Statistical Analysis Plan

A Phase 1b Randomized, Double-blind, Placebo-controlled Multiple-ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, Pharmacodynamics and Clinical Response of MEDI4920 in Subjects with Adult-onset Rheumatoid Arthritis

Protocol Number: D5100C00002

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ACPA	Anti–cyclic Citrullinated Peptide Antibody
ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criteria
AUC	Area Under the concentration-time Curve
ATC	Anatomical Therapeutic Chemical
AZ-DD	AstraZeneca Drug Dicitonary
BMI	Body mass index
CDAI	Clinical Disease Activity Score
cDMARD	Conventional Disease Modifying Anti-Rheumatic Drugs
Cmax	Maximum Concentration
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAS28	Disease Activity Score using 28 joints
DMPK	Drug Metabolism & Pharmacokinetics
eCRF	electronic Case Report Form
ECG	Electrocardiogram
ED50	Dose giving 50% of the maximum effect
Emax	Maximum Effect
ESR	Erythrocyte Sedimentation Rate
Ig	Immunoglobulin
IM	Immunogenicity
ITT	Intent-to-Treat
IV	intravenous
IXRS	Interactive voice/web response system
LOCF	Last Observation Carried Forward
MAD	Multiple Ascending Dose
MBDA	Multi-Biomarker Disease Activity
MCP-mod	Multiple Comparison Procedure – modelling
MDGA	Physician Global Assessment
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MMRM	Mixed Model for Repeated Measures

Abbreviation or Specialized Term	Definition
MTX	Methotrexate
PGA	Patient Global Assessment
PK	Pharmacokinetics
PRO	Patient Reported Outcome
Q2W	Every 2 weeks
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
sCD40L	Soluble CD40 ligand
SD	Standard Deviation
SJC	Swollen Joint Count
SPP	Statistical Programming Plan
TJC	Tender Joint Count
Anti-TNFα	Anti-Tumour Necrosis Factor alpha
VAS	Visual Analogue Score

1 INTRODUCTION

This document describes the statistical analyses for protocol D5100C00002, a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and tolerability of multiple ascending doses of MEDI4920 in subjects with adult-onset rheumatoid arthritis (RA) (moderate to severe, as defined by disease activity score in 28 joints using C-reactive protein (DAS28 CRP) ≥ 3.2 at screening) with an inadequate response to methotrexate (MTX) or other conventional disease-modifying anti-rheumatic drugs (cDMARDs) or a biologic anti-tumor necrosis factor alpha (anti-TNFα) agent.

A separate statistical programming plan (SPP) will contain the table templates, detailed specifications and programming code for the statistical analyses.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective

To assess the safety and tolerability of multiple ascending intravenous (IV) doses of MEDI4920 in subjects with adult-onset RA.

2.1.2 Secondary Study Objectives

To evaluate the pharmacokinetics (PK) and immunogenicity of MEDI4920 in subjects with adult-onset RA.

2.1.3 Exploratory Study Objectives

1. CCI [redacted]
2. CCI [redacted]
3. CCI [redacted]
4. CCI [redacted]

2.2 Study Design

This is a multicenter, randomized, double-blind (investigator, subject, and sponsor will be blinded to treatment assignment), placebo-controlled study to evaluate the safety and tolerability of multiple ascending doses (MADs) of MEDI4920 in subjects with adult-onset

RA (moderate to severe, as defined by DAS28 CRP ≥ 3.2 at screening) with an inadequate response to MTX or other cDMARDs or a biologic anti-TNFα agent.

Approximately 40 subjects on stable MTX or another cDMARD will be randomized across 3 cohorts to receive either 75 mg (Cohort 1), 500 mg (Cohort 2), or 1500 mg (Cohort 3) MEDI4920, or placebo once every 2 weeks (Q2W).

An additional 14 subjects may be randomized to an additional cohort (Cohort 4) if required, to understand the dose (exposure) - response relationship. The selected dose and exposure (maximum concentration (C_{max}) and area under the concentration-time curve (AUC)) will not be higher than 1500 mg Q2W and could include a less frequent dosing regimen (eg, once every 4 weeks).

