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

Study dates:
First subject enrolled: 09 Dec 2019
Last subject last visit: 23 Feb 2022
The analyses presented in this report are based on a clinical data lock date of 05 May 2022.

Phase of development: Phase 1

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

Study centre

The study was conducted at a single centre in Germany.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 CCI

CCI

Study design

This was a single-centre, randomised, double-blind, placebo-controlled study of single doses of MEDI0618 in healthy male and non-fertile female volunteers, aged 18 to 55 years.

The study included 9 cohorts, including 2 cohorts of 4 subjects each and 7 cohorts of 8 subjects each. Eight cohorts received single ascending doses of MEDI0618 CCI CCI or placebo administered via intravenous infusion (iv); 1 additional cohort received a single dose of CCI MEDI0618 or placebo by subcutaneous (sc) injection. Within each cohort of 4 subjects, 3 subjects were randomised to receive MEDI0618, and 1 subject was randomised to receive placebo. Within each cohort of 8 subjects, 6 subjects were randomised to receive MEDI0618, and 2 subjects were randomised to receive placebo.

A Safety Review Committee (SRC) reviewed available safety, tolerability, pharmacokinetic and immunogenicity data before progression from one dosage-level cohort to the next higher dosage-level cohort occurred. Cohorts could also be added or removed based on the review and recommendation of the SRC. The total number of cohorts in the study could not exceed 11.

On Day 1, each randomised subject received a single 60-minute intravenous infusion or a subcutaneous injection of MEDI0618 or placebo in double-blind fashion and underwent scheduled safety, tolerability, pharmacokinetic and immunogenicity assessments. Subjects remained in the clinical research unit for at least 48 hours after the end of study drug administration before discharge on Day 3 and returned to the unit as outpatients for further study assessments at defined timepoints to the end of the follow-up period, for which the duration was dose-dependent and up to 12 weeks.

Target population and sample size

Study subjects were healthy men or women of non-childbearing potential (ie, post-menopausal or surgically sterile), aged 18 to 55 years inclusive, who weigh ≥50 kg and have a body mass index between 18.0 and 30.0 kg/m^2, inclusive.

Number of subjects (planned and analyzed): A total of 68 subjects were planned to be randomized with the aim of obtaining 64 evaluable subjects to be included in the 9 cohorts. A total of 259 subjects were screened and 68 subjects were randomized and analyzed as follows (see **Table S2**).

Table S2 Number of subjects in the analysis sets (randomised patients)

	Cohort 9		Cohort 8	Cohort 7	Cohort 6	Cohort 5	Cohort 4	Cohort 3	Cohort 2	Cohort 1	Cohort 1-8	Cohort 1-9
	MEDI0618 CCI (sc)	Placebo (sc)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	Placebo (iv)	Total
Randomized	6	2	7	6	6	6	6	6	3	3	17	68
Safety set	6	2	6	6	6	6	6	6	3	3	14	64
PK set	6	0	6	6	6	6	6	6	3	3	0	48

Source: Statistical Analysis Output – Tables, Version 2.0 (2022-07-18): Table SP02

Investigational product and comparator: dosage, mode of administration and batch numbers

CCI [redacted]

Cohort sizes and dose escalation were planned as follows:

- Cohort 1: CCI [redacted] MEDI0618 (3 subjects), placebo (1 subject), intravenous infusion
- Cohort 2: [redacted] MEDI0618 (3 subjects), placebo (1 subject), intravenous infusion
- Cohort 3: [redacted] MEDI0618 (6 subjects), placebo (2 subjects), intravenous infusion
- Cohort 4: CCI [redacted] MEDI0618 (6 subjects), placebo (2 subjects), intravenous infusion
- Cohort 5: CCI [redacted] MEDI0618 (6 subjects), placebo (2 subjects), intravenous infusion
- Cohort 6: [redacted] MEDI0618 (6 subjects), placebo (2 subjects), intravenous infusion
- Cohort 7 CCI [redacted] MEDI0618 (6 subjects), placebo (2 subjects), intravenous infusion
- Cohort 8: CCI [redacted] MEDI0618 (6 subjects), placebo (2 subjects), intravenous infusion
- Cohort 9: CCI [redacted] MEDI0618 (6 subjects), placebo (2 subjects), subcutaneous injection

CCI [redacted]

Further cohorts could be added or removed based on the recommendations of the Safety Review Committee but the total number of cohorts in the study could not exceed 11.

