2 STUDY SYNOPSIS

Clinical Study Report Synopsis D5780C00007

Name of Company: MedImmune	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Section:**	***(For National Authority Use Only)***
Name of Finished Product: MEDI6012		
Name of Active Ingredient: MEDI6012		

Title:

A randomized, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of MEDI6012 in acute ST elevation myocardial infarction (STEMI) (REAL-TIMI 63B)

Investigator(s):

The study was conducted by 40 investigators at the 37 sites that randomized subjects (some investigators were replaced during the study). There was a total of 48 investigators at the 45 sites that were originally initiated (see CSR Appendix 16.1.4).

Study Center(s):

37 study centers in 10 countries (Brazil, Czech Republic, Hungary, Israel, Netherlands, Poland, Russian Federation, Slovakia, Spain, United Kingdom; see Appendix 16.1.4).

Publications:

Bonaca MP, George RT, Morrow DA, Bergmark BA, Park JG, Abuhatzira L, et al. Recombinant human Lecithin-Cholesterol acyltransferase in patients with atherosclerosis: Phase 2a primary results and Phase 2b design. Eur Heart J Cardiovasc Pharmacother. 2021;Jan 25:pvab001.

Bonaca MP, Morrow DA, Bergmark BA, Lima JA, Hoffmann U, Kato Y, et al. Cardioprotection and plaque regression with MEDI6012 in acute ST elevation myocardial infarction - Primary results of the REAL-TIMI 63B randomized clinical trial. J Am Coll Cardiol. 2021;77(18):Suppl 1, p23.

Studied Period (years):	**Clinical Phase:**
Study Start – 05Jun2018 Last Subject Entered – 06Aug2020	Phase 2b

Objectives:

Primary objective

To evaluate the effect of MEDI6012 on reduction of infarct size compared with placebo

Secondary Objectives

1 To evaluate the effect of MEDI6012 on systolic function of the left ventricle (LV) compared to placebo
2 To evaluate the effect of MEDI6012 on non-calcified coronary plaque regression/progression from baseline to 10 to 12 weeks compared with placebo
3 To evaluate the effect of MEDI6012 on remodeling of the LV measured by myocardial mass and volumes
4 To evaluate the safety and tolerability of MEDI6012
5 To describe the pharmacokinetics (PK) and immunogenicity of MEDI6012

Exploratory objectives, endpoints, and results are covered in the Clinical Study Report body only.

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Methodology:

This was a Phase 2b, randomized, placebo-controlled study to evaluate the efficacy, safety, PK/pharmacodynamics (PD), and immunogenicity of repeat doses of MEDI6012 in adult subjects presenting with acute STEMI. The subjects, MedImmune staff, and investigators were to be blinded (although due to the acute nature of the study, members of the research team and, possibly, the investigator may have been unblinded). The study enrolled subjects presenting with acute STEMI within 6 hours of symptom onset who were planned for emergent primary percutaneous coronary intervention (pPCI). After obtaining informed consent, subjects, if considered eligible, were randomized in a 1:1 ratio into either Cohort A [redacted] regimen) or Cohort B ([redacted] regimen). Within each cohort/dose regimen, subjects were randomized in a 2:1 ratio to receive MEDI6012 or placebo as soon as possible prior to pPCI.

Number of Subjects (planned and analyzed):

Approximately 540 subjects were planned to be randomized across approximately 43 study sites. In fact, 596 subjects consented to participate and 593 subjects were randomized at 37 sites. A total of 593 subjects were analyzed for efficacy (Intention-to treat Population [ITT]) and 575 subjects were analyzed for safety (As-treated Population).

Diagnosis and Main Criteria for Inclusion:

Men and women aged 30 to 80 years without child-bearing potential with acute STEMI diagnosed by ST elevation, planned for pPCI, and with ischemic symptoms for ≤ 6 hours.

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

Investigational Product: MEDI6012

Dose and Form: [redacted]

Mode of Administration: IV push

Batch/Lot Numbers: [redacted].

Duration of Treatment:

Cohort A were dosed on Days 1 and 3, with an end-of-study cardiovascular magnetic resonance (CMR) on Day 70 to 84. Cohort B were dosed as for Cohort A, then at weekly intervals for 4 weeks (Days 10, 17, 24, and 31), prior to a CMR on Day 70 to 84.

