Clinical Study Report	
Drug Substance	MEDI3506
Study Code	D9182C00002
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A Phase I, Randomised, Double-blind, Placebo-controlled, Dose-ascending Study to Evaluate the Pharmacokinetics, Immunogenicity, Safety, and Tolerability after Single-dose Subcutaneous Administration of MEDI3506 in Healthy Chinese Participants

Study Dates: First subject enrolled: 23 August 2021
Last subject last visit: 7 February 2022
The analyses presented in this report are based on a clinical data lock date of 25 April 2022

Phase of Development: Phase I

Principal 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.

2. SYNOPSIS

Study Centre(s)

This was a single centre study conducted in China. The study centre is PPD .

Publications

None at the time of finalisation of this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterise the PK of MEDI3506 following single SC administration in healthy Chinese participants.	• The following PK parameters were assessed for MEDI3506: – Apparent total body clearance of drug after extravascular administration (CL/F) – Volume of distribution during the terminal phase after extravascular administration (Vz/F) – Maximum observed (peak) concentration (Cmax) – Dose normalised Cmax – Time to reach peak or maximum observed concentration following drug administration (tmax) – Area under the concentration-time curve from zero to the last quantifiable concentration (AUClast) and from zero to infinity (AUCinf) – Dose normalised AUClast – Dose normalised AUCinf – Half-life associated with the terminal slope (λz) of a semilogarithmic concentration-time curve (t½λz) – Terminal elimination rate constant (λz)
Secondary	
• To evaluate the immunogenicity of MEDI3506 following single SC administration in healthy Chinese participants.	• Immunogenicity was evaluated based on the prevalence and incidence of anti-drug antibodies during the study.
Safety	
• To assess the safety and tolerability of MEDI3506 following single SC administration of MEDI3506 in healthy Chinese participants.	• Safety and tolerability were evaluated in terms of AEs, vital signs, clinical laboratory, and ECG. – Assessments related to AEs cover o Occurrence/frequency

Table S1 Objectives and Endpoints

Objectives	Endpoints
	○ Relationship to IP as assessed by investigator ○ Intensity ○ Seriousness ○ Death – Vital sign parameters included systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. – 12-lead ECGs – Safety laboratory assessments (haematology, clinical chemistry, and urinalysis)

AE(s) = adverse event(s); CSP = clinical study protocol; dose normalised AUCinf = area under the concentration-time curve from time zero extrapolated to infinity divided by the dose administered; dose normalised AUClast = area under the concentration-time curve from time zero to the last quantifiable analyte concentration divided by the dose administered; dose normalised Cmax = maximum observed (peak) concentration divided by the dose administered; ECG(s) = electrocardiogram(s); IP = investigational product; PK = pharmacokinetics; SAP = statistical analysis plan; SC = subcutaneous.
Source: CSP Table 3 and SAP Table 6 for PK parameters

Study Design

Study D9182C00002 was a Phase I, single-centre, randomised, double-blind, placebo-controlled, single-dose study in healthy Chinese male or female participants. For this study, 36 participants were randomised. The first 18 participants were assigned to the CCI mg cohort and randomised to CCI mg MEDI3506 or 2 mL matching placebo in a 2:1 ratio. The remaining 18 participants were assigned to the second cohort (CCI mg cohort) and randomised to CCI mg MEDI3506 or 4 mL matching placebo in a 2:1 ratio.

On Day 1, participants were assigned a randomisation number using sealed randomisation envelopes at the site. The randomisation schedule was generated prior to the study start by a computerised system. Assignment of each participant to a cohort was not blinded due to the difference in dose volume. Within each cohort, the randomisation of each participant to either MEDI3506 or placebo was double blinded. Study participants, investigator, and sponsor were blinded to each participant's assignment within each treatment cohort. Study pharmacists or designee dispensing the investigational product (IP) and study nurses or designee administering the subcutaneous (SC) injection at the Phase I clinical trial centre were unblinded.

