SYNOPSIS

Title of Study:	A Phase I Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety and Pharmacokinetics of MEDI8367 Administered as Single Ascending Doses in Healthy Subjects, and as a Single Dose in Healthy Subjects of Japanese-descent and in Subjects with Chronic Kidney Disease	
Study Numbers:	Parexel Study No.: Pxl 247340 Sponsor Study No.: D6361C00001	
Investigational Medicinal Products:	Study Drug: MEDI8367	
Indication Studied:	Chronic Kidney Disease	
Development Phase:	Phase I	
Sponsor:	AstraZeneca Pharmaceuticals LP 1800 Concord Pike Wilmington, DE 19803 United States of America	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit (EPCU) – Los Angeles	
Publication:	None	
Study Duration:	First subject first visit: 22 July 2020	Last subject last visit: 03 January 2021

Study Objectives:

Primary objective:

- To assess the safety and tolerability of single subcutaneous (SC) ascending doses of MEDI8367.

Secondary objectives:

- To evaluate the pharmacokinetics (PK) of single SC doses of MEDI8367.
- To evaluate the immunogenicity of single SC doses of MEDI8367.

Exploratory objectives:

- CCI [redacted]

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Study Design:

This was a Phase I, first in human, randomized, blinded, placebo-controlled study, to evaluate the safety and PK of MEDI8367 following single ascending doses (SAD) in healthy subjects and as a single dose in healthy subjects of Japanese-descent and in subjects with chronic kidney disease (CKD).

Six cohorts, Cohorts 1 to 5 (healthy subjects including subjects of Japanese-descent in Cohort 5) each consisting of 8 subjects (total 40 subjects), and Cohort 6 (subjects with CKD) consisting of 30 subjects were planned to participate in the study. The starting dose was CCI MEDI8367 with up to 3 dose escalations planned (provisional doses of CCI and CCI mg). Within Cohorts 1 to 5, 6 subjects were to be randomized to receive MEDI8367 and 2 subjects were to be randomized to receive placebo. For Cohort 6 (subjects with CKD), 15 subjects were to be randomized to receive MEDI8367 and 15 subjects were to be randomized to receive placebo.

The study comprised of:

- A Screening Period of a maximum of 28 days
- A Treatment Period during which subjects were resident at the Parexel Clinical Unit/non-Parexel sites from the day before investigational medicinal product (IMP) administration (Day -1) until at least 72 hours after IMP administration (discharged on Day 4)
- A Follow-up Period (out-patient) with 8 visits; the final Follow-up Visit (Visit 10) was to be within 90 ± 4 days after the last IMP dose. The study day for the last visit was to be adjusted based on PK/PD results from the current and previous cohorts

Dosing for Cohorts 1 to 4 and Cohort 6 was to proceed with 2 subjects in a sentinel cohort, such that one subject was to be randomized to receive MEDI8367 and one subject was to be randomized to receive placebo. The blinded safety data from the sentinel subjects up to 3 days post-dose were to be reviewed by the site Principal Investigator before the remaining subjects in the cohort were dosed. Dosing was proposed to continue based on a lack of significant safety findings in the first 2 subjects dosed per cohort. The remaining 6 subjects in Cohorts 1 to 4, respectively, and 28 subjects in Cohort 6, were to be dosed at least 3 days after the sentinel cohort.

For Cohort 6, a primary site was to enroll 2 sentinel subjects. After the 3-day safety review, subsequent sites were to be opened and competitive enrollment for the remaining subjects was to commence. The data were to be reviewed by a Safety Review Committee to decide on the next dose levels throughout the study, considering at each decision point the degree of uncertainty. The choice of the dose levels would take into consideration potential adverse effects. Late emerging safety issues that might have occurred after the timepoint for the dose escalation decision would always be considered.

The MEDI8367 program was put on hold by the Food and Drug Administration (FDA). At the time when the study was terminated, only Cohort 1 was completed: Cohort 1 (8 subjects, 6 of which were dosed with CCI mg MEDI8367) and Cohort 2 (4 subjects, 3 of which were dosed with CCI mg MEDI8367), 3 subjects had received placebo. All subjects were randomized in the Los Angeles EPCU. No significant safety issues were observed in any of these subjects. No further subject was dosed and no additional data were collected for those already enrolled since the temporary hold was implemented.

