2 SYNOPSIS

Title of Study:	A Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Immunogenicity of Multiple Doses of MEDI7352 Administered by the Subcutaneous Route in Healthy Japanese and Caucasian Subjects	
Study Numbers:	Parexel Study No.: CCI Sponsor Study No.: D5680C00004	
Investigational Medicinal Products:	Test Product: MEDI7352 Reference Product: Placebo	
Indication Studied:	Painful Osteoarthritis of the Knee	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD, MD, MSc, DPhil	
Study Centre:	Parexel Early Phase Clinical Unit London, United Kingdom	
Publication(s):	None	
Study Duration:	First subject first visit: 20 April 2021	Last subject last visit: 02 December 2021

Study Objectives:

Primary objective:

To evaluate the safety and tolerability of MEDI7352 in healthy Japanese and Caucasian subjects following multiple dosing by the subcutaneous (SC) route.

Secondary objective:

To further assess MEDI7352 in healthy Japanese and Caucasian subjects with respect to pharmacokinetics (PK) and immunogenicity following multiple dosing by the SC route.

Exploratory objective:

CCI

Study Design:

This study was a double-blind, randomised, placebo-controlled, multiple-dose study of MEDI7352 administered by the SC route in healthy Japanese and Caucasian subjects (males and females of non-childbearing potential), performed at a single centre.

This study was conducted in male and females of non-childbearing potential subjects, 18 to 65 (inclusive) years of age for Caucasian subjects and 20 to 65 (inclusive) years of age for Japanese subjects. Two cohorts of healthy Japanese (N = 10) and Caucasian (N = 14) subjects were enrolled for a total of 24 subjects. Subjects in each cohort were randomised to receive MEDI7352 or placebo in a ratio of 7:3, respectively. Randomisation was performed in the morning before dosing on Day 1 and was completed for each cohort using consecutive randomisation numbers.

The study comprised:

- A Screening Period of up to 36 days (approximately 5 weeks).
- A Treatment Period of 8 weeks where subjects were given 1 dose of study treatment every 2 weeks (4 doses in total). Subjects were required to stay in the Clinical Unit from Days -1 to 8 (Visit 2), from

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Days 14 to 15 (Visit 6), from Days 28 to 29 (Visit 9), and from Days 42 to 50 (Visit 12). In addition, subjects had multiple visits to the Clinical Unit to complete the study assessments.

- A Follow-up Period of 42 days (6 weeks) after the last dose where subjects had multiple visits to the Clinical Unit to complete the study assessments.

Subjects received fixed multiple SC doses of CCI mg MEDI7352 or placebo on 4 occasions; 1 dose every 2 weeks on Days 1, 15, 29, and 43 under fasted conditions.

Study Subjects:

Planned for Inclusion:	**Randomised:**	**Completed Study:**
20 subjects (Japanese [N = 10] and Caucasian [N = 10])	24 subjects	19 subjects

Inclusion Criteria:

1 Provision of signed and dated, written informed consent prior to any study specific procedures.

2 Healthy male or female of non-childbearing potential subjects aged 18 to 65 (inclusive) years for Caucasian subjects and 20 to 65 (inclusive) years for Japanese subjects (at the time of Screening) with suitable veins for cannulation or repeated venepuncture.

3 Subjects had to be of Japanese or Caucasian ethnicity (Definition of Japanese is a subject for whom both parents and all grandparents are Japanese; was born in Japan and has not lived outside Japan for more than 10 years).

4 Post-menopausal women had ≥ 12 months of spontaneous amenorrhea with a follicle stimulating hormone concentration consistently ≥ 40 mIU/mL and had a negative serum or urine pregnancy test result at Screening or Day -1. Surgically sterile women were defined as those who have had a hysterectomy, and bilateral ovariectomy (oophorectomy). Women who were surgically sterile had to provide documentation of the procedure by an operative report or relevant medical records, or by ultrasound, and had a negative serum or urine pregnancy test at Screening or Day -1. Non-pregnant status in a female subject who was post-menopausal or surgically sterile, and with an intermediate or positive pregnancy test, could be confirmed by repeating the pregnancy test and demonstrating non-doubling of β-human chorionic gonadotropin levels every 48 to 72 hours.