Pharmacy personnel at the site prepared all Investigational Product (IP) for each subject according to handling instructions provided by AstraZeneca and the randomisation scheme. To maintain the double-blind requirements, placebo volume administered was equivalent to the MEDI0618 volume administered for each cohort. Further information is included in Section **9.4** of the CSR.

Duration of treatment

Single dose administration

Within each cohort, subjects received a single 60-minute intravenous infusion or a subcutaneous injection of MEDI0618 or placebo in a double-blind manner and underwent scheduled safety, tolerability, pharmacokinetic and immunogenicity assessments. Subjects remained in the clinical research unit for at least 48 hours after the end of study drug administration before discharge on Day 3 and returned to the unit as outpatients for further

study assessments at defined timepoints to the end of the follow-up period, for which the duration was dose-dependent and up to 12 weeks.

Statistical methods

Safety, tolerability, PK and ADA data were summarised descriptively, including tables, listings, and graphs, as appropriate. Unless otherwise stated, descriptive summary statistics for continuous variables include number of subjects (n), mean (ie, arithmetic mean), standard deviation, minimum, median, and maximum. For continuous PK variables, descriptive summary statistics also includes geometric mean, geometric standard deviation, arithmetic coefficient of variation (%), and geometric coefficient of variation (%). Descriptive summary statistics for categorical data include frequency and proportion.

Data have been analyzed by cohort for all subjects treated with MEDI0618. Data for subjects treated with placebo were pooled across dose cohorts with the same schedule of assessments and the same route of administration (cohorts 5-8) and also across all dose cohorts with intravenous administration (cohort 1-8) for the purposes of summarising safety results.

Missing values were not imputed as an observed-cases approach was applied for all the analyses. According to the EMA guideline for missing values this procedure is acceptable "In exploratory studies, especially in the initial phases of drug development" (Guideline on Missing Data in Confirmatory Clinical Trials: EMA/CPMP/EWP/1776/99 Rev. 1 (2010), Committee for Medicinal Products for Human Use). Consequently, data from subjects who discontinued prematurely after randomisation, were used as available unless they have been excluded from the analysis population in question.

Analyses to investigate exploratory objectives will be reported separately from the main Clinical Study Report.

PK analysis

Pharmacokinetic parameters were calculated from the concentration-time data for each subject treated with MEDI0618 in each cohort by standard noncompartmental analysis using Phoenix® WinNonlin® version 8.1.1. and actual elapsed sampling times.

Derivation of the PK parameters followed the AstraZeneca Research and Development Global Guideline.

Dose proportionality and linearity were evaluated for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} first using the power model according to Smith et al. (2000) to relate the natural logarithm of the PK parameter linearly to the natural logarithm of the dose and then using an analysis of variance with dose-normalised logarithm of PK parameter as dependent variable and dose group as explanatory class variable.

Absolute bioavailability after sc administration was evaluated based on the cohort with sc administration of CCI MEDI0618 and the cohort with iv infusion of CCI MEDI0618 using a generalized linear model with dose normalised logarithm of $AUC_{0-\infty}$ as dependent variable and route of administration as well as logarithm of body weight as fixed variables.

Study population

The disposition of the participants in this study is summarised in **Table S3** below.

Overall, 259 subjects were enrolled and 68 subjects were randomised at a single site in Germany. A total of 64 (94.1%) subjects received double blind study medication. Of the 64 subjects in the post-treatment follow up, 63 (98.4%) subjects completed the study. One subject (1.6%) discontinued the post-treatment follow-up at Day 71 due to subject decision.

Demographics and other baseline characteristics: Demographics and baseline characteristics were balanced between the treatment arms of the 9 dose cohorts (n=64, all subjects treated) and reflected a population of healthy volunteers. The median age was 43 years with an average weight of 77.1 kg and body mass index (BMI) of 24.6 kg/m^2 at screening (safety analysis set). The majority of subjects were white (59 subjects, 92.2%). Fifty-three (82.8%) of the 64 participants who received study treatment were male and 11 (17.2%) were female.

Drug and alcohol screen results were negative for all randomized subjects at screening and on Day -1. All randomized subjects tested negative for HIV and Hepatitis B and C. There were no positive findings for SARS-CoV-2, the virus responsible for causing COVID-19, at screening or within 3 months prior to administration of study treatment.

