Clinical Study Report Synopsis

Drug Substance	MEDI5117
Study Code	D4430C00001
Edition Number	1.0
Date	
EudraCT Number	2011-005402-29

A Double-blind, Placebo-controlled, Randomized Study in Rheumatoid Arthritis Subjects to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of MEDI5117 (anti-IL-6)

Study dates: First subject enrolled: 21 May 2012
Last subject last visit: 25 February 2014

Phase of development: Clinical Pharmacology (I)

International Coordinating Investigator:

Sponsor's Medical Monitor:

Sponsor's Project Physician:

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

Study centers

Table S-1 Study centers

Number	Study Center and Address
001	
002	
003	

Publications

None at the time of writing this synopsis.

Objectives and criteria for evaluation

Table S–2 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of single ascending doses of MEDI5117 in patients with rheumatoid arthritis.	Assessment of adverse events (AEs), vital signs (including body temperature), physical examinations, laboratory variables, and electrocardiograms (ECGs). Patient's assessment of overall average pain due to rheumatoid arthritis using numerical rating scale and visual analogue scale (VAS). Patient's assessment of physical function. American College of Rheumatology 20/50 responses over time (mean changes from baseline [last assessment before dosing] in swollen joint count [66 joint counts] and tender joint count [68 joint counts]). Disease Activity Score (DAS) using 28 joint counts. Patient's and physician's global assessment of disease activity by a VAS.
Secondary	Pharmacokinetic (PK)	To characterize the PK of MEDI5117.	C_{max}, t_{max}, λ_z, $t_{½\lambda z}$, $AUC_{(0\text{-}t)}$, AUC, $AUC_{(0\text{-}6w)}$ and $AUC_{(0\text{-}12w)}$, CL, Vd_z, and Vd_{ss}

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Pharmacodynamic (PD)	To characterize the PD effects of MEDI5117 on total interleuken-6 (IL-6) and high sensitive C-reactive protein (hs-CRP) in circulation.	Total IL-6 and if applicable free IL-6 (exploratory) in plasma and hs-CRP in serum prior to and post MEDI5117 or placebo administration and their corresponding change from baseline values had to be evaluated for their association with MEDI5117 treatment. Pharmacodynamic parameters could also have been derived, if appropriate.
	Immunogenicity	To investigate the immunogenicity of MEDI5117.	The outcome variable for the secondary objective had to be a positive or negative for the presence of antidrug antibodies against MEDI5117 in blood. Not reported in the CSR.
Exploratory	Efficacy	To explore the analgesic efficacy of MEDI5117. To explore the efficacy of MEDI5117 on rheumatoid arthritis.	Not reported in the CSR.
		To collect and store deoxyribonucleic acid (DNA) to identify and explore genetic variations that may affect the PK, PD, safety, and/or tolerability related to MEDI5117 treatment or the target (IL-6). In addition, susceptibility genes related to underlying disease may be explored in DNA samples taken from consenting patients (collection of DNA is optional).	Reported separately from the CSR.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		To explore potential biomarkers that may support future pain projects, including biomarkers for development of personal healthcare strategies and patient segmentation.	Exploratory biomarkers in blood based matrices (plasma/serum/whole blood): including but not limited to inflammatory cytokines (such as IL-8), serum amyloid A, messenger ribonucleic acid (mRNA), and erythrocyte sedimentation rate (ESR).
		To characterize the effects of MEDI5117 on a panel of exploratory PD markers.	Not reported in the CSR.

AUC: Area under the serum concentration-time curve; $AUC_{(0\text{-}6w)}$: Area under the serum concentration-time curve from zero to the time of concentration at Week 6; $AUC_{(0\text{-}12w)}$: Area under the serum concentration-time curve from zero to the time of concentration at Week 12; $AUC_{(0\text{-}t)}$: Area under the serum concentration-time curve from zero to the time of the last quantifiable concentration; CL: Systemic clearance; C_{max}: Maximum serum concentration; CSR: Clinical Study Report; t_{max}: Time to C_{max}; λ_z: Terminal rate constant; $t_{½\lambda z}$: Terminal half-life; Vd_{ss}: Volume of distribution at steady state; Vd_z: Volume of distribution during terminal phase.
As the study was prematurely terminated, not all objectives are reported in the CSR.

