Clinical Study Report Synopsis	
Drug Substance	Tozorakimab (MEDI3506)
Study Code	D9182C00001
Edition Number	1
Date	06 June 2023
EudraCT Number	2019-003304-12
NCT Number	NCT04212169

A Phase 2 Randomized, Double-blinded, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI3506 in Adult Subjects with Moderate-to-severe Atopic Dermatitis

Study dates: First subject enrolled: 09 December 2019
Last subject last visit: 20 September 2022

Phase of development: Therapeutic exploratory (II)

Sponsor's Responsible Medical Officer: PPD

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

Study Centre(s)

The study was conducted at 32 sites in 6 countries: Australia (2 centres), Germany (4 centres), Poland (5 centres), Spain (3 centres), United Kingdom (8 centres), and United States (10 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 effects of MEDI3506 compared with placebo on AD disease severity, in adult subjects with moderate-to-severe AD	• Percent change from baseline to Week 16 in EASI score
Secondary	

• To further assess the effects of MEDI3506 compared with placebo on AD disease severity and symptoms, in adult subjects with moderate-to-severe AD	• EASI:
	  ° Percentage of subjects achieving a 90% reduction from baseline in EASI score (EASI 90) at Week 16
	  ° Percentage of subjects achieving a 75% reduction from baseline in EASI score (EASI 75) at Week 16
	  ° Percentage of subjects achieving a 50% reduction from baseline in EASI score (EASI 50) at Week 16
	• Percentage of subjects achieving an IGA of 0 (clear) or 1 (almost clear) with at least a 2 grade reduction from baseline score at Week 16
	• Peak pruritus NRS: Percentage of subjects achieving a reduction of ≥ 3 from baseline to Week 16 in weekly mean of daily peak pruritus NRS
	• Peak pruritus NRS: Change from baseline to Week 16 in weekly mean of daily peak pruritus NRS
	• Skin pain NRS: Change from baseline to Week 16 in weekly mean of daily peak skin pain NRS
	• SCORAD: Percent change from baseline to Week 16
	• PGI-S at Week 16
	• Change from baseline to Week 16 in:
	  ° % BSA affected by AD
	  ° 5-D itch
	  ° POEM
	  ° DLQI

Objectives	Endpoints
• To assess the safety and tolerability of MEDI3506 compared with placebo, in adult subjects with moderate-to-severe AD	During the treatment and follow-up periods: • TEAEs and TESAEs • Vital signs • Safety laboratory analysis • ECGs. The following parameters will be recorded for each ECG: ° Date and time of ECG ° Heart rate (beats/min) ° QT (ms) ° Overall evaluation (normal/abnormal) • Left ventricular ejection fraction as measured by echocardiogram
• To evaluate the PK of MEDI3506 in adult subjects with moderate-to-severe AD	• Serum MEDI3506 concentration profiles during the treatment and follow-up periods
• To evaluate the immunogenicity of MEDI3506 in adult subjects with moderate-to-severe AD	• Incidence of ADA during the treatment and follow-up periods

MEDI3506 was the original product name of tozorakimab.

AD = atopic dermatitis; ADA = anti-drug antibody(ies); BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 50 = 50% reduction from baseline in Eczema Area and Severity Index score; EASI 75 = 75% reduction from baseline in Eczema Area and Severity Index score; EASI 90 = 90% reduction from baseline in Eczema Area and Severity Index score; ECG = electrocardiogram; IGA = Investigator's Global Assessment; NRS = Numerical Rating Scale; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); POEM = Patient-Orientated Eczema Measure; QT = ECG interval measured from the beginning of the QRS complex to the end of the T wave; SCORAD = SCORing Atopic Dermatitis; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Study Design

This was a Phase II randomised, double-blinded, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of MEDI3506 (tozorakimab) in adult subjects with moderate-to-severe atopic dermatitis (AD).

