2 STUDY SYNOPSIS

Clinical Study Report Synopsis Protocol Number D4920C00001

Name of Company: MedImmune	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Section:**	***(For National Authority Use Only)***
Name of Finished Product: MEDI6570		
Name of Active Ingredient: MEDI6570		

Title:
A Phase 1 Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety and Pharmacokinetics of Single and Multiple Ascending Doses of MEDI6570 in Subjects with Type 2 Diabetes Mellitus

Investigator(s):
9 investigators, see Appendix 16.1.4.

Study Center(s):
9 study centers in the United States, see Appendix 16.1.4.

Publication (reference):
None

Studied Period (years):	**Clinical Phase:**
28Sep2018 to 21Jul2020	Phase 1

Objectives:
For Parts A (Single ascending dose, SAD) and B (multiple ascending dose, MAD) of this study in participants with T2DM:

- The primary objective was to assess the safety of single and multiple ascending doses of MEDI6570
- Secondary objectives were to evaluate the pharmacokinetics (PK) and immunogenicity of single and multiple ascending doses of MEDI6570

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Methodology:

This was a Phase 1 randomized, blinded (subject/investigator blinded, sponsor unblinded), placebo-controlled, first time in human (FTIH) study in participants with type 2 diabetes (T2DM), consisting of two parts. In Part A, participants, one cohort of which were Japanese, were to receive subcutaneous (SC) single ascending doses of MEDI6570 or placebo. In Part B, participants were to receive 3 SC multiple ascending doses of MEDI6570 or placebo every 4 weeks (Q4W), which were based on PK and pharmacodynamic (PD) results from Part A. CCI [redacted]

In Parts A and B, blood samples were to be taken for PK, anti-drug antibodies (ADA) and exploratory analyses and in Part B, a follow-up coronary computed tomography angiography (CTA) was to be performed.

Number of Subjects (planned and analyzed):

A total of 88 participants were to be randomized/enrolled, all of whom consented to participate in the study. In Part A, 48 participants were included in the As-treated population and were analyzed for safety, immunogenicity, and exploratory endpoints, and 36 participants were analyzed for PK. In Part B, 40 participants were included in the As-treated population and were analyzed for safety, immunogenicity, and exploratory endpoints, and 30 participants were analyzed for PK.

Diagnosis and Main Criteria for Inclusion:

- All participants in Parts A and B were to have a body mass index of 18 to 45 kg/m^2 and a diagnosis of T2DM, and be on stable medical therapy for at least 6 weeks prior to screening.
- In Part A, participants were to be aged 18 through 65 inclusive at screening and one cohort was to comprise of Japanese participants (eg, natives of Japan or Japanese Americans), defined as having both parents and four grandparents who are Japanese. Female participants were to be of non-childbearing potential.
- In Part B, male participants were to be aged 18 through 65 inclusive, and female participants were to be aged 40 to 65 inclusive and to be of non-childbearing potential, at screening. Participants were also required to meet a number of CTA criteria.

Test Product Dose, Mode of Administration, and Batch Number(s):

Investigational Product: MEDI6570

Dose and Form: Part A: Single doses of 10, 30, 90, 250, and 500 mg; Part B; multiple doses of 90, 150, and 250 mg of MEDI6570 sterile lyophilized product reconstituted with sterile water for injection.

Mode of Administration: SC

Batch/Lot Numbers: One batch of MEDI6570 was used in this study, drug product lot number, CCI [redacted]

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Duration of Treatment:

Part A: Single Dose; Part B: 3 doses administered Q4W

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):

Reference Therapy: Placebo

Dose and Form: Sterile solution of 0.9% (weight by volume) sodium chloride for injection.

Mode of Administration: SC

Batch/Lot Numbers: NA

Criteria for Evaluation:

Primary Safety

Treatment emergent adverse event(s) (TEAE[s]) and treatment emergent serious adverse event(s) (TESAE[s]) and clinically meaningful changes in 12-lead electrocardiogram(s) (ECG[s]), vital signs and safety laboratory analyses during treatment and follow-up periods.

