the first second (FEV_1) < 85% predicted normal at SV1.

Approximately 228 participants were to be randomised 1:1:1 (tozorakimab CCI mg: tozorakimab CCI mg: placebo) to achieve 216 evaluable participants (72 participants per treatment group). A sample size of 216 participants would provide at least 80% power to detect a statistically significant difference in change from baseline to Week 16 in pre-BD FEV_1, assuming a difference of 150 mL between placebo and tozorakimab, a between-participant standard deviation (SD) of 420 mL and a one-sided- 10% alpha level.

Up to 60 participants were intended to be included in the cough sub-study (approximately 20 participants per treatment group). However, given the exploratory nature of the sub-study and that it may not have been activated in all countries, randomisation of participants not included in the sub-study was not restricted and sub-study recruitment was not achieved. The sub-study was considered exploratory and no formal power calculations were performed.

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

Tozorakimab was manufactured by AstraZeneca and supplied as a solution for SC injection in 1 mL vials. Tozorakimab was administered at CCI, and CCI mg per dose CCI for a total of CC doses. In the CCI mg group, participants received CC mL tozorakimab as CCI mL syringe, plus CC mL placebo as CCI mL syringe. In the CCI mg group, participants received CC mL tozorakimab as CCI mL syringes. In the placebo group, participants received CCI mL syringes of placebo. The following batch numbers of tozorakimab and placebo were used:

- Tozorakimab (DP Lot Number / IMP Lot Number): LC0053 / A03374; LL0310 / A03599; LL0310 / A03708; LL0310 / MEDI-03103; NA0001 / A03759; NA0001 / A04194.

- Placebo (DP Lot Number / IMP Lot Number): B18100107 / A03374; B18100107 / A03599; B18100107 / A03708; B18100107 / A03759; B18100107 / A04194; B18100107 / MEDI-03103.

Duration of Treatment

Participants were enrolled in this study for up to 29 weeks. The study comprised 3 periods including the screening period of up to 5 weeks, an intervention period of 16 weeks, and a follow-up period of 8 weeks.

Statistical Methods

Efficacy analyses were performed using the Intent-to-treat (ITT) population. The primary estimand was a 'Treatment Policy' estimand, as follows: the difference in mean change from baseline in pre-BD FEV_1 at Week 16 (tozorakimab – placebo) was to be estimated using a repeated measures mixed effects analysis of covariance model, for the ITT population. This included all available data from all visits up to and including Week 16, irrespective of whether the participant discontinued study intervention or received rescue therapy.

A similar approach was taken for the analysis of ACQ-6, St George's respiratory questionnaire (SGRQ), and fractional exhaled nitric oxide (FeNO). The difference in mean change from baseline in post-BD FEV_1 at Weeks 8 and 16 was to be estimated using a repeated measures mixed effects analysis of covariance model, similar to that described for the primary efficacy analysis. Data may have been log transformed prior to analysis where appropriate. Time to first composite endpoint for severe exacerbations of asthma (CompEx) event was to be analysed using a Cox proportional hazard model, with treatment fitted as a covariate.

Tozorakimab serum concentrations were to be tabulated along with descriptive statistics. Mean and individual serum tozorakimab concentration-time profiles were to be plotted. Population PK modelling was to be performed if data allowed. Positive antibodies to tozorakimab were to be reported by treatment group.

Descriptive statistics of tozorakimab serum concentrations and of serum anti-drug antibody (ADA) results (positive or negative) were reported. The potential impact of ADA to trough PK concentrations was assessed.

Adverse event summaries were based on treatment-emergent adverse events (TEAEs), defined as any new sign, symptom, disease, or other untoward medical event that began or worsened after the first dose of investigational product (IP) up to the follow-up visit.

Owing to concerns regarding the validity of the data and compliance with the principles of good clinical practise at one site, data from that site were excluded from the final analysis after unblinding of the study. This did not impact the interpretation of the primary endpoint.

Study Population

Of the 478 patients screened, 235 participants were randomised in 52 study centres across 7 countries in a 1:1:1 ratio to receive either placebo (81 participants), tozorakimab CCI mg (77 participants), or tozorakimab CCI mg (77 participants). At the end of the study, all participants had either completed (225 [95.7%] participants) or discontinued (10 [4.3%] participants) treatment. Overall, 227 (96.6%) participants completed the study.