Eligible subjects were planned to be randomised in a 3:3:3:1:2 ratio using an interactive voice/web response system to receive CCI tozorakimab by subcutaneous (SC) injection; or placebo CCI SC, or placebo CCI SC; CCI The randomisation ratio was changed during the study: the first 72 subjects in the study were to be randomised using a 3:3:3:1:2 ratio and the remaining subjects were to be randomised using a 1:1 ratio to receive CCI tozorakimab SC or placebo CCI SC; resulting in an overall randomisation ratio of 3:1:1:3 (placebo pooled:tozorakimab

[redacted]:tozorakimab [redacted]:tozorakimab [redacted]). The randomisation was stratified based on total immunoglobulin E (IgE) (< 150 kU/L or ≥ 150 kU/L) at screening.

Target Subject Population and Sample Size

Eligible subjects were adults aged 18 to 65 years inclusive at the time of consent with a documented history of chronic AD for at least one year prior to screening. Subjects had to meet at minimum one of the following criteria: an Investigator's Global Assessment (IGA) score of ≥ 3 within the 6 months prior to screening despite treatment with daily, medium, or high potency topical corticosteroids (TCSs); or requiring intermittent or continuous systemic therapy within the 6 months prior to screening; or subject intolerance to treatment with topical medications for AD; or topical medications were otherwise medically inadvisable. Prior to randomisation, subjects had to have an Eczema Area and Severity Index (EASI) score of ≥ 12 at Visit 1 and ≥ 16 at Visit 3 (Day 1), and, at both Visit 1 and Visit 3, AD that affected ≥ 10% of the body surface area (BSA) and an IGA score of ≥ 3. Subjects also had to have applied a stable dose of topical emollient (moisturiser) twice daily for ≥ 7 consecutive days immediately before baseline with a minimum of 85% compliance. Subjects were also required to apply moisturisers twice daily throughout the treatment and follow-up periods.

A sample size of 144 subjects, in an overall 3:1:1:3 ratio of placebo pooled:tozorakimab [redacted]:tozorakimab [redacted]:tozorakimab [redacted], provided at least 90% power to detect a statistically significant difference in the percent change from baseline to Week 16 in EASI score between the highest dose of tozorakimab and placebo pooled in a responder subgroup, assuming a 35% point difference between placebo and tozorakimab at the highest dose, based on a standard deviation of 40% points, a 2-sided 10% alpha level, and 50% of subjects in the responder subgroup. Based on identical assumptions, the sample size provided > 99% power to detect a statistically significant dose response in percent change from baseline to Week 16 in EASI score in all comers. To allow for the possibility that up to 5% of the subjects per treatment group may have been ineligible for the intent-to-treat (ITT) Population, the total sample size was planned to comprise approximately 152 subjects (58 for placebo pooled, 18 for tozorakimab [redacted], 18 for tozorakimab [redacted], and 58 for tozorakimab [redacted]).

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

Tozorakimab (MEDI3506) and placebo were manufactured by AstraZeneca and supplied as a solution in vials. Tozorakimab at [redacted] per dose or matching placebo was administered by SC injection [redacted]:

- [redacted]
- [redacted]

- CCI
- CCI
- CCI

CCI

- CCI
- CCI

Duration of Treatment

Subjects were enrolled in this study for approximately 7 months (28 weeks), comprising a screening and TCS/topical calcineurin inhibitor (TCI) wash out period of up to 4 weeks, a 16-week treatment period, and an 8-week follow-up period.

Statistical Methods

The ITT Population was used to summarise demographic and baseline characteristics, concomitant medications, and efficacy endpoints. The As-treated Population was used to summarise safety endpoints (adverse events, laboratory tests, electrocardiograms [ECGs], left ventricular ejection fraction, and vital signs) and immunogenicity. The PK Population was used to summarise PK endpoints.

The primary endpoint (percent change from baseline to Week 16 in EASI score) was analysed using a multiple comparison procedure with modelling techniques (MCP-Mod) for dose response analysis and a mixed-effects model for repeated measures (MMRM). All data points for subjects in the ITT Population were included in the analysis, up to and including the day and time rescue therapy was used.

The secondary endpoints IGA responders (percentage of subjects achieving an IGA of 0 [clear] or 1 [almost clear] with at least 2 grade reduction from baseline score at Week 16) and percentage of subjects achieving 75% reduction from baseline in EASI score (EASI 75) at Week 16 were analysed using a logistic regression model and MCP-Mod dose response analysis. Subjects who discontinued investigational product (IP), withdrew from the study, or required rescue therapy were considered as non-responders. Subjects with a missing visit were considered as non-responders for that visit.