Study design

This was a Phase I, first-time in man, randomized (within each cohort), double-blind, placebo-controlled, single ascending dose, multicenter study evaluating the safety, tolerability, PK, PD, and immunogenicity of single intravenous doses of MEDI5117 in male and female patients with rheumatoid arthritis. Three study centers in 3 countries participated in this study. Approximately 32 patients were planned for this study, with 4 dose cohorts of patients receiving escalating single intravenous doses of MEDI5117 or placebo. The starting dose was 30 mg and provisional doses were to be 90, 270, and 600 mg. A Safety Review Committee (SRC) had to determine the exact dose of MEDI5117 to be administered to patients in each dose level. The SRC also had to determine if a fifth cohort was needed.

The investigational product (MEDI5117 or placebo) was administered in the morning as a single intravenous infusion over approximately 60 minutes using an infusion pump. Patients received only 1 dose of investigational product during this study. The administration of the investigational product was to be staggered within each dose cohort. The first 2 patients in a dose cohort were to be randomized in a 1:1 ratio to receive MEDI5117 or placebo, and were to be dosed at least 48 hours before the remaining patients were dosed in that cohort providing there were no serious or unexplained safety issues as determined by the investigator.

A screening visit was performed within 30 days prior to admission to the study center on Day -1. On Day 1, patients received MEDI5117 or placebo. If no safety concerns were identified in any of the patients treated, the patients were discharged from the study center on Day 2 after all study procedures have been completed. Patients had to return to the study center for further follow-up.

Target subject population and sample size

Male and nonpregnant, nonlactating female patients aged 20 to 75 years (inclusive) with rheumatoid arthritis for >6 months, according to the 1987 American College of Rheumatology criteria, and a DAS 28 score of 3.2 or greater and 3 or more tender, painful joints (out of 68 joints examined) at screening and baseline, and a body mass index (BMI) of 19 to 36 kg/m^2 (inclusive), were included in the study.

Approximately 32 patients were planned for this study. Due to difficulties with recruitment, enrollment was stopped after only 4 patients were enrolled.

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

Table S–3 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer	Lot Number
MEDI5117	3 cc vial; 50-mg (nominal) of lyophilized powder	MedImmune	11J14-154
MEDI5117 Placebo	3 cc vial; liquid[a] (nominal) 1.0 mL per vial	MedImmune	11H12-155
MEDI5117 IV bag protectant	3 cc vial; liquid (nominal) 1.8mL per vial	MedImmune	11J21-157

[a] Liquid matches the formulation buffer of the reconstituted MEDI5117 solution (25 mM histidine/histidine-HCl, 225 mM trehalose [8.5% (w/v)], .05% [w/v] plant-derived polysorbate 80, pH 6.0).

Duration of treatment

The study duration for each patient who received MEDI5117 or placebo, had to be approximately 68 weeks (including up to 30 days for screening, 2 days residency for investigational product administration, and 450 days for follow-up). Three patients received active treatment and were followed up until Week 64, while the fourth patient received placebo and was followed up until Week 12 as per the protocol.

Statistical methods

Subject disposition, demographics and subject baseline characteristics were summarized using descriptive statistics. Continuous variables were summarized by treatment group using: n, mean, standard deviation (SD), minimum (min), median, and maximum (max). Categorical variables were summarized in frequency tables (frequency and proportion) by treatment group.

Treatment-emergent adverse events (TEAEs) were summarized by System Organ Class (SOC) and by Preferred Term (PT) within the SOC according to the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs were listed.

All other safety data (clinical laboratory, vital signs, ECG, and physical examination), PD, immunogenicity, PK, and other outcome variables are presented in data listings only.

Subject population

Due to difficulties with recruitment, enrollment was stopped after only 4 patients were enrolled.

A total of 4 patients were randomized at 3 study centers in 3 countries; 3 patients received MEDI5117 and 1 patient received placebo. The patient population comprised 3 white females (MEDI5117), between the ages of 50 and 59 and 1 white male (placebo), 36 years of age. All 4 patients completed the study as per the protocol.