Study Subjects:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
40 healthy subjects and 30 subjects with CKD	12 healthy subjects	11 healthy subjects

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Main Inclusion Criteria:

Cohorts 1 to 4: Healthy male and/or female subjects of non-childbearing potential, aged 18 to 55 years (inclusive), with a body mass index (BMI) between 18 and 30 kg/m^2 inclusive and who weighed at least 50 kg and no more than 100 kg, inclusive.

Cohort 5: Healthy subjects of Japanese-descent; Cohort 6: Subjects with CKD, aged 18 to 70 years (inclusive), with a BMI between 18 and 45 kg/m^2 inclusive, body weight at least 50 kg, and not more than 150 kg.

Investigational Medicinal Product(s):

MEDI8367

Formulation(s):	**Strength/ Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
CCI mg/mL MEDI8367 in CCI [redacted]	CCI mg/mL	CCI [redacted]	28Feb2021

Placebo to match MEDI8367

Formulation(s):	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
Saline solution for injection	Not applicable	6020090	Jul2021

Duration of Treatment:

This was a single dose study, however, the total expected duration for this study for each subject was approximately 90 days (excluding the Screening Period).

Treatment Compliance:

Dosing took place at the Parexel EPCU in Los Angeles. The administration of all medications was recorded in Parexel's electronic source data capturing and information management system ClinBase™. Compliance was assured by direct supervision and witnessing of IMP administration. An unblinded monitor performed drug reconciliation. In addition, bioanalysis of MEDI8367 plasma samples from all presumed placebo-treated subjects could be used to confirm lack of MEDI8367 in the plasma.

All subjects randomized received all planned single doses of IMP.

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Criteria for Evaluation:

Safety and Tolerability Variables:

- Adverse events (AEs).
- Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature).
- Electrocardiograms (ECG).
- Physical examination.
- Structured neurological assessment.
- Retinal imaging.
- Laboratory assessments (hematology, clinical chemistry, urinalysis).

Pharmacokinetic Variables:

Where possible, PK parameters were assessed for MEDI8367 on serum concentrations.

- Maximum observed serum drug concentration (Cmax), area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUClast), area under plasma concentration-time curve from zero to infinity (AUCinf), time to reach maximum observed concentration (tmax), and half-life ($t_{1/2\lambda z}$).

Additional PK parameters could have been determined where appropriate.

Immunogenicity Variable:

- Anti-drug antibody (ADA) incidence and titer.

Pharmacodynamic Variables:

- CCI [redacted]

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Statistical Methods:

Determination of Sample Size:

A total of 40 healthy subjects and 30 subjects with CKD were planned to be randomized into the study (5 cohorts with 8 subjects, randomized in a 3:1 ratio to receive MEDI8367 or placebo). Cohort 6 was planned to have 30 subjects, randomized in a 1:1 ratio to receive MEDI8367 or placebo. The sample size for this SAD study was empirically determined to provide adequate safety, tolerability, and PK/PD data to achieve the study objectives while minimizing subject exposure to MEDI8367.

However, due to the termination of the study, only 12 healthy subjects were randomized, and no CKD subject was randomized.

Presentation and Analysis of Safety and Tolerability Data:

All safety data (scheduled and unscheduled) were presented in the data listings and summarized. Continuous variables were summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], minimum, median, maximum) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion).

The AEs were summarized by system organ class and preferred term using Medical Dictionary for Regulatory Activities vocabulary. Furthermore, listings of serious adverse events (SAEs) and AEs that led to withdrawal were presented and the number of subjects who had any AEs, SAEs, AEs leading to discontinuation, and AEs with severe intensity were summarized. Adverse events that occurred before dosing were reported separately.

Tabulations and listings of data for clinical laboratory tests, vital signs, and ECGs were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was to be reported as an AE. Data were summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from baseline when baseline was defined.

Out-of-range values for safety laboratory, vital signs, and 12-lead ECGs were flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (eg, AstraZeneca, program, or laboratory ranges). Safety measurement with start date/time at the time of or after dosing (for each specific dose) until the Follow-up Visit were assigned to the specific treatment/dose level.