There were no clinically meaningful differences across cohorts with respect to ongoing medical conditions and prior medication.

Table S3 Subject disposition - n (%) of subjects (all subjects)

Subjects	Cohort 9		Cohort 8	Cohort 7	Cohort 6	Cohort 5	Cohort 4	Cohort 3	Cohort 2	Cohort 1	Cohort 1-8	Cohort 1-9
	MEDI0618 CCI (sc)	Placebo (sc)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	MEDI0618 CCI (iv)	Placebo (iv)	Total (sc)+(iv)
Screening period												
Randomized	6 (100)	2 (100)	7 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	3 (100)	3 (100)	17 (100)	68 (100)
Not randomized:												191
Baseline failure												13
Cohort completed												43
Screen failure												135
Treatment (SAD)												
Received/ Completed	6 (100)	2 (100)	6 (85.7)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	3 (100)	3 (100)	14 (82.4)	64 (94.1)
Not received	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (17.6)	4 (5.9)
Adverse event	0	0	1	0	0	0	0	0	0	0	0	1
Failure to meet randomization criteria	0	0	0	0	0	0	0	0	0	0	1	1
Withdrawal by subject	0	0	0	0	0	0	0	0	0	0	2	2
Post treatment follow up												
Completed	5 (83.3)	2 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	3 (100)	3 (100)	14 (100)	63 (98.4)
Subjects Withdrawn from study	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)
Withdrawal by subject	1	´0	0	0	0	0	0	0	0	0	0	1

Percentages are based on number of subjects randomised in the group of interest.
Source: Statistical Analysis Output – Tables, Version 2.0 (2022-07-18): Table SP01

Summary of pharmacokinetic results

Following single iv infusion administration of MEDI0618 over the dose range [redacted], geometric mean Cmax and AUCs increased with increasing dose. Assessment of dose proportionality appeared to indicate that AUC_{0-t} and $AUC_{0-\infty}$ increased in a greater than dose proportional manner. Following iv administration, the tmax was typically observed at the end of infusion, while following sc administration ([redacted]), the median tmax was approximately 7 days. Geometric mean t½λz and CL values ranged from 1.92 days ([redacted]) to 13.09 days ([redacted]), and from 0.261 L/day ([redacted]) to 1.11 L/day ([redacted]), respectively. [redacted] Geometric mean values for t½λz and CL at the highest iv dose investigated ([redacted]) were approaching values that are typically observed for an IgG1 monoclonal antibody targeting a soluble ligand, suggesting saturation of the target in the systemic circulation at [redacted] iv.

Following sc administration, geometric mean t½λz was 10.54 days. Absolute bioavailability following sc administration was estimated to be 0.41 (95% CI: 0.33 - 0.51), based on a dose-corrected exposure comparison of the [redacted] sc dose with the [redacted] iv dose.

In general, as assessed from the geometric CV%, across all cohorts between subject variability for Cmax was low to high (ranging from approximately 1.2% to 129.6%) and for AUCs the between subject variability was low to moderate (ranging from approximately 3.8% to 39.5%).

Summary of safety results

Overall, MEDI0618 was safe and well tolerated when administered up to single [redacted] iv or [redacted] sc doses in healthy volunteers. There were no identified risks associated with MEDI0681 in this study. There were no clinically significant differences between MEDI0618 and placebo with respect to safety outcome measures. There were no severe or serious AEs. All TEAEs were non-serious and considered mild or moderate in intensity by the Investigator.

Common Adverse Events: 16 out of 48 subjects (33.3%) treated with MEDI0618 and 5 of 16 subjects (31.3%) treated with placebo had at least one TEAE. The most common TEAEs by PT were headache, rhinorrhoea and nasopharyngitis in subjects treated with MEDI0618 (across all dose levels); and pruritus, headache, COVID-19, flatulence, nasal congestion and rhinorrhoea for subjects treated with placebo. A higher proportion of subjects treated with MEDI0618 had TEAEs of headache (7 subjects [14.6%]) compared with subjects treated with placebo (1 subject [6.3%]). The overall incidence of TEAEs in the Nervous System Disorders SOC was higher in subjects treated with MEDI0618 compared with subjects treated with

placebo (14.6% and 6.3%, respectively). A higher proportion of subjects treated with MEDI0618 had TEAEs of nasopharyngitis (3 subjects [6.3%]) compared with subjects treated with placebo (0%).

