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Statistical Analysis Plan Approval

Date: 26Oct2017
To: Study File
From: [redacted]
Re: Statistical Analysis Plan Approval for Study D3461C00003

The Statistical Analysis Plan, version 2.0, for Study D3461C00003(CD-IA-MEDI-546-1145) has been reviewed and approved.

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Statistical Analysis Plan

A Phase 2, Open-label Extension Study to Evaluate the Long-term Safety of MEDI-546 in Adults with Systemic Lupus Erythematosus

Protocol Number: CD-IA-MEDI-546-1145

TABLE OF CONTENTS

List of Abbreviations

Abbreviation or Specialized Term	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate transaminase
AZDD	Astra Zeneca Drug Dictionary
BMI	body mass index
ECG	Electrocardiogram
ENA	extractable nuclear antigen
HRQL	health related quality of life
IFN	Interferon
IM	Immunogenicity
IV	Intravenous
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PCS	Physical Component Summary
PD	Pharmacodynamic
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SF-36v2	Short-Form-36 version 2
SID	subject identification
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index - 2000
SLICC	Systemic Lupus International Collaborating Clinics Index
SPP	statistical programming plan
TELVC	treatment-emergent laboratory/vital signs changes
ULN	upper limit of normal

1 INTRODUCTION

This document describes the statistical methodology for CD-IA-MEDI-546-1145 (CD1145), a Phase 2, open-label extension (OLE) study to evaluate the long-term safety of MEDI-546 (anifrolumab) in adults with systemic lupus erythematosus (SLE). Some background information and an overview of the study design are provided in Section 2. Section 3 and onwards of the document details the statistical summaries relating to each study objective as well as describing general conventions and definitions. A separate statistical programming plan (SPP), containing table templates and specifications, would be created to be used in conjunction with this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

The primary objective of this study is to evaluate the long-term safety and tolerability of intravenous (IV) anifrolumab in adult subjects with moderately-to-severely active SLE.

2.1.2 Secondary Study Objectives

The secondary objective of this study is to evaluate the immunogenicity (IM) of anifrolumab.

2.1.3 Exploratory Study Objectives

[redacted]

2.2 Study Design

This is an open-label, multinational, multicenter study to evaluate the long-term safety and tolerability of anifrolumab in adult subjects with chronic, moderately-to-severely active SLE who were previously treated with investigational product (anifrolumab 300 mg, 1000 mg, or placebo) and completed study CD-IA-MEDI-546-1013 (CD1013) through treatment (48 weeks dosing) and follow-up (85 days) periods. The start of this OLE study (first dose) should occur within 28 days of the last visit of study CD1013 or at the discretion of the medical monitor if the start of this OLE study occurs outside the 28-day window.

Approximately 240 subjects will be enrolled to receive IV anifrolumab as a 1000 mg fixed dose administered over at least 30 minutes every 4 weeks starting at Day 1 (Week 0) for up to 3 years or until the sponsor discontinues development of anifrolumab for SLE, whichever

comes first. The dose was changed to 300 mg on 12Feb2015 (protocol amendment 4) as the efficacy and safety data from study CD1013 indicated that the 300 mg dose had a more favorable benefit:risk profile than the 1000 mg dose. All subjects will be followed for 85 days after receiving their last dose of anifrolumab.

2.3 Treatment Assignment and Blinding

Each subject who meets the eligibility criteria will be assigned open-label anifrolumab using an interactive voice/web response system. This study is not blinded.

2.4 Sample Size

Sample size estimation is based on the number of subjects who have completed the treatment period of study CD1013. A total of 307 subjects have been randomized in study CD1013. Assuming that 20% of subjects will be lost to follow up or discontinue from study CD1013, there will be a total of approximately 240 subjects who will be eligible for this long-term safety study.

3 STATISTICAL METHODS

3.1 General Considerations

Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Data will be provided in data listings sorted by treatment group and subject identification (SID) number.

Baseline will be defined as the last non-missing observation on or before Day 1 prior to investigational product administration of study CD1145.

3.1.1 Analysis windows

Analysis visit windows will be used for all scheduled assessments to map longitudinal observations to scheduled visits and thereby allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless otherwise specified, all longitudinal efficacy and safety data analyses will be based on the analysis visit windows. The analysis visit windows will be calculated by bisecting the interval between adjacent scheduled visit days and will be specified in the SPP.