Presentation and Analysis of Pharmacokinetic Data:

All PK concentration, parameter summaries, and statistical analyses were presented for the PK population, unless otherwise specified. The PK concentration and parameter listings were presented for the as-treated population and include all reportable individual PK results. Individual PK concentration and parameter data for any subjects not included in the PK population or excluded from the descriptive summary tables, figures and/or inferential statistical analyses were included in the listings and flagged with an appropriate footnote.

Presentation and Analysis of Pharmacodynamic Data:

Analysis of the PD biomarkers CCI [redacted] was based on the as-treated population. Biomarkers measured at each timepoint, and change and percent change from baseline to each post-baseline timepoint were to be summarized by cohort (SAD Cohorts 1 to 4 and Japanese-descent Cohort 5) and treatment (dose level of MEDI8367 and pooled placebo) for healthy subjects and subjects with CKD separately.

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The comparison for each cohort between each MEDI8367 dose level and placebo at each timepoint was analyzed using an analysis of covariance (ANCOVA) adjusting for treatment and baseline measurement.

Presentation and Analysis of Immunogenicity Data:

Immunogenicity (ADA incidence rate and titer) was to be summarized by cohort (SAD Cohorts 1 to 4 and Japanese descendant Cohort 5) and treatment (dose level of MEDI8367 and pooled placebo) for healthy subjects and subjects with CKD (Cohort 6) separately. Samples confirmed positive could have been used for further characterization of the ADA response.

Protocol Deviations:

One subject PPD in Cohort 2 had at least one important protocol deviation. The subject did not attend a Day 8 Follow-up on 12 October 2020. On 14 October 2020, the site staff were notified that the subject had passed away (refer to the Safety Results for more information).

Pharmacokinetic Results:

- CCI [redacted]
- [redacted]
- Based on the limited data available, comprehensive analysis and interpretation of PK is not possible.

Pharmacodynamic Results:

- No clinically relevant trends were observed for changes in PD results.
- Based on the limited data available, comprehensive analysis and interpretation of PD data are not possible.

Immunogenicity Results:

- CCI [redacted]
- [redacted]
- There were no AEs assessed to be related to ADAs.

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Safety Results:

- A total of 6 AEs (one of which was a SAE) were reported for 5 subjects after receiving treatment:
  - One subject PPD experienced an AE of arthropod bite, mild intensity, not considered related to the IMP by the Investigator, and resolved before the end of the study.
  - One subject PPD experienced an AE of epistaxis, mild intensity, not considered related to the IMP by the Investigator, and resolved before the end of the study.
  - One subject PPD experienced an AE of headache, mild intensity, not considered related to the IMP by the Investigator, and resolved before the end of the study.
  - One subject PPD experienced AEs of headache and dysuria, both were mild intensity. The AE of dysuria was considered by the Investigator as possibly related to the IMP. Both AEs resolved before the end of the study.
  - One subject PPD experienced a SAE of road traffic accident, severe intensity, resulting in death and not considered related to the IMP by the Investigator.
- No clinically relevant trends were observed for laboratory results or vital signs; abnormal ECG parameters were reported for 9 subjects. However, none of the ECG abnormalities were considered clinically significant.
- Coronavirus disease 2019 (COVID-19) did not impact the safety results of this study.
- The AEs that occurred in the limited number of individuals who were dosed with MEDI8367 were in line with the AEs noted in preclinical data.

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Discussion and Conclusion:

This clinical study report (CSR) is presented in a synoptic format as the study was terminated.

PK conclusion:

CCI [redacted]

Based on the limited data available, comprehensive analysis and interpretation of PK is not possible.

PD conclusion:

No clinically relevant trends were observed for changes in PD results.

Based on the limited data available, comprehensive analysis and interpretation of PD data are not possible.

Immunogenicity conclusion:

CCI [redacted]

There were no AEs assessed to be related to ADAs.

Safety conclusion:

Single doses of MEDI8367 or placebo in healthy subjects demonstrated an acceptable safety profile and were well tolerated.

Overall impact of COVID-19:

The COVID-19 pandemic was not considered to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of the results.

Version and Date of Report: Final, 13 April 2022

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.