Treatment-related Adverse Events: 1 out of 48 subjects (2.1%) treated with MEDI0618 (across all dose levels) had 2 TEAEs of headache considered related to study treatment by the Investigator; both TEAEs of headache were judged as non-serious and considered mild in intensity by the investigator, and resolved. In addition, 1 out of 16 subjects (6.2%) treated with placebo had a TEAE considered related to study treatment by the Investigator; this was a TEAE of nasal congestion.

Systemic Infusion-related and Local Infusion/Injection Site Adverse Events: No infusion-related reaction or local injection/infusion site TEAEs were reported in the study.

Adverse Events by Anti-drug Antibody Status: Across iv cohorts, the incidence of TEAEs among subjects treated with MEDI0618 was slightly higher for ADA-positive subjects (3 of the 7 ADA-positive subjects [42.9%]) than for ADA negative subjects (11 of the 35 ADA-negative subjects [31.4%]). This finding was considered not clinically meaningful.

In the sc cohort, the incidence of TEAEs among subjects treated with MEDI0618 was lower for ADA positive (0%) subjects than for ADA-negative subjects (2 of 4 subjects [50%]).

None of the TEAEs in ADA-positive subjects were indicative of hypersensitivity or autoimmune reactions.

Clinical laboratory evaluation: Overall, no clinically notable changes in mean or dose-related trends in changes from baseline in haematology, coagulation, clinical chemistry, and urinalysis parameters were observed in the study. In addition, no important differences between MEDI0618- and placebo-treated subjects were noted in the mean change from baseline for any haematology, coagulation, clinical chemistry, and urinalysis parameters. There were no individual clinically important abnormalities in haematology, coagulation, clinical chemistry, and urinalysis parameters.

Vital Signs and Electrocardiograms: Overall, no clinically important changes, dose-related trends, or important differences between MEDI0618- and placebo-treated subjects were observed in mean values and mean change from baseline over time for any vital sign, body weight or ECG parameters analyzed in the study. There were no individual clinically important abnormalities in vital signs and ECG parameters evaluated in the study.

Physical Findings and Other Observations Related to Safety: No dose-related trends or differences between MEDI0816 and placebo-treated subjects were observed for other safety parameters, including physical examinations.

Immunogenicity: Across iv cohorts, the proportion of subjects ADA- positive at any visit was 16.7% (7 of 42 subjects) for MEDI0618 and 7.1% (1 of 14 subjects) for placebo, and in the sc cohort 33.3 % (2 of 6 subjects) for MEDI0618 and 0% for placebo. Across the iv cohorts 9.5% (4 of 42 subjects) of subjects and in the sc cohort 33.3 % (2 of 6 subjects) of subjects were treatment-emergent (TE)-ADA positive (defined as the sum of treatment-induced ADA positive and treatment-boosted ADA positive) for MEDI0618 and none for placebo iv or sc. There was no obvious relationship between ADA positive at any visit or TE-ADA positivity and dose. Four subjects were ADA-positive at baseline and post-baseline: 3 (7.1%) were treated with MEDI0618 iv (CCI and CCI), and one (7.1%) received placebo iv. In all 4 subjects, titres were not boosted after study drug administration.

Overall in the study, ADA titres were low (maximum titre: 32) and did not seem to overly influence the PK profile of ADA-positive subjects.

Conclusion(s)

- Overall, the results of this first--in-human study indicate that MEDI0618 was in general safe and well tolerated when administered as single iv (up to CCI) or sc (CCI) doses in healthy volunteers.
- After single iv infusion of MEDI0618, geometric mean Cmax and AUCs increased with increasing dose, with AUCs increasing in a more than dose-proportional manner.
- Over the iv dose range CCI to CCI, geometric mean half-life and CL were dose-dependent, suggesting non-linear PK, with values observed at CCI approaching values more typical for an IgG1 monoclonal antibody, suggesting target saturation in the systemic circulation.
- The absolute bioavailability of MEDI0618 via the sc route was 0.41 (i.e., 41%) (95% CI: 0.33 - 0.51).

These data support the further clinical development of MEDI0618.