Statistical Analysis Plan

A Phase 2a, Randomized, Placebo-controlled, Proof of Mechanism Study to Evaluate the Safety and Efficacy of AMG557/MEDI5872 in Subjects with Primary Sjogren's Syndrome

Protocol Number: D5181C00001

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AECG	American-European Consensus Group
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-14}	area under the curve from Days 0 to 14
AUC_{0-168}	area under the curve from Days 0 to 168
AUC_{last}	area under the curve at last time point
BLQ	below limit of quantification
C_{max}	observed maximum concentration
CI	confidence interval
CSR	clinical study report
CV	coefficient of variation
DNA	deoxyribonucleic acid
EBAP	exploratory biomarker analysis plan
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
ESSDAI	European League Against Rheumatism Sjogren's Syndrome Disease Activity Index
ESSPRI	European League Against Rheumatism Sjogren's Syndrome Patient Reported Index
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICOS	inducible T-cell costimulator

Abbreviation or Specialized Term	Definition
Ig	Immunoglobulin
IgG	immunoglobulin G
IgG2	immunoglobulin G2
IgM	immunoglobulin M
IL	Interleukin
ITT	intent-to-treat
IV	Intravenous
IVRS	interactive voice response system
K_m	Michaelis-Menten constant
LLQ	Lower Limit of Quantification
mAb	monoclonal antibody
MCS	mental component score
MDGA	Physician Global Assessment of Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
PB	plasma blast
PC	plasma cell
PCS	physical component score
PD	pharmacodynamics
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
PROF	Profile of Fatigue
PROFAD-SSI-SF	Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form
pSS	primary Sjogren's syndrome
Q2W	every 2 weeks
QW	every week
RF	rheumatoid factor
SAE	serious adverse events
SC	subcutaneous
SD	standard deviation
SF-36v2	Short Form-36 version 2
SGA	Subject Global Assessment of Disease Activity
SID	subject identification
SS	Sjogren's syndrome
sSS	secondary Sjogren's syndrome
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFH	T follicular helper
t_{max}	time to maximum concentration

Abbreviation or Specialized Term	Definition
ULN	upper limit of normal
V_{max}	maximum metabolic rate

1 INTRODUCTION

This document describes the statistical analysis for protocol D5181C00001, a randomized, placebo-controlled, proof of mechanism study to evaluate the safety and efficacy of MEDI5872 in subjects with primary Sjogren's syndrome (pSS).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

To evaluate the effect of AMG557/MEDI5872 compared to placebo in reducing objective measures of overall disease activity in subjects with pSS.

2.1.2 Secondary Study Objectives

1. To evaluate the effect of AMG557/MEDI5872 compared to placebo on peripheral blood and salivary gland biomarkers in subjects with pSS.
2. To evaluate the safety and tolerability of multiple subcutaneous (SC) doses of AMG557/MEDI5872 in subjects with pSS.
3. To evaluate the effect of AMG557/MEDI5872 compared to placebo in reducing subjective measures of overall disease activity.

2.1.3 Exploratory Study Objectives

1. To evaluate the effect of AMG557/MEDI5872 compared to placebo on individual clinical and laboratory components of pSS.
2. To evaluate the effect of AMG557/MEDI5872 compared to placebo on specific subjective symptoms of pSS.
3. To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of AMG557/MEDI5872.

2.2 Study Design

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the clinical and biologic efficacy, as well as the safety of SC doses of AMG557/MEDI5872 in adult subjects with pSS. The study will be conducted at approximately 10 sites in Europe and North America. A total of 42 subjects will be randomized in a 1:1 ratio to receive a fixed SC dose of 210 mg MEDI5872 (n = 21) or placebo (n = 21) every week (QW) for 3 weeks (Days 1 to 15) and then every 2 weeks (Q2W) for 9 weeks (Days 29 to 85). Beginning on Day 99, all subjects (n = 42) will receive a

fixed SC dose of 210 mg AMG557/MEDI5872 QW (Days 99 to 113) and Q2W (Days 127 to 183) for an additional 12 weeks.

On Day 106, subjects who had received placebo will receive a blinded dose of AMG557/MEDI5872, and subjects who received AMG557/MEDI5872 will receive a blinded dose of placebo (as these subjects would have already achieved steady-state levels of AMG557/MEDI5872).

Randomization will be stratified by screening cellular immunophenotyping abnormalities (elevated T follicular helper [TFH] cells or elevated plasma blast/plasma cell [PB/PC] vs normal values for both parameters).

Subjects will receive investigational product on Days 1, 8, 15, 29, 43, 57, 71, 85, 99, 106, 113, 127, 141, 155, 169, and 183 during the active treatment period. Subjects will return to the study site on Days 197, 225, 253, and 296 during the safety follow-up period.

The study flow diagram is shown in Figure 2.1.31.

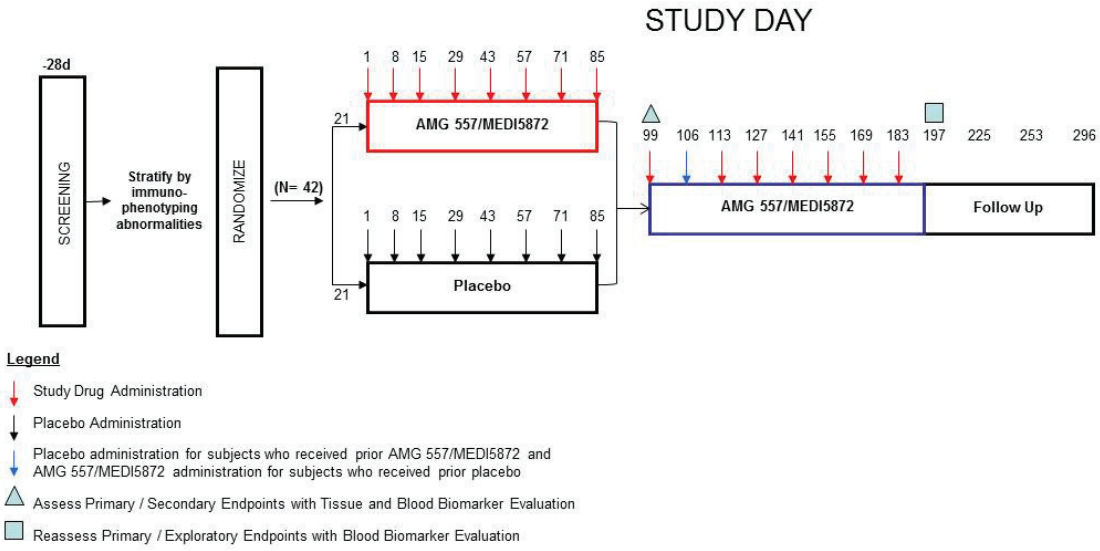

Figure 2.1.31 Study Flow Diagram

d = day; N = number of subjects

2.3 Treatment Assignment and Blinding

2.3.1 Randomization

An interactive voice/web response system (IVRS/IWRS) will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. Subjects will be randomized at a 1:1 ratio to receive either AMG557/MEDI5872 or placebo. Randomization will be stratified by screening cellular immunophenotyping abnormalities (elevated TFH or elevated PB/PC vs normal values for both parameters).

2.3.2 Blinding and Planned Analyses

This is a double-blind study in which AMG557/MEDI5872 and placebo are identically labeled and indistinguishable in appearance. As such, neither the subject/legal representative nor any of the investigator staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received. In addition, sponsor staff will also be blinded up until the time of the primary analysis.

The primary analysis will be performed when all subjects have completed Day 99 or have withdrawn from the study. The primary analysis will include all assessments on the subjects prior to the data cut-off (date of last Day 99/early withdrawal visit) for the primary analysis. The Sponsor staff will be unblinded at the primary analysis (after Day 99). Results from the primary analysis may be shared with investigators and presented at public conferences. Investigators will not be made aware of unblinded treatment assignments for individual subjects ongoing in the open-label phase or follow-up phase of the study, until these subjects have completed the study.

