Clinical Study Report Synopsis	
Drug Substance	Anifrolumab (MEDI546)
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A Phase I, Open-label, Single-arm, Multiple-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Anifrolumab in Chinese Participants with Systemic Lupus Erythematosus (SLE)

Study Dates: First patient enrolled: 27 July 2021
Last patient last visit: 02 June 2022
The analyses presented in this report are based on a clinical data lock date of 07 September 2022

Phase of Development: Clinical pharmacology (I)

National 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 Centres

This study was conducted at 3 study centres in China.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterise the PK profile of multiple doses of anifrolumab CCI via IV infusion in Chinese patients with SLE.	Anifrolumab concentrations and PK parameters: • $C_{max,1}$, $T_{max,1}$, $AUC_{\tau,1}$ based on the first dose, $C_{troughs}$ and $CL_{,1}$. Additional PK parameters (serum) may be determined where appropriate.
Secondary	
• To characterise the safety and tolerability of anifrolumab CCI via IV infusion in Chinese patients with SLE.	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, antibody and complements (including anti-dsDNA, C3, C4, and CH_{50}) [a], and ECG. Assessments related to AEs cover • Occurrence/Frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • AEs of special interest Vital signs parameters include systolic and diastolic blood pressure, and pulse rate, respiration rate, body temperature. Laboratory parameters include clinical chemistry and haematology parameters, as well as urinalysis.
• To characterise the immunogenicity of anifrolumab after multiple doses CCI administration via IV infusion in Chinese patients with SLE.	• Anti-drug antibodies
• To evaluate the baseline IFN status and PD biomarker in Chinese patients with SLE after multiple doses CCI of anifrolumab.	• CCI
Exploratory	
• CCI	• CCI

[a] Antibody and complements were incorrectly categorised as safety endpoints in the CSP and SAP. However, they are efficacy endpoints and are covered in the 'Evaluation of response to study intervention' section in this clinical study report.

AE, adverse event; anti-dsDNA, anti-double-stranded DNA; $AUC_{\tau,1}$, area under the serum concentration-time curve from Day 1 to Day 29; C3/C4, complement component 3/4; CH_{50}, total complement activity; $CL_{,1}$, total body clearance of drug from serum after first intravascular dose administration; $C_{max,1}$, maximum observed serum (peak) concentration of the first dose; $C_{troughs}$, trough observed serum concentration; ECG, electrocardiogram; IFN, interferon; IP, investigational product; IV, intravenous; PD, pharmacodynamic; PGA, physician's global assessment; PK, pharmacokinetic; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; SLE, systemic lupus erythematosus; $T_{max,1}$, time to reach peak or maximum observed concentration or response following the first drug administration.

Study Design

This was a Phase I, open-label, single-arm, multiple-dose study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability profile of intravenous (IV) anifrolumab in Chinese patients with active systemic lupus erythematosus (SLE). All eligible patients were to receive CCI [redacted].

Target Population and Sample Size

Approximately 18 Chinese patients aged 18 to 60 years with moderate-to-severe SLE despite receiving standard-of-care treatment were to receive anifrolumab, with the expectation of no less than 8 evaluable patients at study completion.

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

CCI [redacted] were to be administered to all eligible patients over CCI [redacted].

Duration of Treatment

The treatment period lasted from Day CCI to Day CCI, with follow-up period from Day CCI to Day CCI.

Statistical Methods

There was no statistical hypothesis testing in this study. Pharmacokinetics, safety, and tolerability were evaluated using descriptive statistics. Summary data were presented in tabular format and the following principles were followed throughout the analyses:

- Pharmacokinetic and immunogenicity analyses were to be performed by interferon (IFN) 4-gene test status (high/low/overall) unless there were no patients with low status. For other analyses, summary data were presented for overall treatment group. Pharmacokinetic serum concentrations and parameters were summarised using descriptive statistics.
- Continuous, non-PK variables and PK concentrations were summarised by descriptive statistics.
- Categorical data were summarised by the number and percentage of patients in each category.
- Summaries by timepoint used adjusted analysis-defined visit windows.
- Corresponding listings were produced for all tabulated results unless stated otherwise.

Three analysis sets were defined as follows:

Pharmacokinetic Analysis Set: The PK analysis set included all patients who received anifrolumab (ie, at least one dose), with no important protocol deviations thought to impact the PK profile, and who had at least one measurable post-dose anifrolumab serum concentration. Patients who had intermittent missing PK sampling were evaluated case-by-case for inclusion in the PK analysis set. The PK analysis set was used to analyse the PK data.

Safety Analysis Set: The safety set included all patients who received any (ie, at least one) dose of anifrolumab. The safety population was used for all analyses of baseline demographics, baseline characteristics, disposition, safety, and immunogenicity.