Summary of PK results

After approximately 1 hour intravenous infusion of 30 mg MEDI5117 for 3 subjects, peak serum concentrations of MEDI5117 were reached within 12 hours (2 subjects at 2 hours and 1 subject at 12 hours). After peaks, the concentrations appeared to decline in a biphasic manner. Serum concentrations of MEDI5117 were quantifiable up to the last measured time point at 64 weeks in 2 subjects and up to at least 24 weeks in the third subject.

Summary of PD results

Data of PD and exploratory markers in circulation were obtained up to 40 weeks for total IL-6, 64 weeks for hs-CRP, and 12 weeks for amyloid A in 3 subjects who received MEDI5117 and in 1 subject who received placebo.

Among the 3 MEDI5117-treated subjects, plasma levels of total IL-6 significantly increased after administration of the investigational product and levels of IL-6 remained elevated up to 40 weeks. Compared to baselines (not greater than 1.9 pg/mL), levels of total IL-6 were already at least 15.1 pg/mL at 2 hours and continued to increase up to Weeks 12 to 20 (peak values of 17213.7 to 18873.8 pg/mL). After peaks, the levels appeared to slowly decline. Plasma total IL-6 for the placebo-treated subject remained constantly below the lower limit of quantification (1.2 pg/mL) at most time points.

Serum levels of hs-CRP decreased after administration of MEDI5117, with maximum decreases of 81.3% to 93.9% from baselines. Maximum decreases were observed at 1 to 4 weeks, followed by a gradual trend back towards baseline over the remainder of the 64-week period. The hs-CRP levels of the placebo-treated subject remained stable (ranged from 0.4 to 0.7 mg/L) over most of the measurement period.

Serum levels of amyloid A showed some decreases over the 12 weeks after administration of MEDI5117. Maximum decreases ranged from 38.8% to 63.8% by Week 1, with concentration gradually trending back towards baseline in 2 of the 3 subjects by Week 12.

The amyloid A levels of the placebo-treated subject remained stable (3 mg/L) for most time points.

Summary of safety results

No patients died, no patients reported severe adverse events (SAEs), and no patients discontinued the investigational product or from the study due to an AE. At least 1 AE was reported for each patient. All AEs were considered to be mild to moderate in intensity. Adverse events considered related to the investigational product were nausea, diarrhea, vomiting, headache, and nasopharyngitis; all considered of mild intensity. Productive cough and influenza were considered of moderate intensity.

Overall, the most commonly reported AE was vomiting (3 [100.0%] patients) followed by diarrhea (2 [66.7%] patients), reported by patients on MEDI5117 only. The patient on placebo only reported nausea and gastroenteritis. All events resolved.

Although a decrease in both disease activity and assessment of pain due to rheumatoid arthritis were observed as assessed using VAS, the decreases were noted for MEDI5117 as well as placebo.

All 4 patients needed assistance with walking and dressing as could be seen from the Health Assessment Questionnaire Disability Index (HAQ-DI) where all 4 patients had scores of 0 and 1 for the 8 categories assessed.

Although high and low laboratory values were reported for all 4 patients, no specific trends could be observed, with the exception of changes in the white blood cell (WBC) and neutrophil counts. Whereas the patient who received placebo had no abnormal WBC or neutrophil counts, changes were observed in all 3 patients who received MEDI5117. One patient who received MEDI5117 had normal WBC and neutrophil counts at baseline, then had neutrophil counts below normal during Weeks 1 to 4. A second patient who received MEDI5117 had normal WBC and neutrophil counts at baseline, which decreased between Week 3 to Week 12, reaching a low WBC count of 2.77×10^9/L and a low neutrophil count of 1.46×10^9/L. The third patient who received MEDI5117 had a normal WBC and low neutrophil count (1.35×10^9/L) at baseline which further decreased between Day 2 and Week 20, reaching a low WBC count of 2.31×10^9/L and a low neutrophil count of 0.72×10^9/L. For all 3 patients who received MEDI5117, WBC and neutrophil counts returned to normal by the end of the study.

No clinically important values or changes from baseline were reported for vital signs and ECGs.