Secondary PK

MEDI6570 PK parameters, area under the serum concentration-time curve from time of dose to the last quantifiable concentration (AUC_{last}), area under the serum concentration-time curve from time of dose to infinity ($AUC_{0\text{-}inf}$), maximum observed serum (peak) drug concentration (C_{max}) time to reach peak or maximum observed concentration or response following drug administration (t_{max}) and terminal-phase elimination half-life ($t_{1/2}$) during treatment and follow-up periods.

Secondary immunogenicity

ADA and ADA titer at baseline, and during treatment and follow-up periods.

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Statistical Methods:

Descriptive statistics were to be used to summarize results and no statistical tests were to be performed. However, some additions to the planned analysis were made for some of the exploratory analyses which were captured in the statistical programming plan (SPP). Unless specified otherwise, baseline values were to be defined as the last valid assessment prior to the first administration of investigational product (IP). All available data were to be included in the results and missing data were not imputed apart from the presence or absence of plaque as part of CTA.

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Safety: Adverse event(s) (AE[s]) were to be coded with MedDRA version 21.0 or later. Analysis of AEs was to include the type, incidence, severity, and relationship to IP summarized by the Medical Dictionary for Regulatory Activities Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term by MEDI6570 dose group, all MEDI6570 dose groups combined, combined placebo, and all participants combined for each study part. The AEs to be summarized included only TEAEs, ie, those starting after the first administration of IP until the end of follow-up period.

PK: Free concentrations of MEDI6570 in serum were to be summarised by dose and time point and non-compartmental analysis PK analysis performed.

Immunogenicity: The immunogenic potential of MEDI6570 was to be assessed by summarizing the number and percentage of participants who developed detectable ADA. For those with a positive assessment, the ADA titer results were also to be summarized. The number and percentage of participants in each treatment group showing an immunological response to MEDI6570 were to be summarized by study visit, for the As-treated population.

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Summary and Conclusions:

Study Subjects:

Out of a total of 253 participants screened, 48 were randomly assigned to Part A of the study and 40 randomly assigned to Part B. No participants had IP discontinued in either Part A or Part B. In Part A, one participant withdrew after completing treatment. In Part B, two participants withdrew early after 2 doses of MEDI6570 and a third completed treatment but withdrew due to concerns about Covid-19. In total 97.7% of participants completed treatment per protocol.

All participants had a history of T2DM and the majority were non-smokers.

Part A: The median age in the MEDI6570-treated groups was PPD similar to that of PPD in the placebo group. Most of the participants were white (66.7% in the the MEDI6570-treated groups and the placebo group) apart from the Japanese cohort (J-Coh6) 500 mg MEDI6570 group, which comprised of 100% Asian,

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identifying as Japanese. In the MEDI6570-treated groups, 33.3% of participants were female similar to 25% in the placebo group. The percentage of female participants in the MEDI6570-treated groups ranged between 16.7% and 33.3% in all groups apart from the 90 mg MEDI6570 group where 83.3% of participants were female.

The majority of participants were hyperlipidaemic with 72.2% displaying hyperlipidaemia in the MEDI6570-treated groups and 66.7% of participants being hyperlipidaemic in the placebo group. The proportion of hyperlipidemic participants was similar across MEDI6570-treated groups (66.7%) apart from the 500 mg MEDI6570-treated cohort (coh5) 100% of whom showed dyslipidaemia. The majority of participants were also hypertensive (66.7% of the MEDI6570-treated groups and 83.3% of the placebo group), although the frequency of diagnosis of hypertension was lower, PPD in the 10 mg/kg MEDI6570 group.

Part B: The median age in the MEDI6570-treated groups was PPD similar to that in the placebo group, PPD. Most of the participants were white (83.3% in the MEDI6570-treated groups and 90% in the placebo group) and female (66.7% in the MEDI6570-treated groups and 50% in the placebo group). Whilst there were equal numbers of male and female participants in the placebo and 90 mg MEDI6570-treated groups, females predominated in the 150 mg and 250 mg groups

Over half of participants were hyperlipidemic with 15 of 30 (53.3%) displaying dyslipidaemia in the MEDI6570-treated groups and PPD participants hyperlipidemic in the placebo group. The proportion of hyperlipidemic participants varied across MEDI6570-treated groups from PPD participants in the 150 mg MEDI6570 group to PPD in the 90 mg MEDI6570 group. Most participants were also hypertensive [66.7% of the MEDI6570-treated groups and PPD of the placebo group). The maximum incidence of hypertension was PPD participants in the 250 mg MEDI6570 group.