Treatments were single MEDI3506 SC or placebo SC administration as follows:

- MEDI3506 CCI mg (2 mL, n = 12) or matching placebo (2 mL, n = 6)
- MEDI3506 CCI mg (4 mL, n = 12) or matching placebo (4 mL, n = 6)

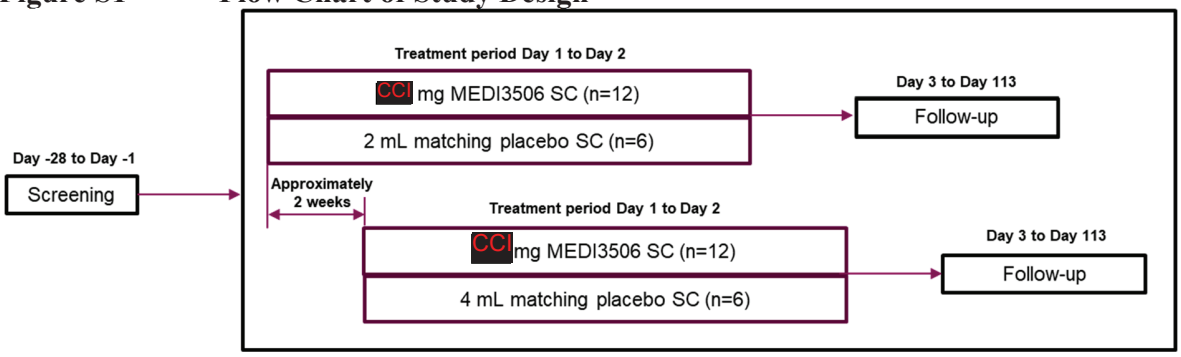
The study consisted of a screening period (maximum of 28 days), a treatment period (Day 1 to Day 2), and a follow-up period (Day 3 to Day 113). Each participant was randomised to one treatment arm (MEDI3506 CCI mg, MEDI3506 CCI mg, or placebo).

Participants underwent an initial screening evaluation (up to 28 days) to determine eligibility prior to randomisation and IP administration. Eligibility for the study was determined by the following procedures: physical examination and medical history, concomitant medications, electrocardiogram (ECG) and vital signs, urinalysis, drug screen, pregnancy test, haematology, serum chemistry, infectious disease testing, and other assessments.

Following the screening period, participants stayed at the study facility for 2 nights starting from the day before dosing (Day –1). Participants received a single SC dose of MEDI3506 or matching placebo on Day 1 and were discharged on Day 2 after Day 2 assessments were completed. Participants returned to the study site for additional blood collection and assessments during the scheduled follow-up visits, which took place from Day 3 to Day 113 postdose.

The design of the study and the sequence of treatment periods are shown below.

Figure S1 Flow Chart of Study Design



n = number of subjects in the treatment group; SC = subcutaneous

Target Population and Sample Size

The study enrolled healthy, nonsmoking, male and female Chinese participants with a body mass index (BMI) between PPD kg/m^2, inclusive. Participants were aged PPD years (inclusive) at the time of signing the informed consent form (ICF). Approximately 36 participants were to be randomised.

The sample size was not based on formal statistical considerations. The planned sample size of 36 participants (12 per treatment group including the combined placebo group of 2 mL and 4 mL) was based on China regulatory/practical considerations that 8 to 12 participants completing each active treatment were required. This sample size could allow a dropout rate

of 30%, which was estimated based on a long study duration of 113 days. The planned sample size was reached in the study; 36 participants were randomised (12 per treatment group).

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

MEDI3506 was supplied by the sponsor in a 2R vial with nominal 1 mL of 150 mg/mL MEDI3506 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, 0.03% weight/volume (w/v) polysorbate 80, pH 5.5.

Placebo was supplied by the sponsor in a 3-cc vial with nominal 1 mL solution of 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, 0.02% (w/v) polysorbate 80, pH 6.0.