Demographics and disease characteristics were representative of the intended population of adults with uncontrolled moderate-to-severe asthma and with the exception of a lower proportion of female participants in the placebo group (53.1%) compared with the tozorakimab group (69.5%) otherwise similar across the treatment groups.

Summary of Efficacy Results

Primary Endpoint

No statistically significant difference from placebo was demonstrated for either the tozorakimab CCI mg or tozorakimab CCI mg group in change from baseline at Week 16 in pre-BD FEV_1 as measured in the clinic (CCI mg: least square mean [LSMean] difference [tozorakimab – placebo] of 0.036 L [80% confidence interval (CI): -0.038, 0.111], p = 0.267; CCI mg: LSMean difference of 0.004 L [80% CI: -0.071, 0.079], p = 0.473).

Secondary Endpoints

- No statistically significant difference at Week 8 or Week 16 was observed compared with placebo for either the tozorakimab CCI mg or CCI mg group for post-BD FEV_1 as measured in the clinic.
- No statistically significant difference was observed between either the tozorakimab CCI mg or CCI mg groups, and placebo for the change from baseline to Week 16 in ACQ-6 score.
- Although a numerically higher proportion of participants achieved a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16 in both the tozorakimab CCI mg and tozorakimab CCI mg groups compared with placebo, this difference between groups in the proportion of responders was not clinically meaningful.
- There was no statistically significant difference in the proportion of participants in either the tozorakimab CCI mg or tozorakimab CCI mg groups achieving well controlled status in their ACQ-6 score at Week 16 compared with placebo.
- No statistically significant difference was observed between either the tozorakimab CCI mg or CCI mg groups, and placebo for the change from baseline to Week 16 in SGRQ domain and total scores.
- There was no statistically significant difference in the proportion of participants in either the tozorakimab CCI mg or tozorakimab CCI mg groups achieving a decrease in SGRQ total score of ≥ 4 points from baseline to Week 16 compared with placebo.

- There was no statistically significant difference in either the tozorakimab [redacted] mg or tozorakimab [redacted] mg groups in the time to first CompEx event based on the period from baseline to Week 16 compared with the placebo group.
- Although there was a numerically lower CompEx annual event rate through Week 16 in the tozorakimab [redacted] mg group (0.69) than the tozorakimab [redacted] mg (0.86) or placebo groups (0.99), the difference between either of the tozorakimab groups and placebo was not statistically significant.

Summary of Pharmacokinetic Results

Data on PK were available for a total of 75 participants in the tozorakimab [redacted] mg group and 77 participants in the tozorakimab [redacted] mg group. Higher systemic exposure was observed at Week 1 (one week post dose [not trough]) (geometric mean [% coefficient of variation {CV}] in the [redacted] mg group: 8939.24 µg/L [367.31]; [redacted] mg group: 18374.15 µg/L [239.89]), compared with later on-treatment timepoints (Week 16: geometric mean [% CV] in the [redacted] mg group: 2742.93 µg/L [128.83]; [redacted] mg group: 5007.93 µg/L [117.76]). An increased exposure was observed in the tozorakimab [redacted] mg group compared with the tozorakimab [redacted] mg group.

Summary of Immunogenicity Results

In the tozorakimab [redacted] mg and [redacted] mg groups, 3 participants (4.0%) and 2 participants (2.6%), respectively were treatment-emergent (TE)-ADA positive (ADA incidence). The ADA prevalence was 3.9% for participants from each of the tozorakimab [redacted] mg and [redacted] mg groups. Due to the small number of ADA positive participants, it was not possible to make a meaningful conclusion on the possible effect of ADA on efficacy.

Summary of Biomarker Results

A nominally significant difference between placebo and each of tozorakimab [redacted] mg and tozorakimab [redacted] mg was observed at Week 16 (estimated geometric LSMean ratio [80% CI] at Week 16 was 0.869 [0.791, 0.956] in the tozorakimab [redacted] mg group and 0.879 [0.800, 0.966] in the tozorakimab [redacted] mg group) for the relative change from baseline in the concentration of fractional exhaled nitric oxide (FeNO) in exhaled breath.