Subjects will undergo a screening period of up to 6 weeks followed by randomization and treatment for 12 weeks. Subjects will be followed for an additional 12 weeks after the treatment period for safety.

Subjects will receive an IV dose of MEDI4920 or placebo Q2W for up to 12 weeks as follows:

- Cohort 1: 75 mg MEDI4920 (N = 8) or placebo (N = 2) as a single IV dose administered over at least 30 minutes Q2W
- Cohort 2: 500 mg MEDI4920 (N = 10) or placebo (N = 4) as a single IV dose administered over at least 60 minutes Q2W
- Cohort 3: 1500 mg MEDI4920 (N = 12) or placebo (N = 4) as a single IV dose administered over at least 90 minutes Q2W
- Cohort 4 (Optional): MEDI4920 (N = 10) or placebo (N = 4) as a single IV dose (duration of infusion and frequency of administration to be determined)

All subjects will receive a total of 7 doses of investigational product (MEDI4920 or placebo) during the 12-week treatment period.

The primary analysis will be performed when all subjects in Cohort 3 have completed the Day 85 assessments or have been withdrawn from the study. The primary analysis will include all assessments on the subjects prior to the data cut-off for the primary analysis.

If a fourth cohort is required, the data will be analyzed when all subjects in the fourth cohort have completed the Day 85 assessments or have been withdrawn from the study.

The final analysis on the subjects will be performed when all subjects have completed the safety follow-up.

2.3 Treatment Assignment and Blinding

An interactive voice/web response system (IXRS) will be used for randomization to a treatment group and assignment of investigational product kit numbers if assigned to an active treatment arm. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of treatment group and allocates active treatment if assigned to the active treatment arm.

Subjects will be randomized in a 4:1 ratio (Cohort 1), in a 5:2 ratio (Cohort 2), in a 3:1 ratio (Cohort 3), and in a 5:2 ratio (Optional Cohort 4) to receive either MEDI4920 or placebo respectively.

This is a double-blind study in which MEDI4920 and the saline placebo are not identical in appearance. For maintaining the blinding of the principal investigator, site staff, sponsor, Contract Research Organization (CRO) or staff, a local unblinded pharmacy staff member will be nominated by each site and will have the responsibility of allocating, dispensing and preparing the investigational product in order to maintain the study blind. In addition, a separate unblinded monitor will be used for the oversight of investigational product management.

MedImmune personnel will be unblinded to the subject treatment assignments at the primary analysis (Day 85). The data from the primary analysis will not be communicated to personnel at the CRO or investigational sites or to enrolled subjects, until the study is complete.

2.4 Sample Size

No formal sample size calculations are presented for the evaluation of the primary objective of safety and tolerability of MEDI4920. The sample size calculations are based on the exploratory endpoint CCI [redacted] CCI [redacted].

The sample size calculation for the change from baseline in DAS28 CRP at Week 12 is based on combining the data from the cohorts and performing a dose response analysis. Based on the assumption CCI [redacted] CCI [redacted], the sample sizes of 10, 8, 10 and 12 subjects for the placebo, 75, 500 and 1500 mg dose groups, respectively, will

provide approximately 80% power for detecting a statistically significant dose response, using a significance level of 0.10.

The power for dose response has been calculated using a multiple comparison procedure with modeling techniques (MCP-Mod; Bretz et al, 2005), with three candidate models for the dose response (linear, maximum effect attributable to the drug [E_{max}], and a Hill-E_{max} model). An overall significance level of 0.10 will be used to test for dose response.

3 STATISTICAL METHODS

3.1 General Considerations

All data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects falling within each category. In general, continuous variables will be summarized by descriptive statistics including mean, standard error or standard deviation (SD), median, minimum, and maximum.

Day 1 will be defined as the day of first investigational product administration. Baseline will be defined as the last non-missing value prior to the first administration of investigation product. The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing.

Unless otherwise stated, all efficacy analyses will be conducted with a two-sided test at a significance level of $\alpha = 0.10$.