The actual assessment day will be mapped to the windows defined for each scheduled study visit with following rules:

- 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.

3.2 Analysis Populations

3.2.1 Definition of Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
As-treated population	Subjects who receive any study investigational product in the OLE study will be included in the as-treated population.

All analyses will be performed on the As-treated population unless otherwise specified.

3.2.2 Treatment Groups for Analysis

Treatment group is Anifrolumab Total for all analyses except the exposure adjusted adverse event which will be summarized by Anifrolumab 300 mg, Anifrolumab 1000mg, and Anifrolumab Total.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

The number of subjects enrolled in the CD1145 study will be summarized overall and by site number. In addition, disposition of subjects throughout the CD1145 study with respect to completion of treatment will be provided overall and overtime (year 1, year 2, year 3). Disposition of subjects with respect to completion of study will also be provided.

3.3.2 Demographics and Baseline Characteristics

Demographics including age in years at Day 1 of CD1145 study, gender, ethnicity, race, weight, height, and body mass index (BMI) will be summarized. A summary of baseline disease characteristics may include, but not be limited to baseline Systemic Lupus Erythematosus Disease Activity Index - 2000 (SLEDAI-2K) score, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Index (SLICC/ACR) damage index score, baseline corticosteroids and other immunosuppressives use, anti-dsDNA

(positive, negative), C3 (normal, abnormal), C4 (normal, abnormal), antinuclear antibody (ANA) status (positive, negative), and 4-gene type I IFN diagnostic (high, low).

3.3.3 Study Drug Exposure

The number of doses received (300 mg, 1000 mg, and total) and the amount of study drug given in mg will be summarized. For a particular subject, the total anifrolumab exposure will be defined as the sum of study drug (mg) received from all administrations.

3.3.4 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD). Non-immunomodulatory medications and immunomodulatory medications used during the study will be summarized by the Anatomical Therapeutic Chemical (ATC) Class level 1 and Preferred Term.

3.4 Exploratory Efficacy Endpoints and Analyses

[redacted]

3.4.4 Handling of Dropouts and Missing Data

If one or some components of SLEDAI-2K are missing, then the last observation carried forward (LOCF) approach will be used to impute the missing component score. No imputation will be performed for missing data in other variables.

[redacted]

3.5 Patient Reported Outcomes

3.5.1 Short Form-36 Version 2 (SF-36v2)

Impact on HRQL will be assessed using the SF-36v2. The SF-36v2 consists of 36 items. These 36 items yield 8 domains of functional health and well-being. These domains include Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The 8 domains can further be combined to provide 2 summary measures: 1) Physical Component Summary (PCS); and 2) Mental Component Summary (MCS). The range of SF-36v2 score and scales is 0-100, with a higher score indicating better HRQL.

The PCS, MCS, and domain scores of 8 domains as well as their change from baseline will be summarized by visit.

3.6 Pharmacodynamic Endpoint and Analyses

3.6.1 Type I IFN Signature

The 21-gene type I IFN signature in whole blood will be used as a PD marker. The gene signature and the neutralization levels will be summarized by visit. Subgroup analysis of 21-gene type I IFN signature will be performed based on ADA status (positive vs negative).

3.7 Other Additional Analyses

3.7.1 Immunology Profile

The ANA and extractable nuclear antigen (ENA) (RNP, Sm, SSA, SSB) results will be summarized by visit for the subjects with abnormal value at baseline. The shift from baseline in ANA and ENA will be summarized by visit.

The quantitative immunoglobulins levels as well as their changes from baseline will be summarized by visit.

3.8 Safety Analyses

3.8.1 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 adverse events 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 acute AEs are defined as events that occur within a 24 hour period after dosing. The acute AEs will be summarized.

The treatment-emergent non-serious AEs will also be summarized.