Additional analyses of the primary endpoint and of IGA responders included data after rescue therapy use or used a last observation carried forward approach for missing data.

The following other secondary efficacy endpoints were analysed by MMRM (for analysis of change from baseline) or logistic regression model (for responder analysis):

- Percentage of subjects achieving a 50% reduction from baseline in EASI score (EASI 50) or a 90% reduction (EASI 90) at Week 16
- Peak pruritus numerical rating scale (NRS) responders and change from baseline at Week 16
- Change from baseline at Week 16 in skin pain NRS, % BSA affected by AD, 5-D itch, Patient-Oriented Eczema Measure (POEM), and Dermatology Life Quality Index (DLQI)
- Percent change from baseline at Week 16 in SCORing Atopic Dermatitis (SCORAD)
- Patient Global Impression of Severity (PGI-S) at Week 16.

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 IP up to the follow-up visit.

Descriptive statistics of tozorakimab serum concentrations and of serum anti-drug antibody (ADA) results (positive or negative) were reported.

Study Population

Of the 329 subjects screened, 148 subjects were randomised in 32 study centres across 6 countries in a 3:1:1:3 ratio to receive either placebo (56 subjects), tozorakimab [redacted] mg (19 subjects), tozorakimab [redacted] (18 subjects), or tozorakimab [redacted] (55 subjects). At the end of the study, all subjects had either completed (113 [76.4%] subjects) or discontinued (35 [23.6%] subjects) treatment. Overall, 112 (75.7%) subjects completed the study.

Demographics and disease characteristics were representative of the intended population of adults with moderate-to-severe AD and were generally similar across the treatment groups.

Summary of Efficacy Results

Primary Endpoint

No statistically significant dose response in percent change from baseline at Week 16 in EASI score was demonstrated. There were no statistically significant or clinically meaningful differences in EASI adjusted mean percent change at Week 16 between the placebo pooled group and any of the tozorakimab treatment groups ([redacted]: difference [tozorakimab – placebo] of 1.27 [90% confidence interval (CI): -13.67, 16.22], p = 0.888; [redacted]: difference of 5.87 [90% CI: -10.36, 22.10], p = 0.549; [redacted]: difference of -1.72 [90% CI: -13.38, 9.95], p = 0.807).

Secondary Endpoints

The percentage of EASI 50, EASI 75, and EASI 90 responders and the percentage of IGA responders at Week 16 were numerically higher in the tozorakimab CCI treatment group than in the placebo pooled group.

The mean change from baseline in peak pruritus NRS and skin pain NRS at Week 16 and the percentage of subjects achieving a reduction of ≥ 3 points from baseline to Week 16 in peak pruritus NRS at Week 16 were numerically higher in the tozorakimab CCI group than in the placebo pooled group.

The PGI-S at Week 16, the percent change from baseline in SCORAD at Week 16, and the change from baseline in % BSA affected by AD, 5-D itch, and POEM at Week 16 were similar across all 3 tozorakimab groups and the placebo pooled group. For DLQI, the adjusted mean reduction from baseline at Week 16 in all 3 tozorakimab treatment groups was numerically less than the reduction in the placebo pooled group.

Summary of Pharmacokinetic Results

Data on PK were available for a total of 19 subjects in the tozorakimab CCI group, 18 subjects in the tozorakimab CCI group, and 55 subjects in the tozorakimab CCI group. From Week 4 until the end of the dosing period (Week 16), the trough concentrations were similar across the timepoints. Higher systemic exposure was observed at Week 1 (geometric mean [% CV] in the CCI group: 1.989 [58.055]; CCI group: 9.311 [42.998]; CCI group: 21.824 [61.048]). An increased exposure was observed with increasing tozorakimab dose.