The final analysis will be performed when all subjects have completed the open-label phase and safety follow-up or have withdrawn from the study

2.4 Sample Size

The planned sample size of 42 subjects (21 subjects per arm) will provide 80% power to detect a difference in mean change in European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) of 4 (assumed standard deviation (SD) of 5; Moerman et al, 2014, Meiners et al, 2012) between two randomized groups at a two-sided 0.1 level of statistical significance by using two sample t-test. This sample size also provides about 80% power to detect 30% relative reduction in plasma cells (PC) from tissue under assumption of coefficient of variation (CV) of 0.5. The sample size was calculated by using nQuery Advisor 7.0.

3 STATISTICAL METHODS

3.1 General Considerations

Unless stated otherwise, baseline will be defined as the last assessment prior to dosing.

Unless stated otherwise, data from the screening visits will not be included in the summary tables but will be listed.

Subjects who prematurely discontinue treatment with investigational product will complete an 'End of Treatment' assessment at the time of discontinuation. Unless stated otherwise, data from the 'End of Treatment' assessment will not be separately summarized but will be slotted to the closest study visit as described in Section 3.4. All 'End of Treatment' results will appear in the listings.

Unless stated otherwise, descriptive summaries of continuous variables will include the number of observations, mean, SD, and the median, minimum and maximum values. Summaries of categorical variables will include the number and percentage of subjects in each category.

When last observation carried forward (LOCF) is used to impute for missing post-baseline data, only post-baseline data will be carried forward (i.e. baseline data will not be carried forward).

All statistical tests will be two-sided at an alpha = 0.1 significance level unless stated otherwise.

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

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	All subjects who are randomized and treated with investigational product. Subjects will be analyzed according to the initial randomization.
As-treated population	All subjects who receive any investigational product. Subjects will be analyzed according to the actual treatment received.

Table 3.2-1 Analysis Populations

Population	Description
Open Label As-treated population	All subjects in the As-treated population who enter the open label phase (defined in Section 3.3) of the study. Subjects will be analyzed according to the actual treatment received.
Any Medi5872 population	All subjects who had at least one dose of MEDI5872 treatment (in any phase of the study). Subjects will be analyzed according to the actual treatment received.

3.3 Study Phases, Analysis and Reporting Plan

This study comprises a double-blind, placebo-controlled phase, a MEDI5872 open-label phase, and a safety follow-up phase. For reporting purposes, the phases are defined as follows:

Placebo-controlled phase: All assessments from the date and time of the first dose through to pre-dose at Visit 10 (Day 99), or date of withdrawal if this occurs sooner.

MEDI5872 Open-label and Follow-Up phase: All visits from post dose at Visit 10 (Day 99) through to end of study Visit 21 (Day 296) or date of withdrawal if this occurs sooner.

The following datasets will be used for analysis and reporting:

Primary Analysis Dataset: This dataset comprises data from the Placebo-controlled phase of the study. It includes data for all subjects from screening and baseline, and all assessments from the date and time of the first dose through to pre-dose at Visit 10 (Day 99), (or date of withdrawal if this occurs sooner).

Final Analysis Dataset: This dataset comprises data from the whole study. It includes data for all subjects from screening and baseline, and all assessments from the date and time of the first dose through to end of study, (or date of withdrawal if this occurs sooner).

At the Primary Analysis, all analyses will be based on the Primary Analysis Dataset. The ITT population will be used for the efficacy analyses, and the 'As-Treated' population will be used for safety analyses.

At the Final Analysis, the efficacy analyses will be based on the Final Analysis Dataset using the ITT population. Safety Analyses will use the Final Analysis Dataset, sub-setting on data from the Medi5872 Open-Label and Follow-Up Phase. The 'Open- Label As- Treated' Population will be used for these analyses. Additional safety analyses will also be produced

based on the Final Analysis dataset using the 'Any Medi5872' population, as indicated in Section 3.10.1.

3.4 Visit Windows

Visit windows will be used for all scheduled assessments (lab data, vital signs, efficacy, PD, patient reported outcomes data and other additional analyses).

To allow for unscheduled and discontinuation assessments the data will be summarized using the assessment (whether reported as a scheduled or unscheduled visit) closest to the nominal visit date, calculated from the first day of dosing. The visit result will be missing if no assessment was reported within the specified visit window around the scheduled date. If two assessments are equidistant from a scheduled visit, the one with the earlier date (and/or time, as applicable) will be used.

The visit windows will be calculated by bisecting the scheduled visit assessments. 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 Day 2. The upper limit of each window will be the mean of the two adjacent planned study days, rounded down to the nearest integer.

Note, when slotting visits to the Day 99 window, this should only occur for assessments prior to the **date and time** of the nominal Day 99 dose. Assessments after this **time** should be slotted to the following visit window. This applies for all data types except for vital signs.

Special note for Vital Signs: For vital signs there are pre and post-dose assessments at the Day 99 visit. In this case, the post-dose assessments on the day of the nominal Day 99 dose should be summarized with the Day 99 data. In other words, when slotting visits to the Day 99 window for vital signs, this should only occur for assessments up to and including those on the **date** of the nominal Day 99 dose. Assessments after this **date** should be slotted to the following visit window.

Here is an example for laboratory data:

Table 3.4-1 Visit windows for hematology and serum chemistry

Nominal study day	Visit window
Screening	Day -28 to Day -1
1	All assessments prior to the start of study treatment
15	Day 2 – 22
29	Day 23 - 43
57	Day 44 - Day 78
99	Day 79- date and time of the dose at Visit 10 (nominal Day 99)
113	After the date and time of the dose at Visit 10 (nominal Day 99)- Day 120
127	Day 121- Day 141
155	Day 142 – Day 176
197	Day 177 – Day 211
225	Day 212 – Day 239
253	Day 240- Day 274
296	Day 275 +

Consider the following example:

Subject ID 5678 attends the nominal Day 99 visit on actual study day 97. They have an unscheduled assessment on actual Day 100. They attend for the nominal Day 113 visit on actual Day 112. For lab data, all results up to pre-dose on Day 97 get slotted to the Day 99 visit. All results post-dose on Day 97 (including the unscheduled visit on Day 100, even though it is closer to Day 99) would be slotted to the Day 113 visit. The results closest to the nominal day within these windows are then used in the summary tables, i.e Day 97 is used for Nominal Day 99 and Day 112 is used for nominal Day 113.

Here is an example for vital signs data:

Table 3.4-2 Visit windows for vital signs

Nominal study day	Visit window
Screening	Day -28 to Day -1
1	Day 1
8	Day 2- Day 11
15	Day 12 – Day 22
29	Day 23 – Day 36
43	Day 37- Day 50
57	Day 51 - Day 64
71	Day 65- Day 78
85	Day 79- Day 92
99	Day 92- up to and including the date of Visit 10 (nominal Day 99)

Table 3.4-2 Visit windows for vital signs

Nominal study day	Visit window
106	After the date of Visit 10 (nominal Day 99) up to and including Day 109
113	Day 110- Day 120
127	Day 121- Day 134
141	Day 135- Day 148
155	Day 149 – Day 162
169	Day 163- Day 176
183	Day 177- Day 190
197	Day 191 – Day 211
225	Day 212 – Day 239
253	Day 240- Day 274
296	Day 275 +

Consider the following example:

Subject ID 5678 attends the nominal Day 99 visit on actual study day 97. They have an unscheduled assessment on actual Day 100. They attend for the nominal Day 113 visit on actual Day 112. For vital signs data, all results on Day 97 get slotted to the Day 99 visit. All results after Day 97 (including the unscheduled visit on Day 100, even though it is closer to Day 99) would be slotted to the Day 113 visit. The results closest to the nominal day within these windows are then used in the summary tables, i.e Day 97 is used for Nominal Day 99 and Day 112 is used for nominal Day 113.

3.5 Study Subjects

3.5.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization, as well as treatment 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 the placebo controlled phase, completion of treatment, and completion of follow-up will be provided. A subject will be considered to have completed the placebo-controlled phase if they are still in the study (have not been withdrawn or lost to follow up) and complete visit 10 (Day 99).

A summary of analysis populations by treatment group, including an overall total for each population, will be produced.

A summary of subjects randomized by country and site by treatment group including an overall total for each country/site, will be provided.

3.5.2 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. This table will be produced for the 'As Treated' and ITT populations.