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

Reference Therapy: Placebo

Dose and Form: [redacted]

Mode of Administration: IV push

Batch/Lot Numbers: [redacted]

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Criteria for Evaluation:

Primary Efficacy:

Infarct size as a percentage of LV mass measured on delayed-enhanced CMR imaging 10-12 weeks post-myocardial infarction (MI) compared to placebo

Secondary Efficacy:

- Ejection fraction (EF) measured by cine magnetic resonance imaging (MRI) at 10-12 weeks post MI compared to placebo
- Change in non-calcified plaque volume (NCPV) in the coronary arteries from index computed tomography angiography (CTA) to 10-12 weeks post MI compared with placebo
- Myocardial mass and LV volumes at end-systole and end-diastole

Secondary Safety:

Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)

Secondary PK and Immunogenicity:

Lecithin-cholesterol acyltransferase (LCAT) mass (MEDI6012) and presence of antidrug antibodies (ADAs)

Statistical Methods:

All statistical tests were 1-sided (based on protocol amendment) at an alpha = 0.05 significance level unless stated otherwise. Confidence intervals (CIs) were 1-sided (based on protocol amendment) and nominal p-values were reported when appropriate.

The primary efficacy endpoint of infarct size was log-transformed due to its skewed distribution and was analyzed by means of 2-sample t-test. The treatment effect was estimated by the geometric mean ratio of MEDI6012 to placebo as well as its 95% CI. Infarct size records with zero value were imputed by half of the minimum of the non-zero records prior to the log transformation. The primary population was the primary efficacy analysis population (TIMI 0-1). Similar analysis was also performed for the Efficacy Analysis Populations with TIMI 0-3 and TIMI 2-3, and the ITT Population.

The secondary efficacy endpoints were analyzed using t-test, based on the Primary Efficacy Analysis Population, the Efficacy Analysis Population with TIMI 2-3, Efficacy Analysis Population with TIMI 0-3, and the ITT Population. Change from index CTA in NCPV was analyzed using t-test, based on CTA Analysis, As-treated, and ITT Populations. Parameters were first evaluated for normality. As the distribution appeared to be log-normal, the endpoint was log-transformed due to its skewed distribution and was analyzed by a 2-sample t-test. The treatment effect was estimated by the geometric mean ratio of MEDI6012 to placebo as well as its 95% CI.

Subgroup analyses were performed. Post-hoc supplementary and sensitivity analyses were also performed (in addition to the planned analyses).

Serum MEDI6012 concentration-time profiles were summarized for MEDI6012-treated subjects by cohort and by visit.

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Anti-drug antibody incidence rate was tabulated for each treatment group. Both the positive immunodepletion and the negative titer results (less than 1.00) were counted as a positive ADA result in the summary table produced. Samples confirmed positive for ADA were tested and analyzed for neutralizing antibodies and summarized similarly.

Safety analyses were based on the As-treated Population. Adverse event (AE) collection began after randomization and lasted until the end of the study. Serious AE collection began after the subject signed the informed consent document and lasted until the end of the study. Specific AEs were counted once for each subject for calculating rates but were presented in total in subject listings. If the same AE occurred multiple times within a particular subject, the highest severity and level of causality was reported. All TEAEs and TESAEs were summarized overall and by MedDRA system organ class (SOC) and preferred term (PT), by severity and relationship to investigational product. In addition, summaries of deaths and treatment discontinuation due to AEs were provided.

Summary and Conclusions:

Study Subjects:

In total, 593 subjects were randomized into the study and 575 subjects were treated. Overall, 85.0% of treated subjects completed treatment, and 97.2% of randomized subjects completed the study.

There was , when the last randomized subject completed the Day 70 to 84 visit, met the protocol-defined criteria for Extended Follow-up). Therefore, an initial database lock was declared and a second [final] database lock will occur once the has completed the protocol-defined criteria for Extended Follow-up.

Sex, age, race, ethnicity, and body mass index were well balanced between treatment groups and cohorts. While there were some numerical differences seen between treatment groups and cohorts with regards to baseline characteristics and CV medical history, there were no differences noted that were considered to have potentially impacted the interpretation of data.

Twenty-six subjects had at least 1 disruption due to the COVID (coronavirus disease) pandemic and had at least 1 pandemic-related important protocol deviation in the ITT Analysis Population of 593. discontinued from the study treatment due to the pandemic but no subjects discontinued the study due to the pandemic.

