Clinical Study Report	
Drug Substance	MEDI0618
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A Randomised, Double-blind, Placebo-controlled Study of the Safety, Tolerability, and Pharmacokinetics of Multiple Ascending Doses of MEDI0618 in Healthy Male and Female Volunteers

Study dates:
First participant enrolled: 12 December 2022
Last participant last visit: 12 December 2023
The analyses presented in this report are based on a clinical data lock date of 23 January 2024.

Phase of development:
Clinical pharmacology (1)

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This study was performed in compliance with ICH/GCP, including the archiving of essential documents.

2 SYNOPSIS

Study Centre

The study was conducted at one site in Germany.

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 safety and tolerability of multiple ascending doses of MEDI0618 versus placebo in male and female healthy participants	• AEs and SAEs • Vital signs, body temperature, body weight measurements, and BMI • Clinical chemistry, haematology, coagulation, thyroid function, renal function, and urinalysis test results • 12-lead dECG results (heart rate and PR, QRS, RR, QT and QTcF intervals) and overall evaluation from 12-lead safety ECG/paper printout and cardiac telemetry • Physical examinations • Treatment-emergent suicidal ideation and behaviour as assessed by C-SSRS • Injection site and infusion site reaction assessments
Secondary	
To assess the PK of multiple ascending doses of MEDI0618 in male and female healthy participants	PK parameters, including: After the first dose: • Cmax, tmax, AUCtau After the last dose: • Cmax, tmax, AUCtau, t1/2, CL, Vss, Vz (IV administration), CL/F, Vz/F, F (SC administration)
To assess the immunogenicity of multiple ascending doses of MEDI0618 in male and female healthy participants	ADA incidence and titres

ADA = anti-drug antibody; AE = adverse event; AUCtau = area under the concentration-time curve over the dosing interval; BMI = body mass index; CL = total body clearance; CL/F = apparent total body clearance; Cmax = maximum observed concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; dECG = digital electrocardiogram; ECG = electrocardiogram; F = absolute bioavailability; IV = intravenous; PK = pharmacokinetic; PR = ECG interval measured from the onset of the P wave to the onset of the QRS complex; RR = Time between corresponding points on 2 consecutive R waves on ECG; QRS = ECG interval measured from the onset of the QRS complex to the J point; QT = ECG interval measured from the onset of the QRS complex to the end of the T wave; QTcF = QT corrected by Fridericia's formula; SC = subcutaneous; t1/2 = terminal half-life; tmax = time to reach maximum observed concentration; SAE = serious adverse event; Vss = volume of distribution at steady state; Vz = volume of distribution based on terminal phase; Vz/F = apparent volume of distribution based on terminal phase.

Study Design

This was a single-centre, randomised, double-blind, placebo-controlled study of multiple ascending doses of MEDI0618 in healthy participants, age 18 to 50 years, inclusive. MEDI0618 is being developed to treat osteoarthritis and migraine.

The study comprised a screening period of up to 30 days: a randomised, double-blind treatment period of 8 weeks, and a follow-up period of 10 weeks after the last dose administration. A total of [redacted] doses of MEDI0618 or placebo were administered [redacted] via a 60-minute intravenous (IV) infusion or subcutaneous (SC) injections via four 1.0 mL injections.

Target Population and Sample Size

Eligible study participants included healthy men and women of nonchildbearing potential (ie, postmenopausal or surgically sterile), age 18 to 50 years, inclusive.

Approximately 36 to 48 participants were to receive [redacted] doses of MEDI0618 or placebo. There were 3 planned and 1 optional MAD cohorts:

- Cohort 1: 12 healthy volunteers, [redacted] mg MEDI0618 or placebo, IV administration
- Cohort 2: 12 healthy volunteers, [redacted] mg MEDI0618 or placebo, IV administration
- Cohort 3: 12 healthy volunteers, [redacted] mg MEDI0618 or placebo, SC administration

An optional Cohort 4, to allow an additional lower dosage level to be tested, was to include 12 healthy volunteers; dose was to be selected based on safety review committee (SRC) review of safety and pharmacokinetic (PK) data of all previous cohorts and was not to exceed [redacted] mg [redacted] for either route of administration. (Note: The SRC did not request an additional lower dosage level to be tested; therefore, Cohort 4 was not required.)

Within each cohort of 12 participants, 8 participants were to be randomised to receive MEDI0618 and 4 to receive placebo.

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

MEDI0618 (batch number [redacted]) and placebo (batch number [redacted]) were supplied by [redacted]. MEDI0618 and placebo were administered as [redacted] mg SC and [redacted] and [redacted] mg IV.

Duration of Treatment

The duration of the treatment period was 8 weeks.

Statistical Methods

Due to the exploratory nature of the study, no formal statistical hypothesis testing for the primary endpoints was planned.

Safety, tolerability, PK, and anti-drug antibody (ADA) data were summarised descriptively, including tables, listings, and graphs. Missing values were not imputed as an observed-cases approach was applied for all the analyses.

In general, data from participants treated with MEDI0618 were summarised by cohort using the as-treated principle, while data for participants treated with placebo were pooled across dose cohorts with same route of administration (ie, Cohort 1 and 2 with IV infusion). In addition, participants with the same route of administration of MEDI0618 were pooled together for analysis if it was deemed meaningful.