Pharmacodynamic Analysis Set: The PD analysis set was the subset of the safety analysis set that included all patients who had high type I IFN 4-gene test status. If no low type I IFN 4-gene test status patients were in the safety analysis set, then the PD analysis set would be identical to the safety analysis set. The PD analysis set was used to analyse PD data.

Study Population

Twenty-three patients were screened at 3 sites in China; 15 patients were treated, and 14 patients completed the study. One patient withdrew from the study (recorded by the investigator as non-compliance with study drug) after receiving only one dose of anifrolumab. Two patients discontinued treatment (due to the coronavirus disease 2019 pandemic) after receiving only 2 doses of anifrolumab but completed the study.

All 15 patients who received treatment were included in the safety, PK, and PD analysis sets.

Median age of patients was 40 years old and all but one patient were female. All patients were Chinese and were type I IFN 4-gene test high. Median body mass index was 22.03 kg/m^2. At baseline, 80.0% of patients had a Systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) score of < 10 (mean score of 7.3), mean Physician's global assessment (PGA) score was 1.53, 100% were type I IFN 4-gene test high, 93.3% were anti-nuclear antibody positive, 73.3% were anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA) positive, 66.7% had low complement component 3 (C3) levels, 26.7% had low complement component 4 (C4) levels, and 33.3% had low total complement activity (CH_{50}) levels. The mean time from initial SLE diagnosis to baseline was 112.3 months.

Summary of Efficacy Results

CCI [redacted]

Summary of Pharmacokinetic Results

CCI [redacted]

A similar shape of anifrolumab geometric mean serum concentration-time profile was observed after the first and third dose administration; anifrolumab serum concentrations peaked at the end of infusion, and anifrolumab was eliminated in an approximately biphasic manner.

CCI [redacted]

CCI [redacted]

Summary of Pharmacodynamic Results

CCI [redacted]

Summary of Pharmacokinetic/Pharmacodynamic Relationship

All patients were type I IFN 4-gene test high so it was not possible to establish a PK/PD relationship between serum concentration and test-high/low status.

Summary of Immunology Results

At 12 weeks post last dose, 6 patients who were anti-dsDNA positive at baseline remained positive, 2 patients who were anti-dsDNA negative at baseline remained negative, and for the other 7 the data were missing. For patients with low C3 and C4 at baseline, mean levels increased and remained higher than baseline throughout the study. For patients with low CH_{50} at baseline, mean values of CH_{50} remained increased and remained higher than baseline until

8 weeks after the third (last) dose and decreased to below baseline levels at 12 weeks after the third dose, although available data were very limited.

Summary of Immunogenicity Results

All 15 patients were anti-drug antibody (ADA) negative at baseline and throughout the study.

Summary of Safety Results

Eleven (73.3%) patients experienced at least one adverse event (AE). Events were typically mild, transient, and resolved without dose interruption. Eight (53.3%) patients experienced an AE that was considered by the investigator to be related to IP. There were no deaths, serious AEs, AEs leading to discontinuation of IP, or other significant AEs in this study. One patient experienced an AE of special interest (herpes zoster).

The system organ classes with the greatest frequency of patients experiencing AEs (more than 2 patients) were Infections and Infestations (8 [53.3%] patients) and Skin and Subcutaneous Tissue Disorders (6 [40.0%] patients). The most common preferred terms (experienced by 2 or more patients) were upper respiratory tract infection (5 [33.3%] patients), and dermatitis allergic, hypokalaemia, pruritis, pyrexia, rash, and urticaria (each experienced by 2 [13.3%] patients). The AEs of hypokalaemia were reported in patients who had low potassium recorded at Day 1 (before dosing). One of the 2 patients who experienced dermatitis allergic had a medical history of this condition. The rash and pyrexia events were not related to SLE.

There were no clear trends over time in haematology, clinical chemistry, urinalysis, vital signs, electrocardiogram parameters, or physical findings.

Conclusions

- A similar shape of anifrolumab geometric mean serum concentration-time profile was seen for anifrolumab first dose and third dose. Exposure (C_{max}, AUC_{τ}) of anifrolumab was slightly higher for the third dose compared to the first dose, indicating minimal accumulation after [redacted] doses. The $t_{1/2}$ after the first dose was approximately 6 days, with geometric mean CL at 362.6 mL/day.
- Treatment with anifrolumab [redacted] IV Q4W was well tolerated and had an acceptable safety profile in Chinese adult patients with moderate-to-severe SLE. There were no new or unexpected findings and no clinically relevant safety concerns were raised.
- No ADA-positive samples were observed in any patients throughout the study.
- [redacted].