Participants were administered a single dose of MEDI3506 CCI mg SC (CCI), MEDI3506 CCI mg SC (CCI), or matched placebo SC (one or two 2-mL injections). Each participant was randomised to one treatment arm.

All participants randomised to MEDI3506 or matching placebo received batch number A03781.

Duration of Treatment

Study participants had a screening period of up to 28 days. Following the screening period, participants received a single dose of MEDI3506 or placebo on Day 1 and were requested to return to the study facility for additional blood collection and study assessments during the scheduled follow-up visits from Day 3 to Day 113 postdose.

Statistical Methods

The as-treated principle was applied to all evaluations, which is participants who received treatment other than the one assigned by randomisation were to be analysed according to the actual treatment received.

Safety, tolerability, pharmacokinetics (PK), and immunogenicity data (observed and derived) were summarised descriptively using tables, listings, and graphs, as appropriate. Unless otherwise stated, descriptive summary statistics for continuous variables included number of observations (n), arithmetic mean, standard deviation (SD), minimum, median, maximum, and quartiles as appropriate. For continuous PK variables, as well as serum concentration of MEDI3506, descriptive summary statistics also included geometric mean and geometric coefficient of variation (geometric CV%). For the time to reach peak or maximum observed concentration following drug administration (tmax), only n, median, minimum, and maximum were presented. Descriptive summary statistics for categorical data included frequency counts and percentages for each category.

Three analysis sets were defined as follows:

- All-subject analysis set: All enrolled participants who signed the ICF, including screening failures.
- PK analysis set: All participants who received any dose of MEDI3506 and who had at least one measurable postdose serum PK observation. Participants were analysed according to the treatment they actually received.
- Safety analysis set: All participants who received any dose of MEDI3506 or placebo. Any erroneously treated participants (eg, those randomised to treatment A but actually given treatment B) were analysed according to the treatment they actually received.

Pharmacokinetic parameters were derived using noncompartmental methods with Phoenix® WinNonlin® version 8.1.1. All descriptive and inferential statistical computations were performed using SAS® version 9.4.

No formal statistical hypothesis tests were made. Consequently, no correction for multiplicity were used. Unless otherwise noted in the statistical analysis plan, no imputations for missing data were made.

Study Population

- This was a single centre study conducted in China. All 36 randomised participants were dosed (12 received MEDI3506 CCI mg, 12 received MEDI3506 CCI mg, and 12 received matching placebo) and completed the study.
- There were no important protocol deviations or coronavirus disease 2019 (COVID-19)-related protocol deviations reported.
- There was no disruption to visits or exposure, and no change in study status due to the global/country situation (ie, COVID-19 pandemic) for any participant during the study period. Therefore, the COVID-19 pandemic was not judged to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of the anti-drug antibodies (ADA), PK, and safety results.
- The study participant enrolment was consistent with the eligibility criteria in terms of demographic and baseline characteristics. The median (minimum to maximum) age of study participants was 25 (PPD) years, inclusive; 7 of 36 participants (19.4%) were female and 29 of 36 participants (80.6%) were male. All participants (100%) were Chinese. None of the participants had a BMI PPD kg/m^2.
- The study population recruited to the study (ie, healthy volunteers) was appropriate for the type of study performed (PK characterisation of a single dose of MEDI3506 administered SC).
- Although there were more males than females participating in the study (80.6% versus 19.4%, respectively), there was no apparent sex-related difference in the proportion of participants in the MEDI3506 and placebo groups or between MEDI3506 dose levels. No other relevant differences were observed between participants who received MEDI3506 or placebo regarding demographic or baseline characteristics.

- No medical or surgical histories and no prior, concomitant, or disallowed medications were reported, which is consistent with a study population of healthy volunteers.