Efficacy:

The primary endpoint was not met. Formal statistical testing showed that a statistically significant relative change in global infarct size was not found between MEDI6012 Cohort A and placebo total (geometric mean ratio (GMR): 1.175, 1-sided 95% CI: NA, 1.530) or between MEDI6012 Cohort B and placebo total (GMR: 1.069, 1-sided 95% CI: NA, 1.380). Statistical significance was also not seen for the other efficacy analysis populations tested. There were no findings of statistical significance for any of the subgroups studied.

There were no findings of statistical significance for any of the secondary efficacy endpoints. The EF in both MEDI6012 cohorts was greater than that in placebo total, but the increase was not statistically significant. A

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greater reduction in NCPV was observed in MEDI6012 treated compared to placebo-treated subjects, which may be of clinical relevance.

Pharmacodynamic findings were in line with previous clinical studies, with an increase in high-density lipoprotein-cholesterol (HDL-C), high-density lipoprotein-cholesteryl ester (HDL-CE), CE (cholesteryl ester), and apolipoprotein A1 (apoA1) seen in MEDI6012 treatment groups, confirming target engagement. There were also decreases in apolipoprotein B (ApoB) on Day 3 in both cohorts, but this was not sustained at later timepoints taken at the nadir of MEDI6012 concentration.

Pharmacokinetic findings showed that overall, MEDI6012 concentration increased post dose.

Immunogenicity results indicated that there were ADA-positive subjects in both Cohort A and Cohort B, at a higher frequency in the MEDI6012-treated groups compared to placebo in both cohorts. The proportion of ADA-positive subjects was higher in Cohort B compared to Cohort A. Most subjects who had a positive ADA readout in Cohort B were ADA positive at Visit 6 (Day 70 to 84) and there was a tendency for increasing titers over time among those subjects who were ADA positive at several study visits (supported by data on file).

Safety:

In total, 66.8% of subjects receiving MEDI6012 experienced at least 1 TEAE versus 59.2% of subjects receiving placebo. The most common SOCs with events reported (in > 10% of MEDI6012-treated subjects) were: cardiac disorders, respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, nervous system disorders, and vascular disorders. The most commonly reported TEAE PTs (in > 3% of MEDI6012-treated subjects) were: cardiac failure, headache, cough, dizziness, atrial fibrillation, hypotension, angina pectoris, diarrhea, and nausea. Of note, although infusion site reactions were not common, they only occurred in MEDI6012-treated subjects.

The percentage of subjects experiencing at least 1 event of grade ≥ 3 was higher in the MEDI6012- versus placebo-treated subjects in Cohort A, but similar between the 2 treatments in Cohort B.

[redacted] (2.4%) subjects (all MEDI6012 treated) had TEAEs considered to be related to study treatment (ECG QC prolonged, diarrhea, lip swelling, nausea, vomiting, drug intolerance, headache, dermatitis allergic, toxic skin eruption, and urticaria); [redacted] had a TESAE that was considered related to study treatment (toxic skin eruption in MEDI6012 Cohort B).

[redacted] MEDI6012-treated subjects (versus zero placebo-treated subjects) died during the study, due to cardiac failure, pneumonia, and MI (all considered unrelated by the investigator).

While a similar percentage of MEDI6012- to placebo-treated subjects in Cohort B experienced TESAEs, a higher percentage of MEDI6012-treated compared to placebo-treated subjects experienced TESAEs in Cohort A (19.0% versus 12.2%).

In total, [redacted] of MEDI6012-treated subjects had an event that led to discontinuation of study treatment, compared to [redacted] of placebo-treated.

No clinically meaningful changes or clinically relevant trends in hematology or chemistry parameters were observed in either the MEDI6012-treated dose group or placebo groups for either cohort. No TEAEs related to hematologic or chemistry abnormalities were reported for any subject.

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Conclusions: There were no unexpected safety findings in either the [redacted] or [redacted] regimens of MEDI6012 in this study and the findings were in line with the known safety profile to date. Treatment with MEDI6012 in the setting of acute MI was not efficacious with regards to decreasing infarct scar size, increasing EF, or reducing atheroma burden		
Date of Original Report: 14May2021		