5 Men who were biologically capable of fathering children had to agree and commit to use of an adequate form of a highly effective method of contraception with their female partners and refrain from sperm donation for the duration of the Treatment Period and for 3 months after the last administration of study treatment. A male subject was considered capable of fathering children even if his sexual partner was sterile or using contraceptives.

6 Had a body mass index between 18 and 30 kg/m^2 inclusive and weighed at least 50 kg.

7 Subjects had to be healthy, in the opinion of the Investigator, with no clinically significant abnormality identified on the medical or laboratory evaluation at Screening. A subject with a clinical abnormality or laboratory test result(s) outside the reference range for his/her age group could have been included only if the Investigator considered that the finding would not have introduced additional risk factors and would not have interfered with the study procedures.

8 Subjects had a 12-lead electrocardiogram (ECG) recorded at Screening and on Day -1 that, in the opinion of the Investigator, was normal for the age group and showed no significant abnormalities that would have compromised safety in this study.

9 Subjects had physical examinations with no significant findings at Screening and on Day -1.

10 Subjects were able to understand and comply with protocol requirements, instructions, and protocol-stated restrictions. For Japanese subjects who required, a translator could have been provided for communication at the Clinical Unit.

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11 Subjects agreed not to post any personal medical data related to the study or information related to the study on any website or social media site (eg, Facebook or Twitter) until the study had been completed and the Sponsor had granted permission.

Exclusion Criteria:

General

1 Involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the Clinical Unit).

2 Had previously received MEDI7352 in another study.

3 Participated in another clinical study or use of any experimental medication, device, or biologic with an investigational medicinal product (IMP) within 5 half-lives of that IMP or 3 months (whichever was longer) prior to the first dosing. This 3-month window (or 5 half-lives of the IMP, whichever was longer) was derived from the date of last dosing in the previous study to Day 1 of the current study.

4 Participated in another study investigating any form of anti-nerve growth factor (NGF) or anti-tumour necrosis factor (TNF) therapy in the 6 months prior to Screening and until after the final Follow-up Visit.

5 Had any positive laboratory result at Screening for Coronavirus disease of 2019.

6 Blood donation or draw in excess of 400 mL within 2 months prior to Screening or plasma donation in excess of 50 mL within 30 days prior to Screening.

7 Was unable to abstain from strenuous physical activity from 72 hours prior to admission to the Clinical Unit until discharge from the unit.

8 Was unable to comply with study-related restrictions and requirements related to consumption of alcohol, provision of meals and snacks, nicotine use, activity, blood donation, and contraception.

9 Was employed by AstraZeneca or by the Contract Research Organisation (CRO) or Clinical Unit participating in this study, or a first-degree relative of an AstraZeneca employee or of an employee at the participating CRO or Clinical Unit.

Medical History

10 Had a history of severe allergy/hypersensitivity reactions or ongoing severe allergy/hypersensitivity reactions, or history of hypersensitivity to immunisations or immunoglobulins or other biological modalities.

11 Had a history of any significant psychiatric disorder according to the criteria of the Diagnostic and Statistical Manual of Mental disorders, 5th Edition (American Psychiatric Association 2013), which, in the opinion of the Investigator, could have been detrimental to subject safety or could compromise study data interpretation.

12 Were vulnerable subjects who were committed to an institution by an official or judicial order.

13 Had a presence of any clinically significant illness, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, rheumatologic, or endocrine disease or disorder. This included exclusion of subjects with abnormal renal function at Screening, defined as an estimated glomerular filtration rate (eGFR) of < 90 mL/min/1.73m^2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

14 Had recent (within the previous 3 months) or active infection considered to be clinically significant, or any infection for which there were unresolved medical sequelae.

15 Had diagnosis of clinically significant osteoarthritis (OA) affecting a major joint in the upper extremity (shoulder, elbow, or wrist) or lower extremity (hip, knee, or ankle) or axial spine; or other degenerative disease affecting any joint in subjects for whom, in the opinion of the Investigator, there was an identified risk of osteonecrosis, rapidly progressing OA, subchondral insufficiency fractures, neurogenic arthropathy, or analgesia-induced arthropathy; or history of trauma or surgery involving any major joint or axial spine.

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16 Had radiological significant abnormalities reported on baseline magnetic resonance imaging (MRI) of hips and knees that were considered to present a risk of osteonecrosis, rapidly progressive OA, subchondral insufficiency fractures; or other coincidental finding(s) that present a risk to the safety or welfare of the subject.