A summary of baseline disease characteristics, by treatment group, for the ITT population will include

- Number and percentage of subjects with elevated peripheral blood TFH at screening,
- Number and percentage of subjects with elevated peripheral blood PB/PC at screening,
- Number and percentage of subjects with elevated peripheral blood TFH or PB/PC at screening (either or both elevated vs neither elevated),
- Summary of baseline peripheral blood TFH and PB/PC,
- Summary of duration of disease at baseline,
- where Duration of disease (yrs) = [date of first dose – date of diagnosis + 1]/365.25
- Summary of baseline ESSDAI score,
- Number and percentage of subjects with ESSDAI > 10 at baseline
- Summary of baseline ESSPRI score,
- Number and percentage of subjects with ANA ≥1:40 at baseline
- Number and percentage of subjects with abnormal Schirmer's test (without anesthetic) at baseline
  - where a subject is considered to have an abnormal result if the score is less than or equal to 5mm in at least one eye
- Summary of Schirmer's test (without anesthetic) at baseline
  - The summary will be for the average of the result in the left and right eyes
- Number and percentage of subjects with abnormal van Bijstervelt score at baseline
  - where a subject is considered to have an abnormal result if the score is greater than or equal to 4 in at least one eye.
- Summary of van Bijsterfeld score at baseline
  - The summary will be for the average of the result in the left and right eyes
- Summary of stimulated salivary flow at baseline,
- Summary of Focus Score (minor salivary gland biopsy)
- Number and percentage of subjects positive at baseline for anti-SS-A,
- Number and percentage of subjects positive at baseline for anti-SS-B,

- Summary of baseline auto-antibody levels: IgG RF, IgM RF and IgA RF.
- Summary of serum IgG level at baseline

A total column will be included in the table.

3.5.3 Investigational Product Exposure

The summary of investigational product exposure will include descriptive statistics for the total number of doses received, cumulative number of doses received, duration of exposure and total subject years exposure. This summary will be produced for the placebo-controlled phase (through day 99) and for the overall study (through day 197). The summary for the overall study will additionally include a column for 'MEDI5782 at any time'. This column will include exposure data from the subjects who were randomized to Placebo but who received Medi5872 during the open label phase, in addition to data from the subjects randomized to Medi5872. The summaries will be produced for the ITT and 'As Treated' populations.

The complete investigational product administration information including dosing date, dosing time and reason for incomplete dosing will be displayed in a by-subject listing classified by treatment group.

3.5.4 Concomitant Medications

All prior and concomitant medications will be summarized by treatment for the ITT population.

A listing of subjects who took one or more prohibited concomitant medications will be produced. A list of preferred terms for the prohibited medications will be provided by Clinical Development prior to DBL.

3.6 Efficacy Analyses

3.6.1 Primary Efficacy Endpoint(s) and Analyses

3.6.1.1 Primary Efficacy Endpoint(s)

The ESSDAI is a validated consensus disease activity index that is able to capture changes in the severity of systemic manifestations of pSS, with 12 domains, with associated weights as shown in Table 3.6.1.1-1.

Table 3.6.1.1-1 ESSDAI Domains, Weights and Activity Levels

Domain	Weight	Activity Levels
Constitutional	3	0-2
Lymphadenopathy	4	0-3
Glandular	2	0-2
Articular	2	0-3
Cutaneous	3	0-3
Pulmonary	5	0-3
Renal	5	0-3
Muscular	6	0-3
Peripheral Nervous System	5	0-3
Central Nervous System	5	0,2,3
Hematological	2	0-3
Biological	1	0-2

The theoretical range of values for the ESSDAI is 0 to 123, with the final score being calculated as follows:

Final Score = Sum of all 12 domain scores
Domain score = Activity level × Domain weight

For example, the domain score for the Muscular domain, with a domain weight of 6 and levels of activity ranging from 0 to 3 (where ‘0’ indicates ‘no activity’, ‘1’ indicates ‘low activity’, ‘2’ indicated ‘moderate activity’, and ‘3’ indicates ‘high activity’) can range between 0 and 18.

Higher ESSDAI scores indicate more severe disease.

ESSDAI is collected at screening, Day 1, 29, 57, 99, 127, 155, 197, 225, 253,296 and End of Treatment.

3.6.1.2 Handling of Dropouts and Missing Data

For the primary analysis through the end of the placebo-controlled period (Day 99), missing data will be imputed using the LOCF approach. This will be applied first to missing domain scores, and, in the event that all domain scores are missing, to the final ESSDAI score. For example, consider a subject with the following pattern of domain scores and missing data:

Domain	Visit 3	Visit 4	Visit 5 and future visits
Constitutional	3	3	Missing
Lymphadenopathy	0	0	Missing
Glandular	2	4	Missing
Articular	0	Missing (0 imputed)	Missing
Cutaneous	0	0	Missing
Pulmonary	0	0	Missing
Renal	0	0	Missing
Muscular	6	Missing (6 imputed)	Missing
Peripheral Nervous System	0	0	Missing
Central Nervous System	0	0	Missing
Hematological	0	0	Missing
Biological	1	0	Missing
ESSDAI Final Score (LOCF analysis)	**12**	**13**	**13 (imputed)**

For the analysis of change in ESSDAI over time (using a longitudinal mixed effects model), no imputation will be performed for missing data. If any ESSDAI domain scores are missing, the final score will also be considered missing in this analysis.

3.6.1.3 Primary Efficacy Analysis

Changes in ESSDAI score from baseline to Day 99 will be analysed using an analysis of covariance (ANCOVA). ESSDAI score at baseline will be included as a covariate, with strata (PC and/or TFH elevated vs neither elevated) and treatment group included in the model as factors. The model may be expressed as below:

Change from baseline in ESSDAI = Intercept + Baseline ESSDAI+ Strata + Treatment

From the model, estimates of the LSMeans for each treatment group will be obtained, together with the associated standard errors (SE). Additionally, an estimate of the difference in LSMeans (MEDI5872 – placebo) will be obtained, together with a two-sided 90% confidence interval, SE and p-value). The significance of treatment effect will be tested by

using a two-sided test at significance level α of 0.1. The analysis will be conducted using the ITT Population with the LOCF approach for missing data as discussed in Section 3.6.1.2.

To assess the validity of the model assumptions, residual plots will be produced (not for inclusion in the clinical study report [CSR]) and inspected by the statistician. In the event that substantial departures from the model assumptions are found, alternative appropriate analyses will be performed, for example ANCOVA using log transformed ratio (Day 99:baseline), or non-parametric methods.

3.6.1.4 Additional Analyses of the Primary Efficacy Endpoint(s)

To assess the effect of MEDI5872 on changes in ESSDAI over time, a longitudinal mixed effects analysis of variance model will be fitted for the change from baseline in ESSDAI, for the ITT population using the observed data only, i.e. no imputation for missing values, as described in Section 3.6.1.2. At the Primary Analysis, all visits up to and including Day 99 will be included in the model. At the Final Analysis, all visits up to and including Day 296 will be included in the model. Only the results from the analysis with all visits will be included in the CSR.

The model will include fixed effects for baseline ESSDAI, strata (PC and/or TFH elevated vs neither elevated), visit, treatment and the *baseline by visit* and treatment by visit interactions. The following covariance matrix structures to describe the correlations between observations on a subject between visits will be considered: unstructured, auto-regressive, and compound symmetry. The selection of the covariance matrix structure for the primary analysis will be the one that gives the lowest value for the Akaike Information Criteria (AIC). For subsequent analyses, the same structure that was used for the primary analysis will be used, unless there are issues with model fit, in which case the AIC will be used to determine the most appropriate structure. The model may be expressed as below:

Change from baseline in ESSDAI = Intercept + Baseline ESSDAI + Strata +
Treatment + Visit + *Baseline*Visit* + Treatment*Visit

Note: The Baseline*Visit interaction is included in the model to avoid potential over or under-correction, should the influence of baseline differ across visits. However, this term may be dropped from the model in the event that there are difficulties with model fit, or to make more degrees of freedom available for estimation of residual variability, if there does not appear to be evidence that the influence of baseline differs over visits. A decision on whether to exclude this interaction term will be made by the statistician, upon review of the output from the full model.

From the model, estimates of the LSMeans for each treatment group at each visit will be obtained, together with the associated SEs. Additionally, an estimate of the difference in LSMeans (MEDI5872 – placebo) will be obtained at each visit, together with a two-sided 90% CI, SE and p-value. The LSMeans (±SE) for each treatment group will be plotted, for each visit.