Summary of Safety Results

All 235 participants received at least one dose of randomised IP. In both tozorakimab treatment groups and the placebo group, at least 89% of participants received all 4 protocol planned doses.

Overall, the majority of participants experienced at least one TEAE. The proportion of participants with at least one TEAE was higher in the tozorakimab [redacted] mg group (57 [74.0%] participants) than in the tozorakimab [redacted] mg group (45 [58.4%] participants) and the placebo group (45 [55.6%] participants).

Treatment-emergent adverse events were most commonly reported (≥ 25% of participants in the tozorakimab total group) in the system organ class (SOC) of Infections and infestations (38.3% and 37.0% of participants in the tozorakimab total and placebo groups, respectively). The most frequent (> 5% of participants) preferred terms (PTs) in the tozorakimab total group were: COVID-19 (19.5%, 13.0%, and 13.6% of participants in the tozorakimab CCI mg, CCI mg and placebo groups, respectively), injection site erythema (5.2%, 9.1%, and 2.5% of participants in the tozorakimab 300 mg, 600 mg and placebo groups, respectively), and nasopharyngitis (7.8%, 6.5%, and 4.9% of participants in the tozorakimab CCI mg, CCI mg and placebo groups, respectively). There was no evidence of a dose-dependent effect on the frequency of any TEAEs, except for the PTs of injection site erythema, injection site swelling and injection site urticaria.

The proportion of participants with IP related TEAEs was higher in the tozorakimab total group (14.9% of participants) than in the placebo group (4.9% of participants). Among the 2 tozorakimab treatment groups, the proportion was higher in the tozorakimab CCI mg group (18.2% of participants) compared with the tozorakimab CCI mg group (11.7% of participants).

The majority of AEs were Grade 1 or 2 and no Grade 4 or 5 events were reported. Four participants were reported with Grade 3 AEs (2 participants in each of the tozorakimab CCI mg and placebo groups). No participants experienced a TEAE leading to death.

The most common (≥ 5% of participants in the tozorakimab total group) adverse events of special interest were of the PTs COVID-19 (16.2% and 13.6% of participants in the tozorakimab total group and placebo group, respectively) and injection site erythema (7.1% and 2.5% of participants in the tozorakimab total group and placebo group, respectively).

Seven participants were reported with treatment-emergent serious adverse events (TESAEs) (one participant in the tozorakimab CCI mg group [PT of clavicle fracture], 4 participants in the tozorakimab CCI mg group [PTs of acid peptic disease, asthma and bronchitis in the same participant, asthma, and asthenia] and 2 participants in the placebo group [PTs of umbilical hernia and clostridium difficile colitis).

Two participants had an AE which led to discontinuation of IP: asthenia in a participant from the tozorakimab CCI mg groups and intervertebral disc protrusion in a participant from the placebo group.

No clinically meaningful trends in haematology, clinical chemistry, or urinalysis parameters over time were observed in any treatment group. There were no Hy's Law or potential Hy's Law cases. No notable trends were observed with respect to vital sign variables, electrocardiograms, left ventricular ejection fraction, or N-terminal prohormone of B-type natriuretic peptide in any treatment group. There were no clinically meaningful additional physical findings or other observations related to safety.

Conclusion(s)

- The study did not meet its primary objective. No statistically significant, or clinically meaningful difference from placebo was demonstrated for either the tozorakimab CCI mg or tozorakimab CCI mg group in change from baseline at Week 16 pre-BD FEV_1 as measured in the clinic for the ITT population.
- There was an increase in PK exposure with increasing tozorakimab dose.
- Few participants receiving tozorakimab developed ADA. There was no apparent effect of ADA on PK and no association of ADA with AEs was evident although the number of ADA positive participants was small. Due to the small number of ADA positive participants a meaningful conclusion on the possible impact of ADA on efficacy was not derived.
- Overall, tozorakimab was well tolerated in the study population of adult participants with uncontrolled moderate-to-severe asthma.