3.8.2 Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI) is one of scientific and medical concern specific to understanding of the investigational product. The AESIs will be summarized. AESIs for this protocol include:

- Hepatic Function Abnormality which are defined as any increase in alanine transaminase (ALT) or aspartate transaminase (AST) to greater than 3 × upper limit of normal (ULN) and concurrent increase in bilirubin to greater than 2 × ULN
- New or Reactivated Tuberculosis Infection
- Herpes Zoster Infection
- Malignancy
- Infusion, Hypersensitivity, and Anaphylactic Reactions
- Vasculitis

3.8.3 Deaths and Treatment Discontinuations due to Adverse Events

Deaths and AEs leading to treatment discontinuation will be summarized and listed.

3.8.4 Exposure Adjusted Adverse Events Rate

The exposure adjusted rate (per 100 patient-year) for treatment emergent AEs, non-serious AEs, acute AEs, investigational product related AEs, AEs by highest severity, AEs leading to treatment discontinuation, AEs resulting in death, SAEs and AESIs will be summarized. The exposure adjusted subject rate per 100 patient-years is defined as [the number of subjects with an event/(total exposure time in days/365.25)]*100.

For treatment emergent AEs leading to treatment discontinuation, AEs resulting in death, SAEs and AESIs, duration of exposure is calculated as follows:

- Anifrolumab Total group: duration of exposure (days) = minimum(end of study date in CD1145, last dosing date in CD1145+85 days) – first dosing date in CD1145+1.

- Anifrolumab 1000 mg group:
    - For subjects who received 1000 mg only during the study: duration of exposure (days) = minimum(end of study date in CD1145, last dosing date in CD1145+85 days) – first dosing date in CD1145+1.
    - For subjects who received both 1000 mg and 300 mg during the study: duration of exposure (days) = (first dosing date of 300 mg – 1) – first dosing date in CD1145 + 1.
- Anifrolumab 300 mg group: duration of exposure (days) = minimum(end of study date in CD1145, last dosing date in CD1145+85 days) – first dosing date of 300 mg +1.

The AEs leading to treatment discontinuation, AEs resulting in death, SAEs and AESIs occurred during the exposure period will be included in the summary.

The non-serious AEs are captured during the first year of subject's participation only. So for treatment emergent AEs, non-serious AEs, acute AEs, investigational product related AEs, and AEs by highest severity, duration of exposure is calculated as follows:

- Anifrolumab Total group: duration of exposure (days) = minimum(end of study date in CD1145, first dosing date in CD1145+364) – first dosing date in CD1145+1.
- Anifrolumab 1000 mg group:
    - For subjects who received 1000 mg only during the study: duration of exposure (days) = minimum(end of study date in CD1145, first dosing date in CD1145+364) – first dosing date in CD1145+1.
    - For subjects who received both 1000 mg and 300 mg during the study: duration of exposure (days) = minimum(first dosing date in CD1145+364, first dosing date of 300 mg-1) – first dosing date in CD1145 + 1.
- Anifrolumab 300 mg group: minimum(end of study date in CD1145, first dosing date in CD1145+364) - first dosing date of 300 mg +1.

The events occurred during the exposure period will be included in the summary.

3.8.5 Clinical Laboratory Evaluation

Hematology, serum chemistry, lipid profile (HDL, LDL, cholesterol, and triglycerides), and urinalysis parameters will be collected in this study. The hematology, serum chemistry, and lipid profile parameters as well as their changes from baseline will be summarized with descriptive statistics by visit. The shift from baseline in hematology, serum chemistry, lipid profile, and urinalysis parameters will be summarized by visit.

Treatment-emergent laboratory/vital signs changes (TELVC) will be defined for post-baseline values according to the reference ranges given in **Appendix E**. Number of subjects with TELVC will be summarized by visit.

3.8.6 Other Safety Evaluations

3.8.6.1 Vital Signs

Vital sign results, as well as changes from baseline, will be summarized with descriptive statistics by visit. Treatment-emergent laboratory/vital signs changes (TELVC) will be defined for post-baseline values according to the reference ranges given in **Appendix F**. Number of subjects with TELVC will be summarized by visit.

For dosing visits, only measurements prior to dosing will be considered for by-visit presentations. In the case of multiple measurements prior to dosing, the first measurement will be used for by-visit presentations, but all measurements will be considered for the TELVC classification.

3.8.6.2 Electrocardiogram

The investigator or qualified designee will review and indicate if the ECG is normal or abnormal. ECG results and shift from baseline will be summarized by visit.