In the event that a transformation of the endpoint (e.g. a log transformation) was required for the primary analysis (Section 3.6.1.3), the same transformation will be applied for this repeated measures analysis, and the results will be back transformed to the original scale.

ESSDAI final score and change from baseline in ESSDAI final score will be summarized descriptively by treatment and visit for the ITT population. A by-treatment listing will also be produced.

3.6.1.5 Subgroup Analyses

Two subgroup analyses of the primary endpoint are planned.

(1) Elevated TFH and/or PC/PB at screening vs both parameters normal at screening

(2) (Baseline ESSDAI >=Median) vs (Baseline ESSDAI < Median)

A table will be produced showing the amount of overlap between these subgroups.

For each subgroup analysis, the ANCOVA model described for the primary analysis at Day 99 will be fitted with the addition of the treatment*subgroup interaction. From the model, estimates of the LSMeans for each treatment within each subgroup will be obtained, together with the associated standard errors (SE). Additionally, an estimate of the difference in LSMeans (MEDI5872 – placebo) will be obtained within each subgroup, together with a two-sided 90% confidence interval and SE). The p value for the interaction of treatment with subgroup will be reported.

3.6.2 Secondary Efficacy Endpoint(s) and Analyses

3.6.2.1 ESSDAI Responders

A subject is considered to be an ESSDAI[3] responder if they achieve a reduction of 3 points or more in ESSDAI score, do not prematurely discontinue IP, and do not receive prohibited concomitant medications.

A subject is considered to be an ESSDAI[4] responder if they achieve a reduction of 4 points or more in ESSDAI score, do not prematurely discontinue IP, and do not receive prohibited concomitant medications.

3.6.2.2 Analysis of ESSDAI Responders

The number and proportion of ESSDAI[3] and ESSDAI[4] responders will be summarized by treatment and visit. The proportion of MEDI5872 and placebo subjects with an ESSDAI[3] and ESSDAI[4] response at Day 99 will be compared using Fisher's Exact test.

3.6.2.3 ESSDAI Domains

ESSDAI Domains are described in section 3.6.1.1.

3.6.2.4 Analysis of ESSDAI Domains

A bar chart will be produced showing the proportion of subjects in each treatment group who had a reduction of at least 1 point in activity level for each of the separate domains of the ESSDAI at Day 99. For each domain, subjects will only be included if they had activity in that domain at baseline.

3.7 Patient-reported Outcomes

3.7.1 Change from Baseline in European League Against Rheumatism Sjogren's Syndrome Patient Reported Index (ESSPRI)

Change from baseline to Day 99 in ESSPRI is a secondary endpoint. ESSPRI is collected at Days 1, 29, 57, 99, 127, 155, 197, 225, 253, 296, and End of Treatment. The ESSPRI is a 3-item, subject-completed assessment of SS symptoms. The instrument captures subject-rated severity of **dryness**, **fatigue**, and **pain** using 0-10 numeric rating scales anchored as no symptom (0) and maximal imaginable symptom (10). The recall period is stated in each question as "the last 2 weeks." The ESSPRI total score is the mean of the 3 items and is calculated as follows:

ESSPRI Total Score = (Dryness + Fatigue + Pain) / 3

A subject will be considered an ESSPRI responder if they have at least a 1 point or >=15% reduction in their ESSPRI score from baseline, do not prematurely discontinue IP, and do not receive prohibited concomitant medications.

3.7.2 Analysis of Assessments Obtained from European League Against Rheumatism Sjogren's Syndrome Patient Reported Index (ESSPRI)

Change in ESSPRI score from baseline will be summarized descriptively by treatment and visit, for the ITT population. Change in ESSPRI score and in each of the ESSPRI domains from baseline to Day 99 will be compared between MEDI5872 and placebo groups using ANCOVA. Missing values for Day 99 ESSPRI will be imputed using the LOCF approach. Where an individual component score is missing, LOCF will be applied for that component before calculation of the total score as described for the primary endpoint (see Section 3.6.1.2).

To assess the effect of MEDI5872 on changes in ESSPRI and each ESSPRI domain over time, a longitudinal mixed effects analysis of variance model will be fitted. The LSMeans (± SE) for each treatment will be plotted, for each visit. For this analysis, no imputation will be performed; the analysis will be based on observed case.
The details of these analyses will be the same as those described for the primary endpoint in Section 3.6.1.3 and Section 3.6.1.4, except that the baseline term will be replaced with the relevant baseline ESSPRI (overall score or domain score).

The number and proportion of ESSPRI responders will be summarized by treatment and visit. The proportion of MEDI5872 and placebo subjects with an ESSPRI response at Day 99 will be compared using Fisher's Exact test.

3.7.3 Subject Global Assessment of Disease Activity (SGA)

The Subject Global Assessment of Disease Activity (SGA) is a single-item question which asks subjects to consider how their illness affects them and report on how they have felt over the last 7 days. Responses range from 0 (very well) to 100 (very poor) on a 100-mm visual analogue scale. The SGA is completed at Day 1, 29, 57, 99, 127, 155, 197, 225, 253, 296 and End of Treatment.

For the analysis of SGA over time, no imputation will be performed; the analysis will be based on observed case.

3.7.4 Analysis of Subject Global Assessment of Disease Activity

Change from baseline in SGA score will be summarized descriptively by treatment and time point, for the ITT population. To assess the effect of MEDI5872 on changes in SGA over time, a longitudinal mixed effects analysis of variance model will be fitted, as described for

the primary endpoint in Section 3.6.1.4, except that the baseline term will be replaced with the baseline SGA. The LSMeans (± SE) for each treatment over time will be plotted.

3.7.5 Short Form 36 Version 2

The Short Form 36 version 2 (SF-36v2 [acute recall]) is a 36-item, subject-completed, general health status assessment. The instrument captures information regarding 8 health domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The SF-36v2 provides scores for each domain, as well as two psychometrically-based summary scores: physical component score (PCS) and mental component score (MCS). The SF-36v2 will be scored according to Version 3.0 of the scoring algorithm (2009). Medimmune will provide the SF-36v2 data from the CRF to a vendor who will run the scoring algorithm and then provide the derived scores back to MedImmune.

The SF-36v2 is completed at Day 1, 29, 57, 99, 127, 155, 197, 225, 253, 296, and End of Treatment.

For the analysis of SF36v2 scores over time, no imputation will be performed, the analysis will be based on observed case.

3.7.6 Analysis of Short Form 36 Version 2

Change in the following SF-36v2 scores from baseline will be summarized descriptively by treatment and time point, for the ITT population:

- Change from baseline in PCS
- Change from baseline in MCS
- Change from baseline in SF-36v2 domain scores

To assess the effect of MEDI5872 on changes in SF36v2 scores over time, a longitudinal mixed effects analysis of variance model will be fitted, as described for the primary endpoint in Section 3.6.1.4, except that the baseline term will be replaced with the relevant baseline SF-36 (component or domain score). The LSMeans (± SE) for each treatment over time will be plotted.

A radar plot (spidergram) will be produced for the SF-36 domains at Day 99 for the overall population and for ESSDAI responders. Both treatment groups will be shown on the same plot.

3.7.7 Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form

The PROFAD-SSI-SF is a 19-item, subject-completed assessment of symptoms associated with pSS (Bowman et al, 2009). The instrument captures information on 8 domains of symptoms: somatic fatigue, mental fatigue, arthralgia, vascular dysfunction, oral dryness, ocular dryness, cutaneous and vaginal dryness. Each symptom domain is comprised of one or more "facets". Patient-reported severity in the past 2 weeks is captured using an 8-point (0 [no/not] to 7 [as bad as imaginable]) scale.