17 Had history of excessive alcohol intake, defined as an average weekly intake of > 21 units or an average daily intake of > 3 units for men and an average weekly intake of > 14 units or an average daily intake of > 2 units for women. One unit is equivalent to 250 mL of beer, 25 mL of spirits, or 125 mL of wine. If a subject was diagnosed with abuse of or dependence on alcohol, he/she was not allowed to enrol in the study, unless the alcohol abuse/dependence was in full (complete, not partial) sustained (> 1 year) remission.

18 Had history of cancer within 5 years of Screening, or between Screening and randomisation, with the exception of non-metastatic basal cell carcinoma of the skin, carcinoma in situ of the cervix or non-progressive prostate cancer.

19 Had history of drug abuse or positive test for drugs of abuse (urine test) or alcohol (urine test) at Screening or on Day -1.

Concomitant Medications

20 Used prescription or non-prescription drugs, including vitamins and herbal and dietary supplements, within 7 days or 5 half-lives of the drug (whichever is longer) prior to the administration of study treatment. This was applicable unless, in the opinion of the Investigator, the medication was indicated for the prophylaxis or treatment of a medical condition that was not exclusionary under the terms of the protocol and would not have interfered with the study procedures or compromise subject safety. Routine vaccination within 30 days of planned dosing was exclusionary.

Physical Examinations, Electrocardiograms, Vital Signs and Laboratory Tests

21 Had any clinically important abnormality as determined by the Investigator at Screening (or on Day -1, if applicable to the specific assessment) on a physical examination, vital signs, ECG, or clinical laboratory test results including but not limited to the specific criteria detailed below, that could be detrimental to subject safety or could compromise the study.

22 Had any clinically significant abnormality in laboratory test results at Screening, including aspartate aminotransferase or alanine aminotransferase >1× the upper limit of normal (ULN), eGFR < 90 mL/min/1.73m^2 or creatinine > 1.5×ULN, confirmed on a repeat assessment at Screening or Day -1.

23 Had any clinically significant abnormality in resting vital signs at Screening or on Day -1, defined in terms of supine systolic blood pressure (BP) that is above 140 mmHg, diastolic BP above 90 mmHg or pulse outside the range 45 to 90 bpm, confirmed on a repeat assessment at Screening or Day -1.

24 Had any clinically significant abnormality in ECG rhythm, conduction or morphology at Screening, including (a) clinically significant PR (PQ) interval prolongation (PR > 220 msec); (b) intermittent second or third degree atrioventricular block (atrioventricular block II Mobitz Type 1, Wenckebach, while asleep or at deep rest is not exclusionary.); or (c) full or intermittent bundle branch block (QRS < 115 msec with normal QRS and T wave morphology is acceptable if there is no evidence of left ventricular hypertrophy).

25 Had prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) interval > 450 msec or family history of long QT syndrome, shortened QTcF interval < 340 msec, or family history of short QT syndrome.

26 Had positive serologic findings at Screening for human immunodeficiency virus antibodies, hepatitis B surface antigen or hepatitis C virus antibodies.

27 Had positive QuantiFERON test for tuberculosis at Screening.

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Procedural Contraindications

28 Had any minor medical or surgical procedure or trauma within 28 days of Day 1 or planned surgical procedure during the duration of the study.

Investigational Medicinal Product:

Formulation:	Strength/Concentration:	Batch/Manufacturing Lot Number(s):	Expiry Date(s):
Reconstituted from lyophilised powder	CCI	CCI	CCI

Duration of Treatment:

The maximum treatment duration for each subject was approximately 8 weeks. Each subject was involved in the study for approximately 17 weeks.

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit, London site. The administration of all IMPs was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing of study treatment administration.