Study Population

Overall, 112 participants were screened at one site in one country, of whom 36 were randomised to treatment groups; 24 participants were randomised to MEDI0618 (CCI mg IV administration, CCI mg IV administration, and CCI mg SC administration), and 12 participants were randomised to placebo (CCI to IV administration and 4 to SC administration).

Of the randomised participants, 35 (97.2%) completed treatment. The Investigator discontinued treatment for one participant after 2 doses of IV placebo due to a decrease in neutrophil and leukocyte counts. This participant did not withdraw from the study, completed all follow-up procedures, and, therefore, was considered to have completed the study.

The demographic and participant characteristics were generally balanced across treatment groups. No imbalances were noted between treatment groups in concomitant medication received that could have had a potential influence on the results and their interpretation, and no important protocol deviations occurred.

Summary of Efficacy Results

Efficacy was not evaluated in this Phase 1 study.

Summary of Pharmacokinetic Results

Following IV administration of MEDI0618, median time to reach maximum observed concentration (tmax) generally occurred at end of infusion following IV administration with the exception of Day 43 at CCI mg IV, where median tmax occurred approximately CCI hours post end of infusion. Following SC administration, median tmax occurred approximately CCI days postdose. Post tmax on Day 43, serum concentration declined in an essentially monophasic manner with geometric mean half-life (t1/2λz) between CCI days.

Between [redacted] mg and [redacted] mg IV administration of MEDI0618, systemic exposure increased in a greater than dose proportional manner with dosed normalised maximum observed concentration (Cmax) and area under the concentration-time curve over the dosing interval (AUCtau) approximately 1.5-fold higher at [redacted] mg compared to [redacted] mg.

Absolute bioavailability of the [redacted] mg SC dose was estimated at approximately [redacted].

Following multiple doses of MEDI0618, accumulation was [redacted] fold (IV administration) and [redacted] fold (SC administration).

Summary of Pharmacodynamic Results

Not applicable (NA).

Summary of Pharmacokinetic/Pharmacodynamic Relationships

NA.

Summary of Pharmacogenetic Results

Among participants who received MEDI0618, ADA incidence was [redacted] for those who received SC administration and [redacted] for those who received IV administration.

In participants with treatment-emergent ADA, ADA titres were low and ranged from [redacted], in the IV and SC cohorts, respectively.

Summary of Safety Results

All 36 study participants received at least one dose of investigational product (IP) (MEDI0618 or placebo).

The Investigator discontinued treatment for one participant after 2 doses of IV placebo due to a decrease in neutrophil and leukocyte counts. According to the Investigator, the events were related to the IP but were considered mild and resolved in approximately 3 days.

Across IV cohorts, 10 (62.5%) participants treated with MEDI0618 and 7 (87.5%) participants treated with placebo had at least one treatment-emergent adverse event (TEAE). In the SC cohort, 4 (50%) participants treated with MEDI0618 and 1 (25%) participant treated with placebo had at least one TEAE. All TEAEs were of mild or moderate severity.

In participants treated with MEDI0618 (IV or SC), no TEAEs were assessed as related to the IP by the Investigator. No deaths or treatment-emergent serious adverse events (SAEs) occurred in any cohort.

None of the TEAEs in ADA-positive participants was indicative of hypersensitivity or autoimmune reactions, and the presence of ADA did not affect the safety profile of MEDI0618.

The most common TEAE by preferred term (PT) in SC MEDI0618-treated participants was nasopharyngitis (3 [37.5%] participants). The most common TEAEs by PT in IV MEDI0618-treated participants were nasopharyngitis (5 [31.3%] participants) and increased blood creatine phosphokinase (2 [12.5%] participants). The increased blood creatine phosphokinase was assessed by the Investigator as mild and not related to the IP.

One (12.5%) participant who received CCI mg IV MEDI0618 experienced a mild infusion site reaction; it was not considered a TEAE.

Four participants (one who received CCI mg IV MEDI0618 and 3 who received IV placebo) had clinically importantly abnormalities in C-reactive protein. These were not considered TEAEs by the Investigator.

No clinically relevant changes or differences between MEDI0618- and placebo-treated participants were observed in urinalysis, coagulation, thyroid and renal function, vital signs, electrocardiogram parameters, or body weight.

Conclusions

- Overall, MEDI0618 was safe and well-tolerated when administered as CCI repeat doses of CCI mg IV, CCI mg IV, or CCI mg SC in healthy volunteers.
- There were no deaths, SAEs, severe TEAEs, identified risks, or clinically significant differences between MEDI0618 and placebo with respect to safety outcomes.
- Median tmax occurred approximately CCI days postdose for SC administration. The geometric t1/2λz was approximately CCI days.
- Between CCI mg and CCI mg IV administration, systemic exposure increased in a greater than dose proportional manner.
- Absolute bioavailability of the CCI mg SC dose was estimated at approximately CCI.
- Following CCI administration of MEDI0618, accumulation was CCI fold (IV administration) and CCI fold (SC administration).
- Among participants who received MEDI0618, the ADA incidence was CCI (SC administration) and CCI (IV administration). The presence of ADAs was not associated with hypersensitivity or immune reactions and had no effect on the PK or safety profile of MEDI0618.