The domain scores are calculated as follows (see also Appendix 1 for further details):

Somatic Fatigue = Item 1 + Item 2 + Item 3 + Item 4 (range 0-28)

Mental Fatigue = Item 5 + Item 6 (Range 0-14)

Arthralgia = Item 7 (Range 0-7)

Vascular Dysfunction = Item 8 + Item 9 (Range 0-14)

Cutaneous Dryness = Item 10 (Range 0-7)

Vaginal Dryness = Item 11 (Range 0-7) [This item is for females only]

Ocular Dryness = Item 12 + Item 13 + Item 14 (range 0-21)

Oral Dryness = Item 15 + Item 16 + Item 17 + Item 18 + Item 19 (range 0-35)

Additionally, the Profile of fatigue (PROF) score and the Profile of Fatigue and Discomfort (PROFAD) scores will be calculated as follows:

PROF score = Somatic Fatigue + Mental Fatigue

PROFAD score = PROF score + Arthralgia score + vascular dysfunction score

The PROFAD-Sicca Symptoms Inventory-Short Form (SSI-SF) is completed at Day 1, 29, 57, 99, 127, 155, 197, 225, 253, 296, and End of Treatment. Where an individual item score is missing, LOCF will be applied for that item before calculation of the domain score, as described for the primary endpoint (see Section 3.6.1.2).

For the analysis of scores over time, if an entire domain or PROF or PROFAD score is missing, no imputation will be performed; the analysis will be based on observed case.

3.7.8 Analysis of Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form

Change in the PROFAD-SSI-SF domain scores from baseline will be summarized descriptively by treatment and visit, for the ITT population:

- Change in somatic fatigue domain from baseline
- Change in mental fatigue domain from baseline
- Change in arthralgia domain from baseline
- Change in vascular dysfunction domain from baseline
- Change in cutaneous dryness domain from baseline
- Change in vaginal dryness domain from baseline (female subjects only)
- Change in ocular dryness domain from baseline
- Change in oral dryness domain from baseline
- Change in PROF score from baseline
- Change in PROFAD score from baseline

To assess the effect of MEDI5872 on changes in PROFAD-SSI-SF domains over time, a longitudinal mixed effects analysis of variance model will be fitted, as described for the primary endpoint in Section 3.6.1.4, except that the baseline term will be replaced with the relevant baseline PROFAD-SSI-SF score. The LSMeans (± SE) for each treatment over time will be plotted.

A radar plot (spidergram) will be produced for the PROFAD domains at Day 99 for the overall population and for ESSDAI responders. Both treatment groups will be shown on the same plot.

3.7.9 Patient Global Impression of Change (PGI-C)

The Patient Global Impression of Change (PGI-C) is a single item designed to capture the subject's perception of change in their overall symptom severity from randomization until the time of completion. Change in severity is captured using a 7-point scale. The PGI-C is completed at Day 1, 29, 99, 197, 296 and End of Treatment.

3.7.10 Analysis of Patient Global Impression of Change

The number and percentage of subjects with each PGI-C score will be summarized by treatment and time point, for the ITT population. The proportion of MEDI5872 and placebo

subjects with improvement at Day 99 will be compared using a Fisher's Exact test, based on observed case data. Improvement is defined as a score of 'Much better' or 'Moderately better'.

3.7.11 Patient Global Impression of Severity (PGI-S)

The Patient Global Impression of Severity (PGI-S) is a single item designed to capture the subject's perception of overall symptom severity at the time of completion on a 5-point categorical response scale. The PGI-S is completed at Day 1, 29, 99, 197, 296, and End of Treatment.

3.7.12 Analysis of Patient Global Impression of Severity

Descriptive statistics for each visit where a PGI-S assessment is completed will be calculated for each treatment, for the ITT population for observed case data.

3.8 Pharmacodynamic Endpoint(s) and Analyses

3.8.1 Peripheral Blood Biomarkers

The following peripheral blood biomarkers are secondary endpoints:

- Change in PC levels (including PB levels) from baseline to Day 99
- Change in TFH from baseline to Day 99

Results will be provided both as a % and as a count of cells/µL:

ENDPOINT	LBTEST	LBORRESU
Plasma Cells (%)	PBPC_CD27+CD38++_T4_%	%
Plasma Cells (count)	PBPC_CD27+CD38++_T4_COUNT	cells/uL
TFH (%)	TFH_ICOS+PD1+_T6_%CD4	%
TFH (count)	TFH_ICOS+PD1+_T6_COUNT	cells/uL

Samples are collected at screening, Day 1, 29, 57, 99, 127, 155, 197, 296 and End of Treatment.

Values that are BLQ will be imputed with a value = 0.5 * LLQ. In the event of many values BLQ, alternative analysis methods may be considered.

For the ANCOVA analysis through the end of the placebo-controlled period (Day 99), missing data for the peripheral blood biomarker endpoints will be imputed using the LOCF approach.

For the repeated measures analysis of biomarkers over time, no imputation will be performed; the analysis will be based on observed case.

3.8.2 Analysis of Peripheral Blood Biomarkers

The peripheral blood biomarker endpoints and their ratio to baseline will be summarized descriptively by treatment and visit for the ITT population. The summary statistics will include number of observations, mean, SD, median, minimum, maximum, geometric mean, SD (log scale) and % CV. A by-treatment listing will also be produced.

Changes in peripheral blood biomarkers from baseline to Day 99 will be compared between MEDI5872 group and placebo group using an ANCOVA. Since the data are likely to be skewed, the dependent variable in the analysis will be the log(Value at Day 99/ Value at Baseline). The log(Value at Baseline), strata (PC and/or TFH elevated vs neither elevated) and treatment group will be included in the model. The model may be expressed as below:

$$\text{Log(Biomarker at Day 99/Biomarker at baseline)} = \text{Intercept} + \text{Log(Baseline Biomarker)} + \text{Strata} + \text{Treatment}$$

From the model, estimates of the LSMeans for each treatment will be obtained, together with the associated SEs. Additionally, an estimate of the difference in LSmeans (MEDI5872 – placebo) will be obtained, together with a two-sided 90% CI, SE and p-value). These estimates will then be back-transformed to provide the geometric means and their ratio, with associated CI. The significance of treatment effect will be tested by using a two-sided test at significance level α of 0.1. The analysis will be conducted using the ITT Population with the LOCF approach for missing data as discussed in Section 3.8.1.

To assess the validity of the model assumptions, residual plots will be produced (not for inclusion in the CSR) and inspected by the statistician. In the event that substantial departures from the model assumptions are found, alternative appropriate analyses will be performed.

To assess the effect of MEDI5872 on changes in peripheral blood biomarkers over time, a longitudinal mixed effects analysis of variance model will be fitted to the log(Value at Visit / Value at Baseline), for the ITT population using the observed data only, i.e. no imputation for missing values. At the Primary Analysis, all visits up to and including Day 99 will be

included in the model. At the Final Analysis, all visits up to and including Day 296 will be included in the model. Only the results from the analysis with all visits will be included in the CSR. The model will include fixed effects for log(baseline), strata, visit, treatment and the *baseline by visit* and treatment by visit interactions. The same covariance structure that was used for the primary analysis will be used, unless there are issues with model fit, in which case the AIC will be used to determine the most appropriate structure from unstructured, autoregressive or compound symmetry.. The models may be expressed as

Log(Biomarker at visit/Biomarker at baseline) = Intercept + Log(Baseline Biomarker) + Strata + Treatment + Visit + *Baseline*Visit* +Treatment*Visit

Note: The Baseline*Visit interaction is included in the model to avoid potential over or under-correction should the influence of baseline differ across visits. However, this term may be dropped from the model in the event that there are difficulties with model fit, or to make more degrees of freedom available for estimation of residual variability if there does not appear to be evidence that the influence of baseline differs over visits. A decision on whether to exclude this interaction term will be made by the statistician.

From the model, estimates of the LSMeans for each treatment at each visit will be obtained, together with the associated SEs and 90% CI. Additionally, an estimate of the difference in LSmeans (MEDI5872 – placebo) will be obtained at each visit, together with a two-sided 90% CI, SE and p-value. These estimates will then be back-transformed to provide the geometric means and their ratio, with associated CI. The geometric LSMeans (± 90% CI) for each treatment will be plotted, for each visit.