Data analyses will be conducted using the SAS® System Version 9.3 or higher (SAS Institute Inc., Cary, NC) in a UNIX platform.

3.1.1 Visit windows

Visit windows will be used for all scheduled assessments to allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless specified otherwise, all efficacy and safety analyses will be based on the analysis visit windows. The actual assessment day will be mapped to the planned study visit following the analysis visit windowing rules below:

- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.

- If two non-missing assessment actual dates are equidistant from the target day, the earlier visit will be used in the analysis.

The visit windows will be calculated by bisecting the scheduled visit days. The lower limit of each window will be the mean of the two adjacent planned study days, rounded up to the nearest integer, except for the first post-treatment visit, which will start at 2. The upper limit of each window will be the mean of the two adjacent planned study days, rounded down to the nearest integer.

Table 3.1.1-1 Visit windows for DAS28, CDAI, Joint Counts, Patient Global Assessment, Physician Global Assessment, CRP and ESR

Planned study day of visit	Visit window
1	All assessments prior to the first administration of investigation product
15	Start of first administration of investigation product – Day 22
29	Day 23 - 43
57	Day 44 - 71
85	Day 72 - 99
113	Day 100 - 127
141	Day 128 - 155
169	Day 156 +

Table 3.1.1-2 Visit windows for Vectra DA

Planned study day of visit	Visit window
1	All assessments prior to the first administration of investigation product
15	Start of first administration of investigation product – Day 22
29	Day 23 - 43
57	Day 44 - 71
85	Day 72 - 99
113	Day 100 - 141
169	Day 142 +

Table 3.1.1-3 Visit windows for laboratory assessments

Planned study day of visit	Visit window
1	All assessments prior to the first administration of investigation product
8	Start of first administration of investigation product – Day 11
15	Day 12 - 22
29	Day 23 - 43
57	Day 44 - 71
85	Day 72 - 88

Table 3.1.1-3 Visit windows for laboratory assessments

Planned study day of visit	Visit window
92	Day 89 - 95
99	Day 96 - 106
113	Day 107 - 127
141	Day 128 - 155
169	Day 156 +

Table 3.1.1-4 Visit windows for ECGs

Planned study day of visit	Visit window
1	All assessments prior to the first administration of investigation product
85	Start of first administration of investigation product – Day 127
169	Day 128 +

Vital signs will be summarized according to the eCRF recorded assessment visit.

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who are randomized and who receive at least one dose of study investigational product will be included in the ITT population and subjects will be analyzed according to their randomized treatment group.
As-treated population	Subjects who are randomized and who receive at least one dose of study investigational product will be included in the as-treated population and subjects will be analyzed according to the highest dose they actually receive.
PK population	The Pharmacokinetics (PK) Population includes all subjects who receive at least one dose of investigational product and have at least one PK sample containing detectable MEDI4920.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment group received (including summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study with respect to completion of treatment and follow-up will be provided.

3.3.2 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, weight, height, and body mass index (BMI) will be presented by treatment group and for all subjects combined. RA history, including years since onset of symptoms, years since diagnosis, current functional capacity and number of nodules will be summarized by treatment group and for all subjects combined. Previously discontinued RA medications along with the reason for discontinuation will be summarized by treatment group and for all subjects combined.

A summary of baseline disease characteristics will include DAS28 CRP, swollen joint count, tender joint count, Physician's global assessment (MDGA), Patient's global assessment (PGA), CRP, erythrocyte sedimentation rate (ESR), Clinical Disease Activity Index (CDAI), anti-cyclic citrullinated peptide antibody (ACPA) (positive/negative) and rheumatoid factor (RF) (positive/negative).

3.3.3 Investigational Product Exposure

The summary of investigational product exposure will include descriptive statistics for the total number of doses received, total amount of MEDI4920 (mg) administered to each treatment arm and the relative dose intensity. The relative dose intensity is defined as the total amount of MEDI4920 administered throughout the trial divided by the planned total dose.