3.8.6.3 Cushingoid features

Cushingoid features results will be summarized by visit.

3.8.7 Subgroup Analyses

The treatment emergent AEs and SAEs will be summarized by 4-gene IFN signature (IFN high vs IFN low) and ADA status (positive vs negative).

3.9 Immunogenicity

The IM results will be analyzed by summarizing the number and percentage of subjects who develop positive ADA. A descriptive summary of actual ADA titers by visit will also be provided.

3.10 Pharmacokinetics

The PK components of the clinical study report will be generated and reported by MedImmune's Clinical Pharmacology & DMPK group.

4 INTERIM ANALYSIS

No interim analysis will be performed for the CD1145 study.

5 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	08Apr2013	Initial document	Initial document
2.0	26Oct2017	• Layout changed • Coding dictionary for medications is changed to WHO Drug Dictionary from AZ-DD	• New SAP template • To be consistent with phase 3 studies.

6 APPENDIX

Appendix E

REFERENCE RANGES AND TELVC FOR LABORATORY VALUES

Parameter	Unit	Low value	Low decrease	High value	High increase
Haematology					
Haemoglobin	g/L	≤6	NA	≥20	NA
		≤7 and decrease from BL ≥1.5			
Haematocrit	V/V	≤0.18	NA	≥0.64	NA
		≤0.21 and decrease from BL ≥15%			
WBC	10E9/L	≤2, <1	NA	≥20	NA
Neutrophils	10E9/L	<0.5	NA	≥20	NA
		<1.0 and decrease from BL ≥0.5			
Lymphocyte	10E9/L	≤0.5, ≤0.25	NA	≥10.0	NA
Monocytes	10E9/L	NA	NA	≥1.4, ≥5.0	NA
Eosinophils	10E9/L	NA	NA	≥1.5, ≥5.0	NA
Basophils	10E9/L	NA	NA	≥1.0, ≥2.0	NA
Platelet Count	10E9/L	≤20		≥600	NA
		≤50 and decrease from BL ≥25			
INR		NA	NA	≥4.5	NA
Biochemistry					
ALT	IU/L	NA	NA	≥3 x ULN, ≥5 x ULN	NA
AST	IU/L	NA	NA	≥3 x ULN, ≥5 x ULN	NA
ALP	IU/L	NA	NA	≥3 x ULN	NA
CK	IU/L	NA	NA	≥500, ≥2000	NA
GGT	IU/L	NA	NA	≥5 x ULN	NA
Total Bilirubin	µmol/L	NA	NA	≥2 x ULN	NA

Parameter	Unit	Low value	Low decrease	High value	High increase
Albumin	g/L	≤20	NA	≥100	NA
		≤25 and decrease from BL ≥10		≥70 and increase from BL ≥10	
BUN	mmol/L	NA	NA	≥18	NA
Creatinine	umol/L	NA	NA	≥140, ≥190	NA
Sodium	mmol/L	≤132	NA	≥152	NA
Potassium	mmol/L	≤3	NA	≥5.5	NA
Chloride	mmol/L	≤90	NA	≥120	NA
Fasting Glucose	mmol/L	≤2.5	NA	≥7.0, ≥11.1	NA
Total Cholesterol	mmol/L	NA	NA	≥7.25	NA
Urinalysis					
Urine protein/ creatinine ratio	g/mmol	NA	NA	≥0.395	NA
Fasting lipid profile					
HDL	mmol/L	≤0.8	NA	NA	NA
LDL	mmol/L	NA	NA	≥5.2	NA
Triglycerides	mmol/L	NA	NA	≥3.6, ≥5.4	NA

Appendix F

REFERENCE RANGES AND TELVC FOR VITAL SIGNS

Parameter	Unit	Low value	Low decrease	High value	High increase
Pulse	Beats per minute	≤50	NA	≥120	NA
		≤50 and decrease from BL ≥20		≥120 and increase from BL ≥20	
Systolic blood pressure	mmHg	≤90	NA	≥160	NA
		≤90 and decrease from BL ≥20		≥160 and increase from BL ≥20	
Diastolic blood pressure	mmHg	≤50	NA	≥100	NA
		≤50 and decrease from BL ≥10		≥100 and increase from BL ≥10	