Criteria for Evaluation:

Pharmacokinetic Parameters:

- Maximum observed concentration (Cmax)
- Time of Cmax (tmax)
- Area under the serum concentration-time curve from time 0 to infinity (AUCinf)
- Area under the serum concentration-time curve from time 0 to the time of the last quantifiable serum concentration (AUClast)
- Area under the serum concentration-time curve over the dosing interval (AUCτ)
- Average drug concentration over a dosing interval (Cavg)
- Apparent volume of distribution during the terminal phase (extravascular administration) (Vz/F)
- Half-life (t½)
- Apparent total body clearance (CL/F)

Safety Variables:

- Adverse events (AEs) and serious adverse events (SAEs)
- Physical examinations
- Neurological examinations
- Neuropathy assessments (Total Neuropathy Score, nurse [TNSn])
- Vital signs (supine and standing BP, pulse, temperature, respiration rate)
- 12-lead ECGs and digital ECGs (dECGs)
- Clinical laboratory testing (haematology, chemistry, coagulation, and urinalysis)
- C-reactive protein (CRP; inflammatory biomarker)
- Concomitant medications and therapies
- Injection site reactions
- Magnetic resonance imaging of the knees and hips (bilateral)

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Immunogenicity Variables:

- Presence of anti-drug antibodies (ADA) to MEDI7352 in serum
- ADA titre

Exploratory Variables:

- CCI [redacted]

Statistical Methods:

Determination of Sample Size:

The sample size was not based on any formal statistical considerations. Cohort sizes of N = 10 was considered sufficient to allow a comparative evaluation of safety and tolerability information, while exposing as few subjects as possible to the investigational treatment.

Presentation and Analysis of Pharmacokinetic Data:

Serum MEDI7352 concentrations at each scheduled time point were summarised using appropriate descriptive statistics, based on subjects in the PK analysis set with placebo subjects excluded. Noncompartmental analysis methods were used. The PK parameters were summarised by MEDI7352 dose, cohort, and day using descriptive statistics.

Presentation and Analysis of Safety and Tolerability Data:

Analysis of safety were based on the Safety analysis set. All safety data (scheduled and unscheduled) were presented in the data listings.

Continuous variables were summarised by treatment group and cohort (MEDI7352 and placebo) using descriptive statistics (number [n], mean, standard deviation [SD], minimum [min], median, maximum [max]).

Categorical variables were summarised in frequency tables (frequency and proportion) by treatment group and cohort, and presented as defined above.

Adverse events were summarised by preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA) dictionary by treatment group and cohort (MEDI7352 and placebo). Furthermore, listings of SAEs and AEs leading to the discontinuation of IMP (DAEs) were made and the number of subjects who had any AEs, SAEs, DAEs, and AEs with severe intensity were summarised. Adverse events that occur before dosing were reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests, and neuropathy assessments (TNSn) were presented. Electrocardiograms, neurological examinations, CRP (inflammatory biomarker), and injection site reactions were only presented in the listings.

Presentation and Analysis of Immunogenicity Data:

A summary of the number and percentage of subjects who developed detectable ADA to MEDI7352 in both treatment groups were presented. Immunogenicity results, including the titre for samples confirmed positive for ADA, of all subjects in the safety analysis set were listed. The effect of ADA on PK, pharmacodynamics, and safety were explored.

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Protocol Deviations:

One (10.0%) protocol deviation was reported for the Japanese cohort and 3 (21.4%) protocol deviations were reported for the Caucasian cohort. During administration of MEDI7352 to a Japanese subject, approximately 0.2 mL of IMP was lost from spillage due to a loose connection between the syringe and the needle used to inject and dose the subject. No incident occurred during dosing with the second needle. Two (14.3%) Caucasian subjects (1 subject in each arm) were both included in the study in violation of both Exclusion Criteria 13 and 22, when their Screening eGFR assessment was below the required minimum specified in the exclusion criteria. One Caucasian subject admitted to vigorous weight training and cardiovascular exercise within 72 hours of the Day 22 visit and therefore violated the study restriction that limited strenuous physical activity until after the final Follow-up Visit.

Subject Disposition:

Twenty-four subjects (10 Japanese and 14 Caucasian subjects) were randomised to the study.

Subjects who completed treatment; 10 (100.0%) Japanese (7 [100.0%] MEDI7352 and 3 [100.0%] placebo) and 10 (71.4%) Caucasian (7 [70.0%] MEDI7352 and 3 [75.0%] placebo) subjects.

Subjects who completed the study: 9 (90.0%) Japanese (6 [85.7%] MEDI7352 and 3 [100.%] placebo) and 10 (71.4%) Caucasian (7 [70.0%] MEDI7352 and 3 [75.0%] placebo) subjects.

Subjects withdrawn from the study: 1 (10.0%) Japanese (1 [14.3%] MEDI7352) and 4 (28.6%) Caucasian (3 [30%] MEDI7352 and 1 [25.0%] placebo) subjects.