3.3.4 Concomitant Medications

Concomitant medications for RA and other current co-morbidities will be coded using the current version of AZ-DD and summarized for each treatment group and for all subjects combined by ATC level 1 and preferred term. The background dose of methotrexate and corticosteroids use will also be summarized by treatment group and for all subjects combined.

3.4 Efficacy Analyses

CCI .

3.4.1 CCI

3.4.1.1 CCI

CCI

CCI

3.4.1.2 CCI

CCI

3.4.1.3 CCI

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CCI

3.4.1.4 CCI

CCI

3.4.1.5 CCI

CCI

3.4.2 CCI

3.4.2.1 CCI

CCI

3.4.2.2 CCI

CCI

CCI

3.4.3 CCI

CCI

3.5 Patient Reported Outcomes

3.5.1 Patient Global Assessment

The only Patient Reported Outcome (PRO) is the PGA. The analysis of the PGA is described in section 3.4.2.2.

3.6 Pharmacodynamic Endpoint(s) and Analyses

3.6.1.1 Pharmacodynamic Endpoint(s)

A commercially available and validated biomarker panel (Vectra DA) measures 12 biomarkers and combines them into a single score to assess the key mechanisms and

pathways that drive RA disease activity. The biomarker panel includes adhesion molecules, growth factors, cytokines, matrix metalloproteinases, skeletal proteins, hormones and acute phase proteins. The Vectra DA biomarker panel has been demonstrated to be a sensitive objective measure of clinical disease activity, with a strong correlation to DAS28 (CRP). Changes in Vectra DA score are also an objective measure of changes in disease activity, showing a significant correlation to changes in DAS28 (CRP).

3.6.1.2 Analysis of Pharmacodynamic Endpoint(s)

The same MMRM analysis as for DAS28 (CRP) will be repeated with Vectra DA change from baseline at each post-baseline visit as the dependent variable. The analysis will only include the on-treatment assessments.

Plots of Vectra DA and its component biomarkers will be presented with study day on the x-axis and result on the y-axis. The mean with standard error bars will be plotted by dose. If appropriate, the y-axis will be presented with log-spacing.

3.7 Safety Analyses

3.7.1 Adverse Events and Serious Adverse Events

Adverse events (AEs) will be coded by MedDRA version 18.0 or higher and the type incidence, severity and relationship to study investigational product will be summarized. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. All treatment-emergent AEs will be summarized overall, as well as categorized by MedDRA System Organ Class and Preferred Term. The placebo subjects from each cohort will be combined for the summaries.

3.7.2 Adverse Events of Special Interest

The following adverse events of special interest (AESIs) have been defined in the protocol:

- Thromboembolic events / bleeding events
- Hepatic function abnormality (meeting the definition of Hy's Law [HL])
- Acute and delayed hypersensitivity reactions including anaphylaxis, immune complex disease and infusion-related reactions
- Infections including serious and opportunistic infections (includes reactivation of latent viral infection [varicella zoster/herpes simplex virus, Epstein-Barr virus/ cytomegalovirus] and tuberculosis)

The AESIs will be identified by medical review of the AEs prior to unblinding the study. All treatment emergent AESIs will be summarized by special interest category and preferred term.

3.7.3 Deaths and Treatment Discontinuations due to Adverse Events

Deaths and treatment discontinuation due to AEs will be summarized and listed by treatment group.

3.7.4 Clinical Laboratory Evaluation

Serum chemistry, hematology, coagulation and urinalysis parameters will be collected in this study, analyzed by central laboratory and will be used to investigate the safety of MED4920.

For continuous variables of laboratory tests, all data at baseline and at each scheduled visit will be summarized by treatment group using descriptive statistics. Changes from baseline to each scheduled time point of post-dose will also be summarized using descriptive statistics. For categorical variables of laboratory tests, the frequency and percentage in each category of the item at baseline and at each scheduled visit of post-dose will be presented for each treatment group.

Boxplots of each laboratory variable by study visit will be presented for each treatment group. The boxplots will contain all the data. The boxes will extend to the limits of the interquartile range and the whiskers will extend to the most extreme observation within 1.5 times the interquartile range from the nearest quartile. The data will be plotted on a logarithmic scale when it improves interpretability of the plot. Reference lines will be included on the boxplots for the limits of the normal range.