3.8.3 Minor Salivary Gland Biopsy Biomarkers

The following minor salivary gland biopsy biomarkers are secondary endpoints:

- Change in Focus Score from baseline to Day 99.
- Change in total PC levels (count/mm^2) from baseline to Day 99
- Change in CD4/ICOS TFH cells (count/mm^2) from baseline to Day 99
- Change in PD-1/ICOS TFH Cells (count/mm^2) from baseline to Day 99

The following minor salivary gland biopsy biomarkers are exploratory endpoints:

- Change in CD3 T Cells (count/mm^2) from baseline to Day 99

- Change in CD20 B Cells (count/mm^2) from baseline to Day 99
- Change in IgG Plasma Cells (count/mm^2) from baseline to Day 99
- Change in IgG Plasma Cells (% of total plasma cells) from baseline to Day 99
- Change in IgA Plasma Cells (count/mm^2) from baseline to Day 99
- Change in IgA Plasma Cells (% of total plasma cells) from baseline to Day 99
- Change in IgM Plasma Cells (count/mm^2) from baseline to Day 99
- Change in IgM Plasma Cells (% of total plasma cells) from baseline to Day 99

Biopsies are performed at screening and Day 99 only. The screening value will be used as the baseline value.

Values that are BLQ will be imputed with a value = 0.5 * LLQ. In the event of many values BLQ, alternative analysis methods may be considered.

3.8.4 Analysis of Minor Salivary Gland Biopsy Biomarkers

The secondary and exploratory minor salivary gland biomarker endpoints at baseline and Day 99 will be summarized descriptively by treatment for the ITT population. The summary statistics will include number of observations, mean, SD, median, minimum, maximum, geometric mean, SD (log scale) and % CV. A by-treatment listing will also be produced.

The secondary minor salivary gland endpoints (change from baseline to Day 99) will be analyzed using ANCOVA in a similar way to the peripheral blood biomarkers as described in Section3.8.2. The model may be expressed as:

Log(Value at Day 99/Value at baseline) = Intercept + Log(Baseline) + Strata + Treatment.

The analysis will be conducted using the ITT Population with the LOCF approach for missing data as discussed in Section 3.8.1.

3.8.5 Other Pharmacodynamic Endpoints

The following biomarkers are exploratory endpoints:

Peripheral blood

- Change in PB from baseline to Day 99

Minor Salivary Gland Tissue

- Change in PB from baseline to Day 99

These exploratory biomarker endpoints will not be presented in the CSR and the analyses are out of scope for this Statistical Analysis Plan (SAP). The analyses of these endpoints will be described in the exploratory biomarker analysis plan (EBAP).

3.9 Other Additional Analyses

3.9.1 Oral evaluation - Salivary Flow

Measurements of unstimulated and stimulated salivary flow are made on Day 1, 29, 57, 99, 127, 155, 197, 225, 253, 296 and End of Treatment. Results will be summarized descriptively by treatment group and time point. A listing will be produced.

Separately for each of unstimulated and stimulated salivary flow, a longitudinal mixed effects analysis of variance model will be fitted, as described for the primary endpoint in Section 3.6.1.4. The LSMeans (± SE) for each treatment over time will be plotted.

3.9.2 Ophthalmological evaluation

Schirmer's test (without anesthetic), tear break up time and van Bijsterfeld score will be performed at Day 1, 99, 197 and End of Treatment. For each test, the average of the result in the right and left eye will be derived. If results are only available for one eye then that result will be used. Results will be summarized descriptively by punctal plug use at baseline (yes or no), treatment group and time point, for the ITT population. Where subjects have a change in punctal plug use during the study, only data where the punctal plug use is the same as at baseline will be included in the summary. All data will be listed.

3.9.3 Physician Global Assessment of Disease Activity

Physician Global assessment will be collected at screening, Day 1, 29, 57, 99, 127,155,197, 225,253, 296 and End of Treatment. Results will be summarized descriptively by treatment and time point, for the ITT population, and the data will be listed.

3.9.4 Autoantibodies

Samples for anti-SS-A and anti-SS-B are collected at screening, Day 1, 29, 57, 99, 127, 155, 197, 296 and End of Treatment. Change from baseline will be summarized descriptively by treatment and time point. The data will be listed.

To assess the effect of MEDI5872 on changes in autoantibodies over time, a longitudinal mixed effects analysis of variance model will be fitted, as described for the primary endpoint in Section 3.6.1.4. The LSMeans (± SE) for each treatment over time will be plotted.

3.9.5 Inflammatory Markers

Samples for the inflammatory markers immunoglobulin levels (IgA, IgG, IgM), beta-2-microglobulin, complements C3, C4, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are collected at screening, Day 1, 99, 197, 296 and End of Treatment. IgA, IgG, IgM, ESR and CRP will be log-transformed prior to analysis. Change from (or Ratio to, for IgA, IgG, IgM, ESR and CRP) baseline in each marker will be summarized descriptively by treatment and time point, for the ITT population. The data will be listed.

To assess the effect of MEDI5872 on changes in inflammatory markers at Day 99, an analysis of variance model will be fitted, as described for the primary endpoint in Section3.6.1.3 The LSMeans (± SE) for each treatment will be plotted. IgA, IgG, IgM, ESR and CRP will be log-transformed prior to analysis and the results back-transformed to the original scale.

3.9.6 IgG, IgM and IgA Rheumatoid Factor

Samples for IgG, IgM and IgA RF are collected at screening, Day 1, 29, 57, 99, 127, 155, 197, 296 and End of Treatment. Ratio to baseline will be summarized descriptively by treatment and time point, for the ITT population. The summary statistics will include number of observations, mean, SD, median, minimum, maximum, geometric mean, SD (log scale) and % CV. The data will be listed.

To assess the effect of MEDI5872 on changes in IgG, IgM and IgA RF over time, a longitudinal mixed effects analysis of variance model will be fitted to log (value at visit/ value at baseline), as described for in Section 3.8.2. The Geometric LSMeans (± 90% CI) for each treatment over time will be plotted.

A boxplot of IgG ratio to baseline at Day 99 will be produced.

3.9.7 28-Joint Count

28-Joint count is collected at screening, Day 1, 29, 57, 99, 127, 155, 197, 225, 253, 296 and End of Treatment. Change from baseline in painful, tender and swollen joint count will be be summarized descriptively by treatment and visit, for the ITT population. The data will be listed.

3.10 Safety Analyses

3.10.1 Adverse Events and Serious Adverse Events

Adverse events (AEs) will be coded by Medical Dictionary for Regulatory activities (MedDRA) and the incidence, severity and relationship to study investigational product will be summarized by system organ class and preferred term. 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.

Treatment emergent adverse events (TEAE)will be presented in the following summaries, for the 'As Treated' population:

	Primary Analysis, As-Treated Population	Final Analysis, Open- label As-Treated Population (MEDI5872 Open-label and Follow-Up phase)	Final Analysis, 'Any Medi5872' Population
Overall summary of adverse events	X	X	X
Number of subjects with treatment emergent adverse events by System Organ Class and Preferred term	X	X	X
Number of subjects with treatment emergent adverse events by highest severity	X		
Number of subjects with treatment emergent adverse events sorted by frequency in the MEDI5872 treatment arm	X		
Number of Subjects with investigational product related Treatment Emergent Adverse Events	X		

Number of subjects with investigational product related treatment emergent adverse events by highest severity	X		
Number of Subjects with Treatment Emergent Serious Adverse Events	X	X	X
Number of Subjects with investigational product related Treatment Emergent Serious Adverse Events	X		
Number of Subjects with Adverse Events Resulting in Permanent Discontinuation of investigational product	X		
Number of Subjects with Adverse Events Resulting Interruption of investigational product	X		
Number of Subjects with treatment emergent adverse events by System Organ Class and Preferred term (ADA positive subjects only)	X	X	X

Treatment-emergent and non-treatment emergent adverse events will be listed. Additionally, serious treatment-emergent and serious non-treatment emergent adverse events will be listed.

3.10.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) include: liver injury (DILI, Hy's law), new or reactivated tuberculosis (TB) infection, malignancy, and hypersensitivity including anaphylaxis. AESIs are indicated by a code list on the eCRF page.

Treatment emergent adverse events of special interest will be presented in the following summaries, for the 'As Treated' population:

Output	Primary Analysis, As-Treated Population	Final Analysis, Open- label As-Treated Population (MEDI5872 Open-label and Follow-Up phase)	Final Analysis, 'Any Medi5872' Population
Number of subjects with treatment emergent adverse events of special interest.	X	X	X
Number of subjects with treatment emergent adverse events of special interest by highest severity.	X		

Adverse events of special interest will be listed for each subject together with additional information collected about the AE as recorded on the case report form (CRF).