Summary of Pharmacokinetic Results

- Maximum concentrations of MEDI3506 in serum occurred at CCI postdose based on median tmax following a single SC dose of MEDI3506 CCI in healthy Chinese participants.
- The concentration-time profiles indicate CCI in serum, which declined slowly over time with a geometric mean half-life associated with the terminal slope of a semilogarithmic concentration-time curve (t½λz) of CCI days for a single dose of MEDI3506 at CCI, respectively.
- Exposure to MEDI3506 CCI based on the geometric mean of the maximum observed (peak) concentration (Cmax) and area under the serum concentration-time curve from zero to infinity (AUCinf), respectively, CCI.
- Variability of Cmax and AUCinf based on the geometric CV was moderate CCI and high for CCI
- CCI, the impact of ADA on the PK profile of MEDI3506 was not evaluated.

Summary of Immunogenicity Results

- CCI

Summary of Safety Results

- MEDI3506 was well tolerated in healthy Chinese participants. No safety concerns were identified in the study.
- Safety analysis was mainly based on treatment-emergent adverse events (TEAEs). Adverse event (AE) in the safety analysis and results generally means TEAE, unless specified otherwise. At least 50% of participants in all treatment groups experienced at least one TEAE: 66.7% (8 of 12 participants) for both MEDI3506 CCI and 50.0% (6 of 12 participants) for placebo. All AEs were nonserious, mild, and did not require treatment.

[1] ADA incidence is the proportion of treatment-emergent ADA-positive participants in a population. TE-ADA positive subjects are those with treatment-induced ADA (baseline is ADA negative and at least one postbaseline assessment is ADA positive) or treatment-boosted ADA (baseline is ADA positive, and the baseline titre is boosted by ≥ 4-fold at ≥1 postbaseline time point).

- No deaths, serious adverse events, IP discontinuations, dose interruptions, or withdrawals from the study due to AEs were reported.
- There were no obvious clinically significant trends observed in the occurrence of AEs across treatment groups.
  - The most common AEs by preferred term (≥ 2 participants) in participants who received MEDI3506 (total) were blood uric acid increased, C-reactive protein (CRP) increased, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased, neutrophil and white blood cell (WBC) count decreased, upper respiratory tract infection, urinary ketone body present, leukocyte esterase positive, and WBC urine positive.
  - Blood uric acid increased and urinary WBC positive were the most common AEs reported at a higher frequency in the placebo group than in the MEDI3506 group.
  - A higher proportion of participants who received MEDI3506 (total) had AEs of blood CRP increased, ALT and AST increased, neutrophil and WBC count decreased, upper respiratory tract infection, and urinary ketone body present compared to participants who received placebo. There is no evidence to confirm a clinically relevant relationship between these events and MEDI3506.
- A nonserious AE of special interest (injections site erythema) was reported in one participant who received MEDI3506 CCI . This event was considered by the investigator to be of mild intensity and related to IP; this event fully resolved on the same day, and no treatment was required.
- No COVID-19-related AEs were reported.
- CCI , the impact of ADA on the safety profile of MEDI3506 was not evaluated.
- There were no clinically relevant trends over time in clinical laboratory (haematology, clinical chemistry, or urinalysis), vital signs, or ECG parameters in any treatment group.

Conclusions

- The PK of MEDI3506 following single SC administration in healthy Chinese participants was well characterised. The median tmax at CCI was CCI days, with geometric mean t½λz values of CCI , respectively. Exposure to MEDI3506 increased by CCI based on geometric mean Cmax and AUCinf, respectively, CCI ; this was considered **not** clinically relevant.
- CCI any relationship between ADA incidence and MEDI3506 dose levels and the impact of ADA on the PK and safety profile of MEDI3506 were not evaluated.
- MEDI3506 was well tolerated in Chinese healthy participants. No safety concerns were identified during the study.

- The COVID-19 pandemic was not judged to have meaningfully impacted the overall quality of the study, including the conduct, data, or interpretation of the PK, ADA, and safety results.