Laboratory results will also be summarized by Common Terminology Criteria for Adverse Events (CTCAE) grade by visit for the parameters included in Table 3.7.4-1.

Table 3.7.4-1 CTC grades

Lab parameter	Toxicity grade	Lab values
White blood cell count (10^9/L)	Grade 0	≥ LLN
	Grade 1	≥ 3 - <LLN
	Grade 2	≥ 2 - <3
	Grade 3	≥ 1 - <2
	Grade 4	<1
Platelets (10^9/L)	Grade 0	≥ LLN
	Grade 1	≥ 75 - <LLN
	Grade 2	≥ 50 - <75
	Grade 3	≥ 25 - <50

Table 3.7.4-1 CTC grades

Lab parameter	Toxicity grade	Lab values
	Grade 4	<25
Lymphocytes (10^9/L)	Grade 0	≥ LLN
	Grade 1	≥ 0.8 - <LLN
	Grade 2	≥ 0.5 - <0.8
	Grade 3	≥ 0.2 - <0.5
	Grade 4	<0.2
Neutrophils (10^9/L)	Grade 0	≥ LLN
	Grade 1	≥ 1.5 - <LLN
	Grade 2	≥ 1.0 - <1.5
	Grade 3	≥ 0.5 - <1.0
	Grade 4	<0.5
ALT (IU/L)	Grade 0	≤ ULN
	Grade 1	> ULN - ≤3*ULN
	Grade 2	> 3*ULN - ≤5*ULN
	Grade 3	> 5*ULN - <20*ULN
	Grade 4	>20*ULN
AST (IU/L)	Grade 0	≤ ULN
	Grade 1	> ULN - ≤3*ULN
	Grade 2	> 3*ULN - ≤5*ULN
	Grade 3	> 5*ULN - <20*ULN
	Grade 4	>20*ULN
Bilirubin (umol/L)	Grade 0	≤ ULN
	Grade 1	> ULN - ≤1.5*ULN
	Grade 2	> 1.5*ULN - ≤3*ULN
	Grade 3	> 3*ULN - <10*ULN
	Grade 4	>10*ULN

3.7.5 Other Safety Evaluations

3.7.5.1 Vital Signs

Vital sign results will be summarized with descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) at each time point. The changes from baseline will also be summarized with descriptive statistics by post-baseline visit.

3.7.5.2 Electrocardiogram

The overall interpretation of the ECG results (Normal; Abnormal, not Clinically Significant; and Abnormal, Clinically Significant) will be summarized using frequency count and percentages by visit and treatment groups.

3.8 Immunogenicity

The anti-drug antibody (ADA) results will be summarized by the number and percentage of subjects positive for ADA at baseline and positive at any post-baseline visit. The incidence rate of persistent positive and transient positive will also be presented. Persistent positive and transient positive are defined as follows:

- Persistent positive is defined as positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment
- Transient positive is defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at ≥ 2 post-baseline assessments (with < 16 weeks between first and last positive)

3.9 Pharmacokinetics

Descriptive statistics of MEDI4920 serum concentrations by treatment group and visit will be provided. Mean and individual serum MEDI4920 concentration-time profiles by treatment group will be plotted. The PK components of the CSR will be generated and reported by MedImmune's Clinical Pharmacology & DMPK group. Separately from the CSR, population PK modeling may be performed and reported, and potential correlation between PK exposure and pharmacodynamic biomarker, efficacy/safety response may be evaluated.

4 INTERIM ANALYSIS

No interim analyses will be performed.

The primary analysis will be performed when all subjects in Cohort 3 have completed the Day 85 assessments or have been withdrawn from the study. The primary analysis will include all assessments on the subjects prior to the data cut-off for the primary analysis.

If a fourth cohort is required, the data will be analyzed when all subjects in the fourth cohort have completed the Day 85 assessments or have been withdrawn from the study.

The final analysis on the subjects will be performed when all subjects have completed the safety follow-up.

5 REFERENCES

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