3.10.3 Deaths and Treatment Discontinuations due to Adverse Events

A listing of all AEs leading to death, and a listing of all AEs leading to permanent discontinuation of investigational product, will be produced.

3.10.4 Clinical Laboratory Evaluation

Hematology, urinalysis, and serum chemistry laboratory evaluations will be conducted at screening and on Days 1, 15, 29, 57, 99, 113, 127, 155, 197, 225, 253, 296 and End of Treatment. Coagulation parameters are collected at Day 1, 99, 197, 296 and End of Treatment.

The hematology, coagulation, urinalysis, and serum chemistry parameters will be summarized with descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) at each visit. The changes from baseline in hematology, and serum chemistry will be summarized with descriptive statistics by post-baseline visit, for the 'As Treated' population. Additionally, tables showing the number of subjects with grade 3 or 4 toxicity in each lab parameter will be produced, for the Placebo Controlled phase and the Medi5872 Open-Label phase.

For laboratory values reported as lower than the limit of quantification (LLQ), a value equal to half of the limit of quantification will be imputed in the summaries. However, all laboratory measurements will be included in the by-subject listings as reported without value or visit imputations.

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.

3.10.5 Other Safety Evaluations

3.10.5.1 Vital Signs

Vital signs (tympanic temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure) will be measured at every visit. Vital signs will be measured at multiple time points on dose administration days. These time points will also be included in the by-visit analyses. All vital signs data will be listed.

The vital signs measurements as well as their changes from baseline will be summarized with descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) by treatment, visit and time point, for the ‘As Treated’ population.

Boxplots of each vital signs 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.

3.10.5.2 Electrocardiogram

Twelve-lead ECGs will be conducted at screening, Day 197, 296 and End of Treatment. ECG results in the study will be summarized descriptively by visit, for the ‘As Treated’ population. ECG results will be listed.

3.10.5.3 Weight

Weight will be measured at screening, Days 29, 57, 99, 127, 155, 197, 225, 253, 296 and End of Treatment. The absolute value and change from baseline will be summarized with descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) by visit, for the ‘As Treated’ population.

3.11 Immunogenicity

Immunogenicity of MEDI5872 will be assessed on Study Days 1, 29, 57, 99, 127, 197, 296 and End of Treatment. The number and percentage of subjects in each treatment group showing an immunological response to MEDI5872 will be summarized by study visit, for the 'As Treated' population. In the summary, all post-dose immunogenicity results will also be summarized under "Any Visit" category. A subject will be counted as having detectable antibodies at "Any Visit", if the subject has detectable antibodies at any post-dose visit. The subject will be counted as not having detectable antibodies at "Any Visit" if all post-dose immunogenicity assessments have no MEDI5872 antibody. The subject will be counted as having a missing result at "Any Visit" if all post-dose results for the given test for the subject are missing or if the subject has at least one missing post-dose result for the given test and the remaining results are normal.

For those with a positive post-baseline assessment the percentage who were persistent positive and transient positive will also be presented.

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).

All valid assay results from subjects who receive any investigational product will be included in immunogenicity summaries. Visit windows will be applied (see Section 3.4). All assay results will be shown in a by-subject listing.

3.12 Pharmacokinetics

PK blood draws will be taken on Days 1, 8, 15, 29, 57, 99, 106, 113, 127, 155, 197, 225, 253, 296 and End of Treatment. MEDI5872 serum concentrations will be reported. Concentration values will be derived for subjects allocated to the MEDI5872 210mg group and also for subjects allocated to the Placebo group during the period in which they received MEDI5872 210mg.

MEDI5872 serum trough concentrations will be summarized by treatment group at each time point using descriptive statistics (number of subjects, mean, geometric mean, SD, CV, median, minimum and maximum). Serum trough concentrations at each visit will be displayed in a boxplot, provided there are sufficient quantifiable concentrations to do this.

The BLQ observations will be changed to zero for mean concentration calculation. However, if the calculated mean is less than the assay LLQ, the mean value will be set to BLQ. Missing observations will be excluded from the mean calculation and PK data analysis. It is anticipated that the PK assay may yield some outlier concentration values. The outlier concentrations will be identified by the visual examination of individual PK profiles. An effort will be made to reanalyze the sample and/or to assess the potential impact of immunogenicity response on PK. However, if the cause of an outlier observation remains unidentified and the inclusion of the outlier has a profound impact on the mean profile, the outlier observation will be excluded from PK data analysis. The exclusion of the outliers will be documented in the clinical PK report. All serum concentration measurements will be displayed in by-subject listings by visit as recorded (no imputations).

The PK data will be analyzed over the 'As Treated' population defined earlier in Section 3.2. The PK analyses will be conducted by Amgen's Clinical Pharmacology, Modelling and Simulation group and the results will be reported by MedImmune.

4 INTERIM ANALYSIS

The primary analysis will be performed when all subjects have completed the Day 99 assessment, i.e. at the end of the double-blind placebo-controlled phase. The primary analysis will include all assessments on the subjects prior to the data cut-off for the primary analysis.

The final analysis will be performed when all subjects have completed the open-label phase and safety follow-up.

5 REFERENCES

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Bowman SJ, Hamburger J, Richards A, Barry RJ, Rauz S. Patient-reported outcomes in primary Sjogren's syndrome: comparison of the long and short versions of the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory. Rheumatology (Oxford). 2009 Feb;48(2):140-3.

6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	05JAN2015	Initial document	Initial document
2.0	25MAY2015	• Throughout the document, assessments at Day 281 are now Day 296	• Protocol Amendment
		• Throughout the document, Per Protocol population has been removed	• Considering the overall small sample size, this analysis would not add value.
		• Throughout the document, Chi-squared tests have been replaced by Fisher Exact tests	• Small sample size so Fisher's Exact is more appropriate test
		• Throughout the document, all ANCOVA and mixed models, the covariates screening TFH and screening PB/PC have been replaced with a factor, randomization strata (PC and or TFH elevated at screening vs neither elevated)	• Changed so that analysis model reflects the randomization
		• Section 2.3.2 some details removed	• Details are in the protocol
		• Section 3.1 – removal of specification that analyses will be run on a UNIX platform	• Change to SAS set up means that UNIX may not be used.
		• Section 3.2 – addition of populations for the Open label phase	• Improve clarification of how data from the open label phase will be reported.
		• Original Section 3.3 'Treatment groups for reporting' has been deleted	• Details are in the SPP
		• Section 3.3 'Study phases, analysis and reporting plan' has been clarified	• Addition of text regarding handling of data from the crossover to open label Medi5872
		• Section 3.4 'Visit Windows' example windows have been updated	• to reflect change of planned visit from Day 281 to Day 296
		• Section 3.5.1 removal of definition of completion of treatment and completion of study	• Details are in the SPP
		• Section 3.5.2 Baseline ANA titer, Proportion of subjects with baseline ESSDAI> 10, and summary of IgA RF added to table of baseline characteristics	• Requested by Clinical Team
		• Section 3.5.4 Listing of prohibited medications added	• To support revised definition of ESSDAI and ESSPRI responders • Clarification to aid interpretation of endpoint