Primary Safety:

There were no deaths in either Part A or Part B of the study and there were no serious adverse events (SAEs) that were assessed as related to IP by the investigator.

Part A: 5.6% of MEDI6570-treated participants reported SAEs and none in the placebo group. Over half of all participants experienced at least one AE, 61.1% of MEDI6570-treated participants and 50% of those treated with placebo. In the MEDI6570 group, 5.6% of participants reported AEs that were assessed as related to IP by the investigator and 16.7% in the placebo group.

The most frequently reported TEAE by PT (defined as occurring in ≥ 5% of participants) was upper respiratory tract infection in MEDI6570-treated participants (11.1% vs 8.3% in placebo-treated participants), most of which occurred ≥ 88 days after the first dose. The next most common TEAEs were pyrexia, vitamin D deficiency, nasal congestion, back pain and osteoarthritis, each of which occurred in 5.6% of MEDI6570-treated participants. There did not appear to be any dose relationship between MEDI6570 dose and incidence of TEAEs. In the placebo group, of the TEAEs that were reported by PT, none occurred in more than one participant (8.3%). There were 55.6% of participants in the MEDI6570-treated group and 50% of the placebo group who reported at least one TEAE that was of Grade 1 or Grade 2 severity.

Part B: 6.7% of MEDI6570-treated participants and 10% of participants in the placebo group experienced an SAE. The majority of participants reported at least one AE, 73.3% across the MEDI6570-treated groups and

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70% in the placebo group. Of these, 6.7% in the MEDI6570 groups and PPD in the placebo group reported AEs that were assessed as related to IP by the investigator. There were no IP related TESAEs or AEs leading to discontinuation during the course of the study.

In MEDI6570-treated participants, the most common TEAE by PT, across all MEDI6570-treated groups was Upper respiratory tract infection (10%; of participants vs 10% in the placebo group). The next most common TEAEs were Constipation, Injection site erythema, Headache and Pain in extremity, each in 2 of 30 participants (6.7%). There did not appear to be any dose relationship between MEDI6570 dose and incidence of TEAEs. In the placebo group, the most common TEAE by PT was diarrhea in PPD participants. There were 70% of MEDI6570-treated participants and 60% of the placebo group who reported at least one TEAE of Grade 1 or Grade 2 severity.

Secondary PK:

In Part A, following a single SC dose of MEDI6570, the concentration-time profile was characterized by a slow absorption (t_{max} around 7 days) and a non-linear elimination phase consistent with target mediated drug disposition. MEDI6570 exhibited a more than dose-proportional increase in exposure over the dose range of 10 to 500 mg resulting in a supra proportional increase in Cmax and AUC between doses of 10 to 250 mg, whereas between 250 and 500 mg, MEDI6570 exposure appeared proportional. Individual serum concentrations of 500 mg MEDI6570 versus time for J-Coh6 and Coh5 T2DM participants overlapped. In Part B, fold change for C_{max}, C_{min} and AUC from the 2nd (PK Day 29) to 3rd (PK Day 57) dose ranged from 1.00 – 1.62.

Secondary Immunogenicity:

Part A: Of 36 participants administered a single dose of MEDI6570, PPD . One subject in the 90 mg dose group had a pre-existing positive response that was not boosted by administration of MEDI6570. PPD participants presented a treatment-emergent response. Of the PPD participants with ADA positive data post-baseline, PPD responses were classed as persistent PPD and PPD was classed as transient PPD

Part B: Of 30 participants administered multiple doses of MEDI6570, PPD . All ADA positive responses were classed as treatment emergent and persistent.

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Conclusions:

- MEDI6570 was well tolerated in both the single and multiple dose parts of the study, and there were no IP related TESAEs (as judged by the investigator), or AEs leading to discontinuations during the course of the study.
- Following a single dose, MEDI6570 exhibited non-linear PK consistent with target mediated drug disposition, supporting a once monthly dosing regimen.
- There were no immunogenicity concerns regarding safety.
- Exploratory analysis of free sLOX-1 levels in serum were suggestive of target engagement.

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