Summary of Immunogenicity Results

Anti-drug antibody results were available for 56 subjects with any ADA result in the placebo pooled group, 19 subjects in the tozorakimab CCI group, 18 subjects in the tozorakimab CCI group, and 55 subjects in the tozorakimab CCI group. The prevalence and incidence of ADA positive subjects was low. In total, 3 subjects were treatment-emergent ADA positive (one subject in the tozorakimab CCI group and 2 subjects in the tozorakimab CCI group); all 3 subjects had persistently positive ADA. In addition, one subject in the placebo pooled group had a positive ADA result at baseline and was persistently ADA positive. Overall, the effect of ADA on the primary efficacy endpoint or safety of tozorakimab was not evaluable due to the small number of ADA positive subjects. There was no effect of ADA on the PK of tozorakimab with the small number of ADA positive subjects.

Summary of Safety Results

In the placebo pooled group and in all 3 tozorakimab treatment groups, at least 70% of subjects received all 4 protocol planned doses. The extent of exposure was consistent across all treatment groups.

The proportion of subjects with at least one TEAE was numerically higher in the placebo pooled group (66.1% of subjects) than in the tozorakimab total group (59.8%). Among the tozorakimab treatment groups, the proportion of subjects with at least one TEAE was numerically lower compared with the placebo pooled group in the tozorakimab CCI (47.4% of subjects) and CCI (58.2%) groups and higher in the tozorakimab CCI group (77.8%).

In the tozorakimab total group, TEAEs were most commonly reported in the system organ classes of Infections and infestations (26.8% and 28.3% of subjects in the placebo pooled and tozorakimab total groups, respectively) and Skin and subcutaneous tissue disorders (32.1% and 25.0% in the placebo pooled and tozorakimab total groups, respectively). The most frequent preferred terms (PTs) in the tozorakimab total group were dermatitis atopic (17.4% of subjects), nasopharyngitis (6.5%), and injection site reaction (5.4%). The most frequent PTs in the placebo pooled group were dermatitis atopic (21.4% of subjects), COVID-19 (12.5%), and ear pain, eczema, headache, and pruritus (5.4% each). There was no evidence of a dose-dependent effect on the frequency of any TEAEs, except for the PT of injection site reaction.

Most TEAEs were considered not related to IP, as judged by the investigator. In the tozorakimab CCI group, a higher proportion of subjects experienced at least one IP related event compared with the placebo pooled group. The proportion of subjects with IP related events was similar to the placebo pooled group for the tozorakimab CCI and CCI groups.

The majority of TEAEs were Grade 1 or 2. No Grade 4 or 5 TEAEs were reported.
No subjects experienced a TEAE leading to death. The proportion of subjects with Grade 3 events was generally balanced between the placebo pooled group and the 3 tozorakimab treatment groups.

A similar proportion of subjects experienced at least one treatment-emergent AESI in the placebo pooled group and the tozorakimab total group.

In total, treatment-emergent serious adverse events (TESAEs) were reported for 5 subjects; 2 subjects in the placebo pooled group (PTs of dermatitis exfoliative generalised and food allergy) and 3 subjects in the tozorakimab total group (PTs of COVID-19 pneumonia, medical device removal, and venous thrombosis limb). One TESAE (PT of venous thrombosis limb in the tozorakimab CCI group) was judged by the investigator to be related to the IP.

Two subjects (both in the tozorakimab CCI group) discontinued IP due to a TEAE (PT of dermatitis atopic in both subjects).

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, ECGs, 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 dose response in percent change from baseline at Week 16 in EASI score was demonstrated. There were no statistically significant or clinically meaningful differences in EASI percent change from baseline at Week 16 between any of the tozorakimab treatment groups and the placebo pooled group.
- The percentage of EASI 75 responders and the percentage of IGA responders at Week 16 were numerically higher in the tozorakimab [redacted] group than in the placebo pooled group.
- There was an increase in PK exposure with increasing tozorakimab dose. The prevalence and incidence of ADA positive subjects was low. Overall, the effect of ADA on the primary efficacy endpoint or safety of tozorakimab was not evaluable due to the small number of ADA positive subjects. There was no effect of ADA on the PK of tozorakimab with the small number of ADA positive subjects.
- Overall, tozorakimab was well tolerated in the study population of adult subjects with moderate-to-severe AD.