		• Section 3.6.1.1 Sentence added to state that higher ESSDAI scores reflect more severe disease	• Clarification
		• Section 3.6.1.3 and 3.8.2 Clarified that if model assumptions do not hold, alternative methods will be used (instead of may)	• Clarification added since inclusion of later assessments at the Primary analysis would results in incomplete data which could result in model fit issues and/or bias.
		• Section 3.6.1.4 and 3.8.2 Clarified that at the primary analysis, only assessments up to Day 99 will be included, and at the final analysis, all assessments through Day 296 will be included	• Improves model selection.
		• Section 3.6.1.4 Changed approach to selection of covariance matrix, to be based on Akaike Information Criteria. For analyses of other endpoints, the structure used for the primary analysis will be applied.	• ESSDAI response is a secondary endpoint
		• Section 3.6.1.4 Definition and analysis of ESSDAI responders moved to Secondary efficacy analysis section	• Clarification
		• Section 3.6.1.5 Additional details of subgroup analyses have been added	• ESSDAI response definition has been changed to align with anifrolumab program. Domain plot added to aid exploration of data.
		• Section 3.6.2 .1 ESSDAI response definition has been changed, and a bar chart of ESSDAI domains has been added	• ESSPRI response definition has been changed to align with anifrolumab program.
		• Section 3.7.1 ESSPRI response definition has been added	• ESSPRI analysis added to align with anifrolumab program
		• Section 3.7.2 ESSPRI response analysis has been added	• For exploratory endpoints this analysis is superfluous, since the mixed model will provide results for the full study duration.
		• Section 3.7.3,3.7.4,3.7.5,3.7.6, 3.7.7,3.7.8, 3.7.1, the ANCOVA analysis at Day 99 has been removed	• SF-36 scoring algorithm has changed and is no longer in the public domain.
		• Section 3.7.5 Summary and domain scores will now be provided by a vendor	• Requested by Clinical team
		• Section 3.7.6 and 3.7.8 Radar plot at Day 99 has been added	• Clarification
		• Section 3.8.1 Table of peripheral blood biomarkers has been added	• Change of analysis model to reflect randomization strata so it is now appropriate to use the standard baseline definition
		• Section 3.8.1 definition of baseline has been changed, to be the last assessment prior to dosing	• Updated information available from translational sciences
		• Section 3.8.3 Clarification of secondary endpoints from salivary gland biopsy, and addition of exploratory endpoints	• Salivary flow is an exploratory endpoint and subgroup analyses are not required

		• Section 3.9.1.1 Removal of subgroup analysis of salivary flow • Section 3.9.2 Removal of Schirmer's test with anaesthetic • Sections 3.9.4, 3.9.5, 3.9.6 Addition of longitudinal mixed model analysis of autoantibodies and RF and ANCOVA for inflammatory markers • Section 3.9.5 log transform IgA, IgG and IgM • Section 3.9.6 addition of IgA RF • Section 3.9.6 addition of boxplot of IgG • Section 3.9.6 log transform data for anlaysis • Section 3.9.7 Joint count analysis added • Section 3.10.1 Removal of MedDRA version number • Section 3.10.1 addition of exposure adjusted summaries of TEAES and TESAES • Section 3.10.1 Addition of tables for Investigational Product Related Adverse Events by Highest Severity and for Adverse Events for ADA positive subjects. • Section 3.10.2 Removal of exposure adjusted analysis of AESIs • Section 3.10.4. Addition of tables of subjects with grade 3 or 4 toxicity lab values. • Section 3.10.4 Removal of scatter plots of lab values • Section 3.10.5.2 Changed ECG analyses to descriptive statistics instead of summary of normal/abnormal results • Section 3.11 Removal of derivation of PK parameters and addition of boxplots of PK concentration data. Other wording changes also incorporated. • Section 4: Some detail removed • Section 6: Version History added	• Assessment removed in protocol amendment • Requested by Clinical team to enable more thorough exploration of these endpoints • Consistency with other studied • Correction of oversight in original SAP • Requested by Clinical team • Consistency with other studies • Overlooked in original SAP • Version may change prior to the analysis taking place • To enable overall assessment of AEs for subjects who received Medi5872 at any time • Requested by Clinical Team • Low incidence of AESIs so output not required. • Requested by Clinical team • These plots are not standard and no longer required • Correction since the CRF does not collect the normal/abnormal evaluation • PK analyses are being performed by Amgen and they provided updated text for this section of the SAP. • Simplification, text not needed. • SAP template updated

Appendix 1 Profile of Fatigue and Discomfort

PROFILE OF FATIGUE AND DISCOMFORT

Please assess how bad at its worst each symptom has been in the last two weeks, by ringing one of the numbers 0 to 7.

1. The **worst** problem that I've had in the last two weeks with **needing to rest, feeling** tired, **being** exhausted **or** needing to sleep:

no need to rest at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

2. The **worst** problem that I've had in the last two weeks with it **being hard to GET going, things taking an effort** or me feeling that **'it's a battle':**

not hard to <u>get</u> going at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

3. The worst problem that I've had in the last two weeks with it being hard to KEEP going, me being easily worn out or lacking in energy:

not hard to <u>keep</u> going at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

4. The **worst** problem that I've had in the last two weeks with **lack of strength in my muscles** or feeling **weak:**

no lack of strength at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

SOMATIC FATIGUE DOMAIN = ITEM 1 + ITEM 2 + ITEM 3 + ITEM 4

5. The **worst** problem I've had in the last two weeks with **not thinking clearly** or finding it **hard to concentrate:**

no such problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

6. The **worst** problem I've had in the last two weeks with **forgetting things** or **making mistakes:**

no such problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

MENTAL FATIGUE DOMAIN = ITEM 5 + ITEM 6

7. The **worst** problem that I've had in the last two weeks with **discomfort in my limbs:** e.g. discomfort, aches or pains in your big joints (hips, knees, shoulders) or in your muscles or aching all over

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

ARTHRALGIA = ITEM 7

8. The worst problem in the last 2 weeks with discomfort or swelling of fingers or wrists:

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

9. The **worst** problem I've had in the last two weeks with **uncomfortably cold hands:**

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

VASCULAR DYSFUNCTION DOMAIN = ITEM 8 + ITEM 9

10. The **worst** problem that I've had in the last two weeks with **dry or itchy skin:**

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

CUTANEOUS DRYNESS = ITEM 10

11. The **worst** problem that I've had in the last two weeks with **vaginal dryness:** e.g. experienced discomfort during sex due to vaginal dryness

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

VAGINAL DRYNESS = ITEM 11

12. The **worst** problem that I've had in the last two weeks with **sore eyes:** e.g. eyes felt gritty, painful eyes, burning eyes, itchy eyes or irritation in eyes

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

13. The **worst** problem that I've had in the last two weeks with **eye irritation:** e.g. eyes irritated by smoky atmosphere, eyes were uncomfortable in the wind, and/or eyes were uncomfortable in air-conditioning or low-humidity places

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

14. The **worst** problem that I've had in the last two weeks with **poor vision:** (even if wearing spectacles) e.g., blurred vision, poor vision, problem with eyes limited reading, watching TV or night driving, hard to see computer screen or cash machine screen

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

OCULAR DRYNESS = ITEM 12 + ITEM 13 + ITEM 14

15. The **worst** problem that I've had in the last two weeks with **difficulties in eating:** e.g. mouth felt dry when eating, difficult to swallow foods, needed liquid to swallow food, food stuck to the mouth, needed to rinse away remains of food or have appreciated food less

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

16. The **worst** problem that I've had in the last two weeks with **dry throat or nose:** e.g. mouth felt dry when breathing, had difficulty talking with dry mouth, needed a drink to talk easily, nose felt dry, dry throat, air-conditioning dried my mouth

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

17. The **worst** problem that I've had in the last two weeks with **bad breath:** e.g. felt that your breath has smelt, saliva felt sticky

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

18. The **worst** problem in the last two weeks with **needing fluid to wet my mouth:** e.g. carried drink to bed, needed drink during the night, woke at night to pass urine, had urgent need to pass urine

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

19. The **worst** problem that I've had in the last two weeks with **other mouth problems:** e.g. mouth ulcers, swollen salivary glands, felt as though choking because of dryness, change in flavours or tastes, needed to visit the dentists

no problem at all	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	as bad as imaginable

ORAL DRYNESS = ITEM 14 + ITEM 15 + ITEM 16 + ITEM 17 + ITEM 18 + ITEM 19

SUMMARY SCORES

- DOMAINS
  - EACH DOMAIN CAN AND SHOULD BE SCORED SEPERATELY

- PROFILE OF FATIGUE SCORE (PROF) SCORE
  - SOMATIC DOMAIN + MENTAL FATIGUE DOMAIN

- PROFILE OF FATIGUE AND DISCOMFORT (PROFAD) SCORE
  - PROF (SOMATIC + MENTAL FATIGUE) + ARTHRALGIA DOMAIN + VASCULAR DYSFUNCTION DOMAIN

- SICCA SYMPTOMS INVENTORY
  - NO SUMMARY SCORE.
  - PRESENT EACH DOMAIN INDEPENDENTLY.
  - VAGINAL DRYNESS (ITEM 11) TO BE COMPLETED BY FEMALES ONLY