Pharmacokinetic Results:

MEDI7352 median AUClast and Cmax results were slightly higher in Japanese subjects compared with Caucasian subjects on Day 1 and generally similar on Day 43 between Japanese and Caucasian subjects following SC administration of CCI mg. A small trend toward higher exposure in Japanese subjects on Day 1 appeared attributable to differences in the kinetics of ADA emergence and mean body weight.

MEDI7352 median tmax occurred 3 days post-dose, CCI for both cohorts, following single and repeat administration of CCI mg MEDI7352 SC.

The emergence of ADA appeared to impact PK parameters, leading to lower drug exposure, most notably for Ctrough. This trend was most notable for 3 Caucasian subjects with relatively high ADA titres on Day 15 (the end of the Day 1 profile) and for all Japanese subjects with positive ADA status on or after Day 43 (3 Japanese subjects), regardless of ADA titre.

Safety Results:

MEDI7352 administered in multiple SC doses was found to have a good safety profile and to have been generally well tolerated in the studied populations.

At least 1 AE was reported across 15 subjects (5 [71.4%] Japanese and 10 [100%] Caucasian subjects) who were administered MEDI7352 and across 4 subjects (2 [66.7%] Japanese and 2 [50%] Caucasian subjects) administered placebo. No SAEs or deaths were reported for this study.

For subjects in the MEDI7352 groups who were ADA-positive at any visit, AEs were reported by 2 (28.6%) Japanese subjects and 7 (70.0%) Caucasian subjects. For both the Japanese and Caucasian subjects, there were no discernible differences in the safety profiles when comparing subjects who were either ADA-positive or ADA-negative.

Discussion:

In this placebo-controlled, multiple-dose study of MEDI7352 administered by the SC route, healthy Japanese (10) and Caucasian (14) subjects (23 males and 1 female of non-childbearing potential) were randomised to receive fixed multiple SC doses of CCI mg MEDI7352 or placebo on 4 occasions: 1 dose every 2 weeks on Days 1, 15, 29, and 43 under fasted conditions.

The AEs experienced by 15 (5 Japanese and 10 Caucasian subjects) subjects that received MEDI7352 were mild to moderate in intensity, except for 1 AE of increased aspartate aminotransferase (AST) which was severe in intensity. The severe AE of increased AST was of potential medical importance but was not considered clinically significant as it was related to the subject's vigorous exercising. Fifteen AEs were considered by the Investigator as related to the IMP. The AE considered by the Investigator as related to MEDI7352 reported by the majority of participants was injection site erythema (5 Japanese and 6 Caucasian subjects). No deaths or SAEs were reported for either cohort during the study. CCI

The only blood chemistry abnormalities for Caucasian subjects that were considered to be of potential medical importance, but not considered clinically significant, were alanine aminotransferase (ALT) increased, AST increased, and increased creatine kinase. However, these were considered unrelated to the IMP but subject's vigorous exercising. No blood chemistry abnormalities were reported for the Japanese subjects.

Although there were fluctuations in vital signs, 12-lead ECGs, dECGs, telemetry, and CRP from baseline and some were outside of the normal range, none of them met the criteria for clinical significance.

No clinically significant observations were reported during neurological examination or neuropathy assessments using the TNSn instrument. No neurological or neuropathy-related AEs were reported.

Overall, PK profiles were variable within each cohort and this appeared partly attributable to ADA emergence and the timing thereof. Generally, positive ADA status was associated with decreased drug exposure, most notably for Ctrough. Pharmacokinetic parameters for Caucasian subjects appeared to be impacted by ADA to a greater extent following the first dose on Day 1, where high ADA titres CCI observed for 3 subjects at 14 days post-dose were correlated with reduced drug exposure. Pharmacokinetic parameters for Japanese subjects were relatively unaffected by ADA following the first dose on Day 1 (1 of 7 subjects was ADA-positive on Day 15), but impacted following the last dose on Day 43, where 3 Japanese subjects were ADA-positive and exhibited the lowest MEDI7352 exposure in their cohort.

Due to the skewed distribution of the PK parameters as a result of the emergence of ADA, median values were used for comparison between ethnicity cohorts. Overall, MEDI7352 PK appeared similar between Japanese and Caucasian subjects, with a slight trend toward higher median Cmax in Japanese subjects on Day 1 that may have been partly due to differences in mean body weight between the cohorts (mean of 62.73 and 81.15 kg in Japanese and Caucasian subjects, respectively). Median tmax and t½λz values were similar between cohorts, while small cohort-based differences in median AUCs were inconsistent between PK profile days and generally attributable to trends in ADA.

During the FIH study (Study D5680C00001) conducted in subjects with painful OA of the knee, MEDI7352 exposure increased with increasing dose after both single (up to CCI µg/kg) and repeat doses (up to CCI µg/kg), and the increase was overall dose proportional after a single intravenous (IV) dose over the range of 0.3 to CCI µg/kg. Estimated mean t½ ranged CCI doses in the single ascending dose (SAD) and multiple ascending dose (MAD) phases. Absolute bioavailability of MEDI7352 via SC administration of CCI µg/kg was estimated CCI. No accumulation of MEDI7352 was observed after repeat IV administration; on the contrary, a decrease in exposure was observed from Day 1 to Day 43. Intravenous single dose administration at CCI µg/kg in D5680C00001 provided

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clinical coverage for exposures observed following SC administration of CCI mg in terms of Cmax in this study, however, AUCinf observed after the first dose was higher at CCI mg SC CCI [redacted] Repeat administration of CCI mg SC in healthy subjects resulted in 3- to 4-fold higher drug exposures (AUCτ) compared to repeat IV administration at CCI µg/kg in subjects with painful OA of the knee in the FIH study. Mean body weight normalised doses in the current study were approximately CCI µg/kg for Caucasian and Japanese subjects respectively; CCI these doses would be expected to yield similar exposure to IV doses of approximately CCI µg/kg respectively. Although we cannot rule out the possibility of a difference in the bioavailability of MEDI7352 between healthy subjects and OA patients, the magnitude of the difference in exposure is notable and unusual. Alternative potential explanations such as differences in drug batches as well as issues with blood samples handling, treatment preparation, and bioanalytical assay were investigated and no concerns were identified. Therefore, at the time of writing, the underlying reasons for the higher exposure observed in this study remain unknown and warrant further investigations. Exposures in different cohorts may also be influenced by variability in ADAs. No safety concerns were identified in these cohorts of Caucasian and Japanese subjects following CCI mg MEDI7352 SC repeat administration.

Anti-drug antibodies were first detected at the first sampling time point at Day 15 in both Japanese and Caucasian subjects. The number of ADA-positive subjects over time remained relatively steady or tapered off. The prevalence and incidence of ADA was CCI [redacted] All ADA-positive subjects who received MEDI7352 were treatment-emergent-ADA-positive. CCI [redacted]. In the FIH MAD cohorts, ADA prevalence was found to be CCI. It was found that the formation of ADA appeared to impact the PK of MEDI7352 by generally reducing exposure. CCI [redacted]

The safety and immunogenicity data generated in the present study are consistent with the data previously observed in the FIH study (Study D5680C00001); however, in terms of PK exposures for MEDI7352, the results for both ethnicity cohorts, are not entirely consistent with the FIH study and would require further investigation.

Conclusion:

Primary objective

- MEDI7352 administered in multiple CCI mg SC doses was found to have a good safety profile and was generally well tolerated in healthy Caucasian and Japanese subjects.

Secondary objective

- MEDI7352 median AUClast and Cmax results were slightly higher in Japanese subjects compared with Caucasian subjects on Day 1 and generally similar on Day 43 between Japanese and Caucasian subjects following CCI mg SC repeat administration. A small trend toward higher exposure in Japanese subjects on Day 1 can be explained most likely in terms of differences in the kinetics of ADA emergence and mean body weight.
- MEDI7352 median tmax occurred 3 days post-dose, with a gmean CCI [redacted] for both cohorts, following single and repeat administration of CCI mg MEDI7352 SC.

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- The emergence of ADA appeared to impact PK parameters, leading to lower drug exposure, most notably for Ctrough. This trend was most notable for 3 Caucasian subjects with relatively high ADA titres on Day 15 (the end of the Day 1 profile) and for all Japanese subjects with positive ADA status on or after Day 43 (3 Japanese subjects), regardless of ADA titre.

Exploratory objective

- CCI [redacted]

Version and Date of Report: Version 1.0, 31 October 2022

This study was conducted in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines.