

## **A Phase 2a, Randomized, Placebo-controlled, Proof of Mechanism Study to Evaluate the Safety and Efficacy of AMG 557/MEDI5872 in Subjects with Primary Sjogren's Syndrome**

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## PROTOCOL SYNOPSIS

<b>TITLE</b> A Phase 2a, Randomized, Placebo-controlled, Proof of Mechanism Study to Evaluate the Safety and Efficacy of AMG 557/MEDI5872 in Subjects with Primary Sjogren's Syndrome
<b>HYPOTHESES</b> The primary hypothesis is that subjects with primary Sjogren's syndrome (pSS) treated with AMG 557/MEDI5872 will have improvement in objective measures of disease activity. The secondary hypotheses are that AMG 557/MEDI5872 will lead to a decrease in biomarkers (peripheral blood and minor salivary gland tissue), reflecting the activity of the inducible T-cell costimulator (ICOS):B7-related protein-1 (B7RP-1) pathway in subjects with pSS; that AMG 557/MEDI5872 will have an acceptable safety profile in subjects with pSS; and that subjects with pSS treated with AMG 557/MEDI5872 will have improvement in subjective measures of disease activity.
<b>OBJECTIVES</b> The primary objective is to evaluate the effect of AMG 557/MEDI5872 compared to placebo in reducing objective measures of overall disease activity in subjects with pSS. The secondary objectives are: <ul style="list-style-type: none"><li>• To evaluate the effect of AMG 557/MEDI5872 compared to placebo on peripheral blood and salivary gland biomarkers in subjects with pSS.</li><li>• To evaluate the safety and tolerability of multiple subcutaneous (SC) doses of AMG 557/MEDI5872 in subjects with pSS.</li><li>• To evaluate the effect of AMG 557/MEDI5872 compared to placebo in reducing objective and subjective measures of overall disease activity.</li></ul> The exploratory objectives are: <ul style="list-style-type: none"><li>• To evaluate the effect of AMG 557/MEDI5872 compared to placebo on individual clinical and laboratory components of pSS.</li><li>• To evaluate the effect of AMG 557/MEDI5872 compared to placebo on specific subjective symptoms of pSS.</li><li>• To evaluate the pharmacokinetics, immunogenicity, and pharmacodynamics (PD) of AMG 557/MEDI5872.</li></ul>
<b>STUDY ENDPOINTS</b> The primary endpoint of the study is the change in the European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) score from baseline to Day 99. The secondary endpoints of the study are: <ul style="list-style-type: none"><li>• Biomarkers:<ul style="list-style-type: none"><li>◦ Outcomes in peripheral blood<ul style="list-style-type: none"><li>◦ Change in plasma cell (PC) levels (including plasma blast [PB] levels) from baseline to Day 99</li><li>◦ Change in T follicular helper (TFH) levels from baseline to Day 99</li></ul></li><li>◦ Outcomes in minor salivary gland tissue<ul style="list-style-type: none"><li>◦ Change in PC levels from baseline to Day 99</li><li>◦ Change in TFH levels from baseline to Day 99</li></ul></li><li>◦ Focus score<ul style="list-style-type: none"><li>◦ Change in focus score from baseline to Day 99</li></ul></li></ul></li><li>• Safety and tolerability of multiple SC doses of AMG 557/MEDI5872 as measured by the incidence of treatment-emergent adverse events, treatment-emergent serious adverse events, adverse events of special interest, and laboratory abnormalities</li><li>• Change in European League Against Rheumatism Sjogren's Syndrome Patient Reported Index (ESSPRI) score from baseline to Day 99</li></ul>

- ESSDAI[3] and ESSDAI[4] response, defined as a decrease of at least 3[4] points from baseline in the ESSDAI at Day 99 without premature discontinuation of investigational product and without receiving prohibited concomitant medications
- The exploratory endpoints of the study are:
- Biomarkers:
    - Outcomes in peripheral blood
      - Change in PB levels from baseline to Day 99
      - Change from baseline in PC gene signature at Day 99
      - Change from baseline in TFH gene signature at Day 99
    - Outcomes in minor salivary gland tissue
      - Change in PB levels from baseline to Day 99
      - Change from baseline in PC gene signature at Day 99
      - Change from baseline in TFH gene signature at Day 99
  - All of the secondary and biomarker exploratory endpoints (except for outcomes in minor salivary gland tissue) may be assessed at other time points
  - ESSPRI response, defined as a decrease of at least 1 point or  $\geq 15\%$  from baseline in the ESSPRI at Day 99 without premature discontinuation of investigational product and without receiving prohibited concomitant medications
  - Primary Sjogren's syndrome symptoms as measured by the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form
  - Health status as measured by the Short Form-36 version 2 Health Survey (acute recall)
  - Patient Global Impression of Severity
  - Patient Global Impression of Change
  - Subject Global Assessment of Disease Activity
  - Physician Global Assessment of Disease Activity
  - Pharmacokinetic/immunogenicity/PD profile of AMG 557/MEDI5872
  - Change in individual clinical and laboratory components of pSS at Day 99 and Day 197:
    - Salivary gland dysfunction: change from baseline in unstimulated or stimulated whole salivary flow
    - Lachrymal gland dysfunction: change from baseline in Schirmer's or change from baseline in van Bijsterveld score
    - Change from baseline in autoantibodies (SS-A, SS-B)
    - Change in levels of markers of inflammation from baseline (hypergammaglobulinemia, beta-2 microglobulin, erythrocyte sedimentation rate, C-reactive protein)
    - Change in levels of immunoglobulin G and immunoglobulin M rheumatoid factor from baseline

#### **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 multiple SC doses of AMG 557/MEDI5872 in adult subjects with pSS. The study will be conducted at approximately 15 sites in Europe and North America. A total of approximately 42 subjects will be randomized in a 1:1 ratio to receive a fixed SC dose of 210 mg AMG 557/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 AMG 557/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 AMG 557/MEDI5872, and subjects who received AMG 557/MEDI5872 will receive a blinded dose of placebo (as these subjects would have already achieved steady-state levels of AMG 557/MEDI5872).

Randomization will be stratified by screening cellular immunophenotyping abnormalities (elevated TFH or elevated PB/PC vs normal values for both parameters).

<p>Investigational product (210 mg AMG 557/MEDI5872 or placebo) will be administered by SC injections in the anterior abdomen on each dosing day. Two 1.5 mL SC injections are required to deliver the investigational product. The injections should be administered at a distance of at least 2 cm apart and within 1 minute.</p> <p>Screening visit(s) will be performed within 28 days prior to dosing, or at the discretion of the medical monitor, after signing the informed consent form. Screening assessments can be performed over multiple visits if necessary. 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.</p> <p>Subjects will be in this study for approximately 46 weeks, which includes a screening period of up to 28 days and a safety follow-up period of 113 days.</p>
<p><b>TARGET SUBJECT POPULATION</b></p> <p>The study population is representative of the subset of SS subjects with pSS who have more systemic inflammation and, in general, would be considered for treatment with biologic therapies. Existing data from the literature strongly suggest that this is also the subset of subjects where abnormalities related to B7RP-1-ICOS activation are more pronounced. Based on the gender distribution of pSS, it is anticipated that a predominantly (&gt; 80%) female population will be recruited. Vulnerable populations will not be included in this study.</p>
<p><b>INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION</b></p> <p>Subjects will receive a fixed SC dose of 210 mg AMG 557/MEDI5872 (n = 21) or placebo (n = 21) QW for 3 weeks (Days 1 to 15) and then Q2W for 9 weeks (Days 29 to 85) as follows:</p> <ul style="list-style-type: none"><li>• Fixed SC dose (two 1.5 mL SC injections in the anterior abdomen, administered at a distance of at least 2 cm apart and within 1 minute) on Days 1, 8, 15, 29, 43, 57, 71, and 85.</li></ul> <p>Beginning on Day 99, all subjects (n = 42) will receive a fixed SC dose of 210 mg AMG 557/MEDI5872 QW (Days 99 to 113) and Q2W (Days 127 to 183) for an additional 12 weeks as follows:</p> <ul style="list-style-type: none"><li>• Fixed SC dose (two 1.5 mL SC injections in the anterior abdomen, administered at a distance of at least 2 cm apart and within 1 minute) on Days 99, 106, 113, 127, 141, 155, 169, and 183.</li></ul> <p>On Day 106, subjects who had received placebo will receive a blinded dose of AMG 557/MEDI5872, and subjects who received AMG 557/MEDI5872 will receive a blinded dose of placebo (as these subjects would have already achieved steady-state levels of AMG 557/MEDI5872).</p>
<p><b>STATISTICAL ANALYSIS PLAN</b></p> <p>The planned sample size of 42 subjects (21 subjects per arm) will provide 80% power to detect a difference in mean change in ESSDAI of 4 (assumed standard deviation of 5) between two randomized groups at a two-sided 0.1 level of statistical significance by using a two sample t-test. This sample size also provides about 80% power to detect 30% relative reduction in PC from tissue under assumption of coefficient of variation (CV) of 0.5. It should be noted that a smaller CV has been observed in blood from a previous study by Amgen (Study 20060169), which could result in higher statistical power. The sample size was calculated by using nQuery Advisor 7.0.</p> <p>Changes in ESSDAI score from baseline to Day 99 will be compared between AMG 557/MEDI5872 group and placebo group using an analysis of covariance adjusting for ESSDAI score at baseline, randomization stratum, and treatment group. The analysis will be conducted using the intent-to-treat Population. The significance of treatment effect will be tested by using a two-sided test at significance level <math>\alpha</math> of 0.1.</p>

## TABLE OF CONTENTS

PROTOCOL SYNOPSIS .....	2
LIST OF ABBREVIATIONS .....	10
1 INTRODUCTION .....	13
1.1 Disease Background.....	13
1.2 AMG 557/MEDI5872 Background .....	14
1.3 Summary of Nonclinical Experience .....	14
1.4 Summary of Clinical Experience .....	17
1.5 Rationale for Conducting the Study.....	20
1.6 Research Hypotheses .....	20
1.6.1Primary Hypothesis .....	20
1.6.2Secondary Hypotheses.....	21
2 OBJECTIVES .....	21
2.1 Objectives .....	21
2.1.1Primary Objective .....	21
2.1.2Secondary Objectives .....	21
2.1.3Exploratory Objectives .....	21
2.2 Study Endpoints.....	21
2.2.1Primary Endpoint .....	21
2.2.2Secondary Endpoint(s) .....	22
2.2.3Exploratory Endpoint(s) .....	22
3 STUDY DESIGN.....	23
3.1 Description of the Study.....	23
3.1.1Overview.....	23
3.1.2Treatment Regimen .....	25
3.2 Study Design and Dose Rationale .....	26
3.2.1Dose Rationale .....	26
3.2.2Rationale for Study Population .....	27
3.2.3Rationale for Endpoints .....	27
4 MATERIALS AND METHODS.....	28
4.1 Subjects .....	28
4.1.1Number of Subjects.....	28
4.1.2Inclusion Criteria .....	28
4.1.3Exclusion Criteria.....	30
4.1.4Subject Enrollment and Randomization.....	32
4.1.5Withdrawal from the Study.....	32
4.1.6Discontinuation of Investigational Product .....	33
4.1.7Replacement of Subjects .....	34

4.1.8	Withdrawal of Informed Consent for Data and Biological Samples ...	34
4.2	Schedule of Study Procedures .....	35
4.2.1	Enrollment/Screening Period .....	35
4.2.2	Active Treatment Period .....	36
4.2.3	Follow-up Period .....	40
4.3	Description of Study Procedures .....	41
4.3.1	Efficacy .....	41
4.3.1.1	European League Against Rheumatism Sjogren’s Syndrome Disease Activity Index .....	41
4.3.2	Patient-reported Outcomes .....	42
4.3.2.1	Subject Global Assessment of Disease Activity .....	43
4.3.2.2	Short-form 36 Version 2 .....	43
4.3.2.3	Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form .....	43
4.3.2.4	European League Against Rheumatism Sjogren’s Syndrome Patient Reported Index .....	44
4.3.2.5	Patient Global Impression of Change .....	44
4.3.2.6	Patient Global Impression of Severity .....	44
4.3.3	Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs .....	44
4.3.3.1	Medical History .....	44
4.3.3.2	Physical Examination, Height, and Weight .....	44
4.3.3.3	Vital Signs .....	45
4.3.3.4	Electrocardiogram .....	45
4.3.4	Chest Radiograph .....	45
4.3.5	Clinical Laboratory Tests .....	46
4.3.6	Pharmacokinetic Evaluation and Methods .....	48
4.3.7	Immunogenicity Evaluation and Methods .....	48
4.3.8	Biomarker Evaluation and Methods .....	48
4.3.8.1	Biopsy of Salivary Gland .....	48
4.3.8.2	Immunophenotyping Assay .....	49
4.3.8.3	PAXgene Ribonucleic Acid .....	49
4.3.8.4	Cell Pellet for Deoxyribonucleic Acid Methylation .....	49
4.3.8.5	Exploratory Biomarker Sample .....	50
4.3.8.6	Optional Biomarker Repository Samples .....	50
4.3.9	Disease Evaluation and Methods .....	51
4.3.9.1	Training .....	51
4.3.9.2	Sjogren’s Classification Worksheet .....	51
4.3.9.3	Physician Global Assessment of Disease Activity .....	52



4.3.9.4	28-joint Count .....	52
4.3.9.5	Oral Evaluation .....	52
4.3.9.6	Ophthalmological Evaluation .....	53
4.3.10	Estimate of Volume of Blood to Be Collected .....	53
4.4	Study Suspension or Termination .....	54
4.5	Investigational Products .....	55
4.5.1	Identity of Investigational Product(s) .....	55
4.5.1.1	Investigational Product Dose Preparation .....	56
4.5.1.2	Investigational Product Inspection .....	56
4.5.1.3	Investigational Product Thawing Instructions .....	56
4.5.1.4	Dose Preparation Steps .....	58
4.5.1.5	Treatment Administration .....	59
4.5.1.6	Monitoring of Dose Administration .....	59
4.5.1.7	Reporting Product Complaints .....	60
4.5.2	Labeling .....	60
4.5.3	Storage .....	60
4.5.4	Treatment Compliance .....	61
4.5.5	Accountability .....	61
4.6	Treatment Assignment and Blinding .....	61
4.6.1	Methods for Assigning Treatment Groups .....	61
4.6.2	Methods for Ensuring Blinding .....	62
4.6.3	Methods for Unblinding .....	62
4.6.3.1	Unblinding in the Event of a Medical Emergency .....	62
4.6.3.2	Unblinding for the Primary Analyses .....	62
4.7	Restrictions During the Study and Concomitant Treatment(s) .....	63
4.7.1	Permitted Concomitant Medications .....	63
4.7.2	Prohibited Concomitant Medications .....	63
4.8	Statistical Evaluation .....	64
4.8.1	General Considerations .....	64
4.8.2	Sample Size and Power Calculations .....	65
4.8.3	Efficacy .....	65
4.8.3.1	Primary Analysis .....	65
4.8.3.2	Secondary Analyses .....	65
4.8.3.3	Exploratory Analyses .....	66
4.8.4	Safety .....	66
4.8.4.1	Analysis of Adverse Events .....	66
4.8.4.2	Analysis of Clinical Laboratory Parameters .....	66
4.8.4.3	Other Safety and Tolerability Endpoints .....	66

4.8.5	Patient-Reported Outcomes .....	67
4.8.5.1	Analysis of ESSPRI .....	67
4.8.5.2	Analysis of PROFAD-SSI-SF .....	67
4.8.5.3	Analysis of SF-36v2.....	67
4.8.5.4	Analysis of Subject Global Assessment of Disease Activity .....	68
4.8.5.5	Patient Global Impression of Severity .....	68
4.8.5.6	Patient Global Impression of Change .....	68
4.8.6	Analysis of Immunogenicity/Pharmacokinetics .....	68
4.8.7	Planned Analyses .....	68
5	ASSESSMENT OF SAFETY .....	68
5.1	Definition of Adverse Events .....	68
5.2	Definition of Serious Adverse Events.....	69
5.3	Definition of Adverse Events of Special Interest .....	70
5.4	Recording of Adverse Events .....	70
5.4.1	Time Period for Collection of Adverse Events.....	70
5.4.2	Follow-up of Unresolved Adverse Events.....	71
5.5	Reporting of Serious Adverse Events .....	71
5.6	Other Events Requiring Immediate Reporting .....	72
5.6.1	Overdose.....	72
5.6.2	Hepatic Function Abnormality .....	72
5.6.3	Pregnancy.....	73
5.6.4	Adverse Events of Special Interest.....	73
6	STUDY AND DATA MANAGEMENT .....	74
6.1	Training of Study Site Personnel.....	74
6.2	Monitoring of the Study .....	74
6.2.1	Source Data.....	75
6.2.2	Study Agreements .....	75
6.2.3	Archiving of Study Documents.....	75
6.3	Study Timetable and End of Study .....	75
6.4	Data Management .....	75
6.5	Medical Monitor Coverage.....	76
7	ETHICAL AND REGULATORY REQUIREMENTS .....	76
7.1	Ethical Conduct of the Study.....	76
7.2	Subject Data Protection.....	76
7.3	Ethics and Regulatory Review.....	77
7.4	Informed Consent.....	77
7.5	Changes to the Protocol and Informed Consent Form.....	78



7.6	Audits and Inspections .....	78
8	REFERENCES .....	80
9	CHANGES TO THE PROTOCOL.....	84

## LIST OF IN-TEXT TABLES

Table 3.1.2-1	Investigational Product Dose and Treatment Regimen .....	25
Table 4.1.2-1	Highly Effective Methods of Contraception .....	30
Table 4.2.1-1	Schedule of Screening Procedures .....	35
Table 4.2.2-1	Schedule of Study Procedures.....	37
Table 4.2.3-1	Schedule of Follow-up Procedures.....	40
Table 4.3.10-1	Estimate of Blood Volume to be Collected.....	53
Table 4.5.1-1	Identification of Investigational Products.....	55
Table 4.5.1.3-1	Allowable Time and Temperatures for Investigational Product Thawing .....	57
Table 4.5.1.4-1	Preparation of Investigational Product Dose.....	59
Table 4.5.3-1	Storage of Investigational Product .....	61

## LIST OF IN-TEXT FIGURES

Figure 3.1.1-1	Study Flow Diagram.....	25
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## LIST OF APPENDICES

Appendix 1	Signatures.....	92
Appendix 2	Additional Safety Guidance .....	96
Appendix 3	American European Consensus Group Criteria .....	98
Appendix 4	European League Against Rheumatism Sjogren’s Syndrome Disease Activity Index.....	99
Appendix 5	Subject Global Assessment of Disease Activity .....	103
Appendix 6	Short-form 36 Version 2 .....	104
Appendix 7	Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form.....	110
Appendix 8	European League Against Rheumatism Sjogren’s Syndrome Patient Reported Index .....	115
Appendix 9	Patient Global Impression of Change .....	116
Appendix 10	Patient Global Impression of Severity.....	117
Appendix 11	Guidance for Abnormal Liver Function Tests Management .....	118

## LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
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 <sub>0-14</sub>	area under the curve from Days 0 to 14
B7RP-1	B7-related protein-1
C <sub>max</sub>	observed maximum concentration
CI	confidence interval
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DNA	deoxyribonucleic acid
EBAP	exploratory biomarker analysis plan
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	End of Study
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
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICOS	inducible T-cell costimulator
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assay
IL	interleukin

<b>Abbreviation or Specialized Term</b>	<b>Definition</b>
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IVRS/IWRS	interactive voice/web response system
KLH	keyhole limpet hemocyanin
$K_m$	Michaelis-Menten constant
LA	lupus arthritis
MCP	metacarpophalangeal
MCS	mental component score
MDGA	Physician Global Assessment of Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect-level
NSAID	nonsteroidal anti-inflammatory drug
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
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PRO	patient-reported outcome
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
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SF-36v2	Short Form-36 version 2
SGA	Subject Global Assessment of Disease Activity
SID	subject identification
SLE	systemic lupus erythematosus
SS	Sjogren's syndrome
sSS	secondary Sjogren's syndrome
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

<b>Abbreviation or Specialized Term</b>	<b>Definition</b>
TFH	T follicular helper
$t_{\max}$	time to maximum concentration
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
$V_{\max}$	maximum metabolic rate

## 1 INTRODUCTION

### 1.1 Disease Background

Sjogren's syndrome (SS) is an autoimmune disease characterized by chronic inflammation involving the exocrine glands. Salivary and lacrimal glands are predominantly affected leading to dry mouth and dry eyes (sicca symptoms) but other exocrine organs are also frequently involved. It is the second most common rheumatic autoimmune disease and predominantly affects women, with a female to male ratio of 9:1. The annual incidence rate has been estimated to be between 0.11 to 0.53 cases per 10,000 adults ([Alamanos et al, 2006](#); [Pillemer et al, 2001](#); [Plesivcnik Novljan et al, 2004](#); [Yu et al, 2013](#)) and the annual prevalence rate has been estimated to be between 2 to 330 cases per 10,000 adults ([Alamanos et al, 2006](#); [Birlik et al, 2009](#); [Goransson et al, 2011](#); [Miyasaka, 1995](#); [Thomas et al, 1998](#); [Tomsic et al, 1999](#); [Trontzas and Andrianakos, 2005](#); [Zhang et al, 1995](#)).

Sjogren's syndrome may occur alone (pSS), or may coexist with other systemic connective tissue disorders (secondary Sjogren's syndrome [sSS]). In about 20% to 25% of patients, systemic manifestations, such as arthritis, vasculitis, lung disease, peripheral or central neuropathy, and autonomic nervous system dysfunction accompany glandular involvement. Certain laboratory abnormalities, such as cryoglobulinemia, low complement levels, and markers of increased B-lymphocyte activation (increased levels of autoantibodies and hypergammaglobulinemia) are also more common in patients with systemic manifestations and can be used to identify this subpopulation. Patients with systemic manifestations are at higher risk of lymphoma, the incidence of which is increased 4- to 14-fold in SS. The treatment of sicca symptoms is mainly symptomatic. The management of extraglandular manifestations is unsatisfactory and is based on treatment of similar manifestations in other autoimmune diseases ([Ramos-Casals et al, 2010](#)).

The cause and pathogenesis of SS is still largely unknown. Key events include epithelial cell activation and a protracted inflammatory response with features of autoimmunity. B7-related protein-1 (B7RP-1) is the sole ligand for inducible T-cell costimulator (ICOS). The interaction between ICOS and B7RP-1 plays a significant role in T-cell cytokine production and differentiation into T follicular helper (TFH) cells, effector memory T cells and T-helper 17 cells ([Yoshinaga et al, 1999](#); [Coyle et al, 2000](#); [McAdam et al, 2001](#); [Paulos et al, 2010](#); [Crotty, 2011](#); [Deenick and Ma, 2011](#)). T follicular helper cells are CD4+ T cells specialized in providing help to B cells ([Crotty, 2011](#), [Deenick and Ma, 2011](#)). Inducible T-cell costimulator expression on TFH cells is critical for optimal B-cell differentiation and immunoglobulin (Ig) isotype switching ([Yoshinaga et al, 1999](#); [Coyle et al, 2000](#), [McAdam et al, 2001](#), [Paulos et al, 2010](#)). Inducible T-cell costimulator-null patients have a

significant reduction in B cells and TFH and a significant decrease in serum immunoglobulin G (IgG) levels ([Grimbacher et al, 2003](#); [Bossaller et al, 2006](#); [Warnatz et al, 2006](#); [Takahashi et al, 2009](#)), which suggests, by inference, that targeting the ICOS and B7RP-1 interaction may lead to the reduction in antibody production, including autoantibodies.

Subjects with pSS have elevated ICOS and elevated percentages of TFH cells in the blood ([Hutloff et al, 2004](#); [Simpson et al, 2010](#); [Li et al, 2012](#); [Ma et al, 2012](#); [Szabo et al, 2013](#)). The frequency of TFH cells in the blood correlates with various markers of disease activity, such as anti-SS-A and anti-SS-B autoantibody levels and the presence of extraglandular manifestations. Higher focus scores on labial salivary gland biopsies correlate with TFH cells (defined by CD4+CXCR5+ICOS+PD-1+; [Szabo et al, 2013](#)), whereas the European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) correlates with CD4+CXCR5+CCR6+TFH ([Li et al, 2012](#)). In addition, in systemic lupus erythematosus (SLE), which shares many immune abnormalities with SS, ICOS+ T cells co-localize with B cells in SLE nephritis lesions ([Hutloff et al, 2004](#); [Liarski et al, 2014](#)); this suggests that ICOS+ T cells may not be only dysregulated in the central lymphoid compartment but also in the inflamed tissues, such as the salivary gland in SS.

Based on the role of the ICOS:B7RP-1 pathway in several key steps in the immunopathogenesis of SS, we propose that blocking B7RP-1 will lead to an improvement in blood and tissue markers of T- and B-cell activation with eventual clinical benefit.

## **1.2 AMG 557/MEDI5872 Background**

AMG 557/MEDI5872 is briefly described below. Refer to the current Investigator's Brochure (IB) for details.

AMG 557/MEDI5872 is a fully human immunoglobulin G2 monoclonal antibody that binds an epitope in the first Ig-like domain of B7RP-1 and inhibits its interaction with the ICOS receptor expressed by activated T cells. AMG 557/MEDI5872 has potential relevance in a number of autoimmune diseases including SLE and pSS and is being developed in partnership between Amgen and MedImmune.

## **1.3 Summary of Nonclinical Experience**

Cynomolgus monkeys were selected as the nonclinical toxicology species because the in vitro potency of AMG 557/MEDI5872 was similar in cynomolgus monkeys and humans. Additionally, AMG 557/MEDI5872 does not cross react with rat or murine B7RP-1. Repeat-dose studies with weekly administration of AMG 557/MEDI5872 (1 to 300 mg/kg) included a 15-day subcutaneous (SC) repeat-dose study, a 6-week intravenous (IV) and

SC repeat-dose study, and a 3-month and 6-month SC repeat-dose study. In addition, a single-dose safety pharmacology study evaluating cardiovascular, respiratory, and central nervous system effects was conducted in cynomolgus monkeys.

Results of a safety pharmacology study with AMG 557/MEDI5872 were unremarkable. No adverse toxicologic effects have been observed in repeat-dose studies with AMG 557/MEDI5872 at weekly doses of  $\leq 300$  mg/kg IV or 30 mg/kg SC for 15 days,  $\leq 10$  mg/kg IV for 6 weeks, or  $\leq 5$  mg/kg SC for 3 months in cynomolgus monkeys. In a 6-week repeat-dose study, doses of 75 and 300 mg/kg IV were associated with toxicologic effects that included clinical manifestations that required the euthanasia of 1 male and 1 female in the 300 mg/kg IV group. Slight to marked chronic periarteritis was observed in various organs of 1 male and 1 female given 300 mg/kg/dose IV and in the cervix of 1 female given 75 mg/kg/dose IV necropsied at the termination of dosing. The chronic periarteritis was characterized by perivascular inflammation with occasional increased intimal cellularity and rarely medial hypertrophy in various organs (gastrointestinal tract, pancreas, kidney, gallbladder, heart, tongue, urinary bladder, ureter, uterus, cervix, vagina, and seminal vesicles). This periarteritis was rarely observed in animals administered 300 mg/kg AMG 557/MEDI5872 by SC injection (only occurring in the gallbladder of 1 male). The anatomic pathology findings of decreased germinal centers in lymphoid tissues were considered to be related to the expected pharmacology of ICOS/B7RP-1 blockade. Similar histopathologic changes were not observed in the earlier dose range-finding study where weekly IV (1 to 300 mg/kg) or SC (30 mg/kg) doses of AMG 557/MEDI5872 were administered for 15 days.

The test article-related findings in the 3-month study included chronic periarteritis characterized by increased intimal cellularity in the seminal vesicle in 1 male given 25 mg/kg/dose. This lesion affected a majority of vessels and was characterized microscopically by hypertrophy of the endothelial cells with accumulated cells in the intima. The chronic periarteritis with increased intimal cellularity in the seminal vesicle was considered an adverse finding. Other test article-related findings included an increased incidence of decreased germinal centers in the spleen and mesenteric lymph node of animals given 25 or 90 mg/kg/dose, an increased incidence of decreased germinal centers in the mandibular lymph node of animals given 90 mg/kg/dose, and an increased incidence of lymphocyte depletion in the thymus of males given 90 mg/kg/dose; these findings were considered to be related to the expected pharmacology of AMG 557/MEDI5872. Microscopic changes seen in the lymphoid organs appeared reversible because they were not noted at the end-of-recovery-phase necropsy. In addition, no vascular lesions were seen in any organ, including the seminal vesicles, suggesting that if any lesions had been present,



they also had resolved. Immunohistochemical evaluation of the arterial lesions from animals treated for 6 weeks or 3 months with AMG 557/MEDI5872 compared with controls showed that these lesions had increased granular deposits of cynomolgus monkey (IgG and immunoglobulin M [IgM]) or human (AMG 557/MEDI5872) Igs consistent with immune complex deposition, suggesting this as an etiology for the lesion. Many of these immune complexes contained AMG 557/MEDI5872 and cynomolgus monkey Igs that supported anti-AMG 557/MEDI5872 antibodies and suggested that these may have been a contributing or inciting factor for the lesion.

In the 6-month repeat-dose study, male and female cynomolgus monkeys were administered AMG 557/MEDI5872 at a dose level of 0, 5, 25, or 90 mg/kg via SC injection once weekly for 6 months. A decrease in the size/number of germinal centers were noted in the spleen of some animals at  $\geq 25$  mg/kg/dose, which is an anticipated pharmacological effect of AMG 557/MEDI5872; the changes in the spleen were not present or had partially reversed following the 4-month (16-week) treatment-free phase. Macroscopic findings at the SC injection site that correlated with microscopic findings of subacute inflammation were observed at all doses, and were not present or were partially reversed following the 4-month (16-week) treatment-free phase. Due to the mild severity of the findings, none of the effects in the study noted were considered adverse, and the no-observed-adverse-effect-level (NOAEL) was determined to be the highest dose, 90 mg/kg. The 90 mg/kg dose level corresponds to mean observed maximum concentration ( $C_{max}$ ) and area under the curve from Days 0 to 168 values of 1,930  $\mu\text{g/mL}$  and 279,000  $\mu\text{g}\cdot\text{hour/mL}$ , respectively. The NOAEL established in the chronic 6-month study of 90 mg/kg is higher than previous studies where the NOAEL was determined based on toxicities that are caused by the development of neutralizing antibodies to AMG 557/MEDI5872 in the cynomolgus monkey. The NOAEL of 90 mg/kg following 6 months of treatment with AMG 557/MEDI5872 is appropriate for determining safety margins in patients. Anti-AMG 557/MEDI5872 antibodies will continue to be monitored in the clinical studies. Results of the histopathology data further support that the chronic periarteritis observed in the prior 6-week and 3-month studies were most likely caused by anti-AMG 557/MEDI5872 antibodies; anti-AMG 557/MEDI5872 antibodies were observed only at a low incidence in the 6-month study when AMG 557/MEDI5872 was administered by the SC route.

Pharmacokinetic (PK) data were obtained from 2 cynomolgus monkey studies after single-dose IV and single-dose SC administration of 0.1 to 10 mg/kg AMG 557/MEDI5872. AMG 557/MEDI5872 exhibited a greater than dose-proportional increase in exposure in the 0.1 to 1 mg/kg IV and 0.1 to 10 mg/kg SC dose range, and an approximately dose-proportional increase in the 1 to 10 mg/kg IV dose range.

Multiple-dose toxicokinetic data were obtained from 4 cynomolgus monkey studies after once weekly, multiple-dose IV or SC administration for 15 days, 6 weeks, 13 weeks, or 6 months (1 to 300 mg/kg). After multiple IV or SC administrations, the exposure increased approximately dose proportionally after the first dose and the last dose. No notable sex-based differences in toxicokinetics were observed. Moderate accumulation was observed after IV and SC dosing under the various aforementioned multiple dosing schedules with accumulation ratios ranging from 1.35 to 2.82.

A total of 77 of 158 monkeys (48.7%) treated with single or multiple doses of AMG 557/MEDI5872 tested positive for anti-AMG 557/MEDI5872 antibodies. The presence of anti-AMG 557/MEDI5872 antibodies was associated with a general decrease in exposure of AMG 557/MEDI5872 in the systemic circulation.

Additional details regarding the nonclinical experience of AMG 557/MEDI5872 are provided in the IB.

#### **1.4 Summary of Clinical Experience**

AMG 557/MEDI5872 has been or is being investigated in 5 Amgen-sponsored clinical studies in subjects with mild, stable SLE, subacute cutaneous lupus erythematosus, lupus arthritis (LA), and moderate to severe psoriasis. Two studies (Studies 20060132 and 20060169) in subjects with SLE have been completed. Two studies (Studies 20110105 and 20100037) in subjects with moderate to severe psoriasis and subacute cutaneous lupus erythematosus, respectively, have been prematurely terminated due to slow enrollment. One study (Study 20101103) in subjects with SLE with active LA is ongoing.

Study 20060132 was a randomized, single-dose, placebo-controlled, double-blind, dose-escalation study that evaluated the safety, tolerability, PK, and pharmacodynamics (PD) of AMG 557/MEDI5872 in subjects with SLE (n = 57). Subjects were randomized to receive 1.8, 6, 18, 60, 140, or 210 mg SC, or 18 mg IV AMG 557/MEDI5872 or placebo, with dose escalation occurring after consideration of the safety results seen at lower doses. Subjects were also immunized with keyhole limpet hemocyanin (KLH) on Days 2 and 29 (60 mg SC cohort), Days 8 and 36 (140 mg SC and 6 subjects in the 210 mg SC), and Days 15 and 43 (2 subjects in the 210 mg SC cohort) to assess the impact of AMG 557/MEDI5872 on the anti-KLH IgM and IgG responses. After a single administration of AMG 557/MEDI5872, serum concentrations exhibited nonlinear PK behavior. Serum AMG 557/MEDI5872 exposure, as measured by area under the curve at last time point and  $C_{max}$ , increased greater than dose proportionally across the dose range of 1.8 to 140 mg SC. However, an approximate dose-proportional increase in exposure was observed in the range of 140 to

210 mg SC. After single SC administration, the median time to maximum concentration ( $t_{max}$ ) ranged from 3 to 7 days. Because of the nonlinear PK behavior, the bioavailability of AMG 557/MEDI5872 could not be assessed by comparison of SC and IV areas under the curves. However, based on simultaneous compartmental modeling of the available data, bioavailability after SC dosing was estimated to be 57%. Target occupancy results showed reversible and dose-related AMG 557/MEDI5872 coverage of B7RP-1 on circulating B cells. Flow cytometric data indicated a dose-related increase in mean total B7RP-1 and a dose-related decrease in mean free B7RP-1 on peripheral B cells. No difference in either the anti-KLH IgG or IgM response was detected between the AMG 557/MEDI5872 and placebo groups. Single doses of AMG 557/MEDI5872 up to 210 mg SC and 18 mg IV were reasonably tolerated. No deaths were reported, and no subjects withdrew from the study or investigational product due to an adverse event (AE).

Study 20060169 was a randomized, double-blind, placebo-controlled, ascending, multiple-dose study that evaluated the safety, tolerability, PK, and PD of AMG 557/MEDI5872 in subjects with SLE (n = 58). Subjects were randomized to receive 6, 18, 30, 45, 70, 140, or 210 mg SC AMG 557/MEDI5872 or placebo, administered every 2 weeks (Q2W) for 7 doses. Subjects were also immunized with KLH on Days 57 and 85 to assess the impact of AMG 557/MEDI5872 on the anti-KLH IgG responses. AMG 557/MEDI5872 exposure, as measured by area under the curve from Days 0 to 14 ( $AUC_{0-14}$ ) and  $C_{max}$  after the first and seventh doses, increased greater than dose proportionally across the dose range of 6 to 70 mg SC. However, an approximate dose-proportional increase in exposure was observed in the dose range of 70 to 210 mg SC. Median  $t_{max}$  ranged from 4 to 7.6 days. Moderate accumulation was observed after 7 doses of AMG 557/MEDI5872 at 6 to 210 mg SC, with median accumulation ratios for  $AUC_{0-14}$  ranging from 1.94 to 4.41. Based on trough values, steady state appeared to be reached during this time period in all SC dose groups. Target occupancy results showed reversible and dose-related AMG 557/MEDI5872 coverage of B7RP-1 on circulating B cells. Flow cytometric data indicated a dose-related increase in mean total B7RP-1 and a dose-related decrease in mean free B7RP-1 on peripheral B cells. A significant reduction in the anti-KLH IgG response was observed in the AMG 557/MEDI5872 group compared with the placebo group (p = 0.0044). Although KLH is considered a neoantigen, 9 of the 56 subjects were found to have detectable levels of anti-KLH IgG antibodies prior to the first immunization in the study. To ensure a more appropriate comparison between groups that were homogeneously naive to the administered antigen (and associated epitopes), a post-hoc analysis was conducted in which data from these subjects were censored. A clearer dose response was observed along with reduced variability in the data. The inhibition of the primary response (between Days 57 and 85) was more readily achieved compared with the secondary response,

with all the dose levels showing decreases in anti-KLH IgG responses relative to placebo. In the secondary response following the Day 85 immunization, greater degrees of inhibition of the anti-KLH antibody responses were observed with increasing dose levels. The 140 and 210 mg dose levels appeared to have comparable effects, separable from the lower dose levels. Unlike the decreases observed with AMG 557/MEDI5872 administration on anti-KLH IgG responses, no decreases were seen on anti-KLH IgM responses. This lack of impact of ICOS blockade on the antigen-specific IgM response is consistent with the human and mouse genetic studies and in studies of pharmacologic blockade in mice ([Metz et al, 2009](#); [Bossaller et al, 2006](#); [Grimbacher et al, 2003](#); [Takahashi et al, 2009](#); [Yusuf et al, 2014](#)). Multiple doses of AMG 557/MEDI5872 up to 210 mg SC were reasonably tolerated. No deaths were reported. Five subjects who received AMG 557/MEDI5872 had serious adverse events (SAEs; cellulitis, respiratory failure, tachycardia, uterine leiomyoma, and viral cardiomyopathy) and 2 subjects who received placebo had SAEs (chest pain and cholecystitis). All SAEs occurred in a single subject each and all SAEs but one (respiratory failure) were considered to be not related to investigational product. One subject who had a related SAE of respiratory failure withdrew from the study.

Study 20110105 was a randomized, double-blind, placebo-controlled, multiple-dose study that evaluated the safety, tolerability, PK, and PD of AMG 557/MEDI5872 in subjects with moderate to severe psoriasis (n = 6). Subjects were randomized to receive 105 or 210 mg SC AMG 557/MEDI5872 or placebo on Days 1, 8, 15, 29, 43, 57, and 71. The study was prematurely terminated by Amgen because of slow enrollment; 6 out of 10 planned subjects had been enrolled (4 subjects had received AMG 557/MEDI5872 and 2 subjects received placebo), 5 had completed the study and 1 had withdrawn from the study. After administration of 210 mg SC on Days 1, 8, 15, 29, 43, 57, and 71 in 4 subjects, steady-state concentrations of AMG 557/MEDI5872 were reached on Day 15 (predose of the third dose). The mean trough concentrations on Days 43 and 57 were slightly low (24 to 26 µg/mL), mainly because 1 subject had decreasing AMG 557/MEDI5872 concentrations due to the presence of anti-drug antibodies. Without these two time points, mean steady-state trough concentrations were 28 to 29 µg/mL. No deaths were reported. Two subjects who received AMG 557/MEDI5872 had 4 SAEs (cyst rupture and oedema peripheral in 1 subject; pulmonary embolism and deep vein thrombosis in 1 subject); however, none of these events were considered to be related to investigational product.

Study 20100037 was a randomized, double-blind, placebo-controlled, multiple-dose study that evaluated the safety, tolerability, PK, and PD of AMG 557/MEDI5872 in subjects with subacute cutaneous lupus erythematosus. In this study, subjects were to be randomized to receive 140 or 210 mg SC AMG 557/MEDI5872 or placebo every week (QW) for 3 weeks

followed by 6 additional doses Q2W. The study was prematurely terminated by Amgen because of slow enrollment; 1 subject received placebo and completed the study.

Study 20101103 is a randomized, double-blind, placebo-controlled, multiple-dose, parallel-group study evaluating the safety, tolerability, PK, PD, and clinical effect of AMG 557/MEDI5872 in subjects with SLE with active LA. Subjects will be randomized to receive 210 mg SC QW for 3 weeks followed by 10 additional doses Q2W. The study is currently ongoing; approximately 40 subjects are planned to be enrolled in the study.

Additional details regarding the clinical experience of AMG 557/MEDI5872 are provided in the IB.

## **1.5 Rationale for Conducting the Study**

There is an unmet medical need for disease-modifying therapies in SS. This is the first time the ICOS:B7RP-1 pathway will be targeted in subjects with pSS. Therefore, there may be no direct benefit to subjects participating in the study. However, based on the role of the ICOS:B7RP-1 pathway in several key steps in the immunopathogenesis of SS, blocking B7RP-1 may improve some underlying immunologic abnormalities, which may result in clinical benefit. Changes observed in the blood and tissue markers of T- and B-cell activation will contribute to generalizable knowledge.

There are no identified risks with AMG 557/MEDI5872. Potential risks with AMG 557/MEDI5872 include injection-site reactions. Important potential risks include anaphylaxis and serious allergic reactions, immune complex disease, bacterial, viral, and opportunistic infections, including progressive multifocal leukoencephalopathy, and malignancy. As with the administration of any foreign protein or biologic agent, subjects will be closely monitored for anaphylaxis and serious allergic reactions, as well as injection-site reactions. Immune complex disease, infections, and malignancies will also be monitored.

The results of this study will provide proof of mechanism of AMG 557/MEDI5872 in autoimmune diseases and will be informative for the design of larger Phase 2b studies.

A detailed assessment of benefit-risk is provided in the IB.

## **1.6 Research Hypotheses**

### **1.6.1 Primary Hypothesis**

The primary hypothesis is that subjects with pSS treated with AMG 557/MEDI5872 will have improvement in objective measures of disease activity.

## **1.6.2 Secondary Hypotheses**

The secondary hypotheses are that:

1. AMG 557/MEDI5872 will lead to a decrease in biomarkers (peripheral blood and minor salivary gland tissue), reflecting the activity of the ICOS:B7RP-1 pathway in subjects with pSS.
2. AMG 557/MEDI5872 will have an acceptable safety profile in subjects with pSS.
3. Subjects with pSS treated with AMG 557/MEDI5872 will have improvement in subjective measures of disease activity.

## **2 OBJECTIVES**

### **2.1 Objectives**

#### **2.1.1 Primary Objective**

To evaluate the effect of AMG 557/MEDI5872 compared to placebo in reducing objective measures of overall disease activity in subjects with pSS.

#### **2.1.2 Secondary Objectives**

1. To evaluate the effect of AMG 557/MEDI5872 compared to placebo on peripheral blood and salivary gland biomarkers in subjects with pSS.
2. To evaluate the safety and tolerability of multiple SC doses of AMG 557/MEDI5872 in subjects with pSS.
3. To evaluate the effect of AMG 557/MEDI5872 compared to placebo in reducing objective and subjective measures of overall disease activity.

#### **2.1.3 Exploratory Objectives**

1. To evaluate the effect of AMG 557/MEDI5872 compared to placebo on individual clinical and laboratory components of pSS.
2. To evaluate the effect of AMG 557/MEDI5872 compared to placebo on specific subjective symptoms of pSS.
3. To evaluate the PK, immunogenicity, and PD of AMG 557/MEDI5872.

### **2.2 Study Endpoints**

#### **2.2.1 Primary Endpoint**

The primary endpoint of the study is the change in the ESSDAI score from baseline to Day 99.



### **2.2.2 Secondary Endpoint(s)**

The secondary endpoints of the study are:

1. Biomarkers:
  - a. Outcomes in peripheral blood
    - i. Change in plasma cell (PC) levels (including plasma blast [PB] levels) from baseline to Day 99
    - ii. Change in TFH levels from baseline to Day 99
  - b. Outcomes in minor salivary gland tissue
    - i. Change in PC levels from baseline to Day 99
    - ii. Change in TFH levels from baseline to Day 99
  - c. Focus score
    - i. Change in focus score from baseline to Day 99
2. Safety and tolerability of multiple SC doses of AMG 557/MEDI5872 as measured by the incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and laboratory abnormalities
3. Change in European League Against Rheumatism Sjogren's Syndrome Patient Reported Index (ESSPRI) score from baseline to Day 99
4. ESSDAI[3] and ESSDAI[4] response, defined as a decrease of at least 3[4] points from baseline in the ESSDAI at Day 99 without premature discontinuation of investigational product and without receiving prohibited concomitant medications

### **2.2.3 Exploratory Endpoint(s)**

The exploratory endpoints of the study are:

1. Biomarkers:
  - a. Outcomes in peripheral blood
    - i. Change in PB levels from baseline to Day 99
    - ii. Change from baseline in PC gene signature at Day 99
    - iii. Change from baseline in TFH gene signature at Day 99
  - b. Outcomes in minor salivary gland tissue
    - i. Change in PB levels from baseline to Day 99
    - ii. Change from baseline in PC gene signature at Day 99
    - iii. Change from baseline in TFH gene signature at Day 99
2. All of the secondary and biomarker exploratory endpoints (except for outcomes in minor salivary gland tissue) may be assessed at other time points
3. ESSPRI response, defined as a decrease of at least 1 point or  $\geq 15\%$  from baseline in the ESSPRI at Day 99 without premature discontinuation of investigational product and without receiving prohibited concomitant medications



4. Primary Sjogren's syndrome symptoms as measured by the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form (PROFAD-SSI-SF)
5. Health status as measured by the Short Form-36 version 2 (SF-36v2) Health Survey (acute recall)
6. Patient Global Impression of Severity (PGI-S)
7. Patient Global Impression of Change (PGI-C)
8. Subject Global Assessment of Disease Activity (SGA)
9. Physician Global Assessment of Disease Activity (MDGA)
10. Pharmacokinetic/immunogenicity/PD profile of AMG 557/MEDI5872
11. Change in individual clinical and laboratory components of pSS at Day 99 and Day 197:
  - a. Salivary gland dysfunction: change from baseline in unstimulated or stimulated whole salivary flow
  - b. Lachrymal gland dysfunction: change from baseline in Schirmer's or change from baseline in van Bijsterveld score
  - c. Change from baseline in autoantibodies (SS-A, SS-B)
  - d. Change in levels of markers of inflammation from baseline (hypergammaglobulinemia, beta-2 microglobulin, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP])
  - e. Change in levels of IgG and IgM rheumatoid factor (RF) from baseline

### **3 STUDY DESIGN**

#### **3.1 Description of the Study**

##### **3.1.1 Overview**

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 multiple SC doses of AMG 557/MEDI5872 in adult subjects with pSS.

The study will be conducted at approximately 15 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 AMG 557/MEDI5872 (n = 21) or placebo (n = 21) QW for 3 weeks (Days 1 to 15) and then 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 AMG 557/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 AMG 557/MEDI5872, and subjects who received AMG 557/MEDI5872 will receive a

blinded dose of placebo (as these subjects would have already achieved steady-state levels of AMG 557/MEDI5872).

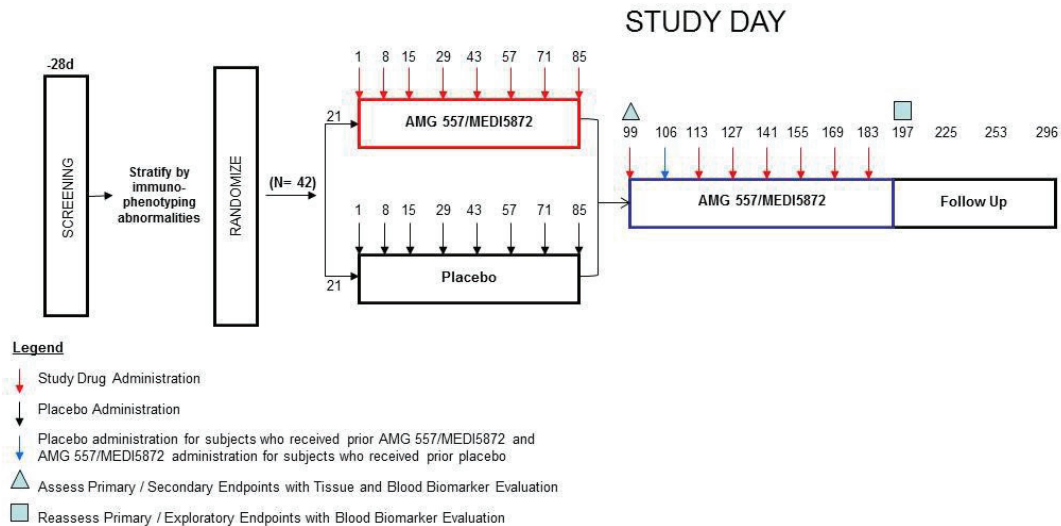
Randomization will be stratified by screening cellular immunophenotyping abnormalities (elevated TFH or elevated PB/PC vs normal values for both parameters).

Investigational product (210 mg AMG 557/MEDI5872 or placebo) will be administered by a qualified healthcare professional by SC injections in the anterior abdomen on each dosing day. Two 1.5 mL SC injections are required to deliver the investigational product. The injections should be administered at a distance of at least 2 cm apart and within 1 minute.

Screening visit(s) will be performed within 28 days prior to dosing, or at the discretion of the medical monitor, after signing the informed consent form (ICF). Screening assessments can be performed over multiple visits if necessary. 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.

Subjects will be in this study for approximately 46 weeks, which includes a screening period of up to 28 days and a safety follow-up period of 113 days.

The study flow diagram is shown in [Figure 3.1.1-1](#).



**Figure 3.1.1-1 Study Flow Diagram**

d = day; N = number of subjects

The endpoints to be measured in this study are described in Section 2.2.

### 3.1.2 Treatment Regimen

A total of 42 subjects are planned for this study. Investigational product dose and treatment regimen for the active treatment periods is described in Table 3.1.2-1.

**Table 3.1.2-1 Investigational Product Dose and Treatment Regimen**

N	Dose	Treatment Regimen
<b>Days 1 to 85</b>		
42 (AMG 557/MEDI5872: 21 Placebo: 21)	210 mg AMG 557/MEDI5872 or placebo	Fixed SC dose (two 1.5 mL SC injections in the anterior abdomen, administered at a distance of at least 2 cm apart and within 1 minute) on Days 1, 8, 15, 29, 43, 57, 71, and 85.
<b>Days 99 to 183</b>		
42	210 mg AMG 557/MEDI5872 (or placebo on Day 106)	Fixed SC dose (two 1.5 mL SC injections in the anterior abdomen, administered at a distance of at least 2 cm apart and within 1 minute) on Days 99, 106 <sup>a</sup> , 113, 127, 141, 155, 169, and 183.

N = number of subjects; SC = subcutaneous

<sup>a</sup> On Day 106, subjects who had received placebo will receive a blinded dose of AMG 557/MEDI5872, and subjects who received AMG 557/MEDI5872 will receive a blinded dose of placebo.

## 3.2 Study Design and Dose Rationale

### 3.2.1 Dose Rationale

The AMG 557/MEDI5872 dose and treatment regimen for this study is based on the dose and schedule used in an ongoing study by Amgen in subjects with SLE with active LA (Study 20101103). The selected dose and treatment regimen are expected to be adequately tolerated in subjects with pSS based on a lack of dose-limiting toxicities up to 210 mg SC Q2W for 7 doses in subjects with SLE (Study 20060169). The selected dose and treatment regimen is also expected to ensure sufficient coverage of the target up to Week 28 to adequately test the impact of B7RP-1 blockade on the chosen PD and clinical endpoints.

A 2-compartment, nonlinear PK model with parallel linear and nonlinear (maximum metabolic rate [ $V_{max}$ ] and Michaelis-Menten constant [ $K_m$ ]) elimination has been developed based on emerging concentration data from the Phase 1 studies, which describe the PK profiles of single doses of AMG 557/MEDI5872 up to 140 mg SC and multiple doses of AMG 557/MEDI5872 up to 70 mg Q2W for 7 doses. Predicted exposures associated with multiple doses of 140 mg SC AMG 557/MEDI5872 or multiple doses of 210 mg SC AMG 557/MEDI5872 were extrapolated based on the model. In addition, PK model predictions have been compared with all data available as of the 18Oct2011 database snapshot from the multiple-ascending dose study (Study 20060169) and all data from the completed single-ascending dose study (Study 20060132). The PK model reasonably predicts the available data for both 210 mg single-dose and 140 mg multiple-dose regimens (see IB for further details). While full-time course profiles are available from only a subset of the 140 and 210 mg cohorts in the multiple-dose study (Study 20060169), comparison of model predictions and clinical observations provides additional support for the dosing regimen.

Pharmacokinetic-receptor occupancy modeling of serum concentrations of AMG 557/MEDI5872 and flow cytometric analyses of B7RP-1 occupancy on circulating B cells based on final data from the single-ascending dose study (Study 20060132) and multiple-ascending dose study (Study 20060169) indicates a 90% effective concentration of 0.80  $\mu\text{g/mL}$  (95% confidence interval [CI]: 0.31-1.3  $\mu\text{g/mL}$ ) and a 99% effective concentration of 8.8  $\mu\text{g/mL}$  (95% CI: 3.5-14  $\mu\text{g/mL}$ ) using a simple maximum effect model. Pharmacokinetic modeling indicates that at serum AMG 557/MEDI5872 concentrations less than 2  $\mu\text{g/mL}$ , B7RP-1 target-mediated (ie, nonlinear) elimination is the predominant AMG 557/MEDI5872 clearance pathway, suggesting that the B7RP-1 target is not saturated at these drug concentrations. At 2.92  $\mu\text{g/mL}$  ( $= 9 \times K_m$ ) serum AMG 557/MEDI5872 concentrations and above, drug elimination transitions to predominantly normal IgG turnover

processes (ie, linear). This concentration likely represents target (receptor) 90% saturation in vivo, and takes into account compartments not measured (or accessible) using flow cytometric methods. The 210 mg SC dose and regimen proposed is projected to reach steady-state trough serum concentrations of AMG 557/MEDI5872 above the 99% effective concentration for approximately 35 weeks.

In order to rapidly achieve the target concentrations and to maintain this coverage for the duration of dosing, subjects randomized to AMG 557/MEDI5872 will receive 210 mg AMG 557/MEDI5872 QW for 3 weeks followed by 12 additional doses of 210 mg AMG 557/MEDI5872, providing treatment duration of 26 weeks. Beginning on Day 99, those subjects who had been randomized to placebo, will receive 210 mg AMG 557/MEDI5872 QW for 3 weeks followed by 5 additional doses of 210 mg AMG 557/MEDI5872, providing treatment duration of 13 weeks.

### **3.2.2 Rationale for Study Population**

The study population is representative of the subset of SS subjects with pSS who have more systemic inflammation and, in general, would be considered for treatment with biologic therapies. Existing data from the literature strongly suggest that this is also the subset of subjects where abnormalities related to B7RP-1-ICOS activation are more pronounced ([Li et al, 2012](#); [Szabo et al, 2013](#)). Based on the gender distribution of pSS, it is anticipated that a predominantly (> 80%) female population will be recruited. Vulnerable populations will not be included in this study.

### **3.2.3 Rationale for Endpoints**

The key objectives of this study are to evaluate the effect of AMG 557/MEDI5872 compared to placebo in reducing objective measures of overall disease activity in subjects with pSS. Currently, there are no validated or uniformly accepted efficacy criteria for SS. In addition, there have been no successful efficacy studies with immunomodulating agents in SS. The efficacy measures in previous treatment studies used either selected measures of glandular function, such as salivary flow, or composite outcome measures combining objective and subjective measures of disease activity. Recently, an international panel of Sjogren's experts created and validated two indices to capture both the objective (ESSDAI) and subjective (ESSPRI) measures of SS ([Seror et al, 2010](#); [Seror et al, 2011](#)). Although, neither of these indices has been used as a primary efficacy measure in clinical studies, retrospective application of the ESSDAI to treatment studies with belimumab (Benlysta; [Mariette et al, 2013](#)) and rituximab ([Meiners et al, 2012](#); [Moerman et al, 2014](#)) supports its use as a primary outcome measure in populations similar to this study. Unpublished data

from the ESSDAI development group identified the ESSDAI score of 5 as the cutoff between mild and moderate to severe disease, recommended the score as the lower threshold for entry in clinical studies, and also identified a change of at least 3 on the ESSDAI as a clinically significant improvement in this subpopulation.

The biomarkers to be assessed are justified on the basis that B7RP-1:ICOS interactions play a significant role in TFH cell differentiation. T follicular helper cells provide help to B cells in the germinal centers and promote their differentiation into antibody producing PB and PC.

The ESSPRI will be used to capture the subjective aspects of pSS. Measuring changes in individual elements of SS and general health status will allow a more detailed analysis of the results and better understanding of the impact of AMG 557/MEDI5872 on various pathologic processes in SS.

Safety and tolerability will be evaluated by standard measures.

The exploratory biomarker endpoints reflect the expected changes based on the mechanism of action of AMG 557/MEDI5872.

## **4 MATERIALS AND METHODS**

### **4.1 Subjects**

#### **4.1.1 Number of Subjects**

A total of 42 subjects will be randomized in a 1:1 ratio to receive a fixed SC dose of 210 mg AMG 557/MEDI5872 (n = 21) or placebo (n = 21) QW for 3 weeks (Days 1 to 15) and then 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 AMG 557/MEDI5872 QW (Days 99 to 113) and Q2W (Days 127 to 183) for an additional 12 weeks.

#### **4.1.2 Inclusion Criteria**

Subjects must meet all of the following criteria:

1. Age 18 through 75 years at the time of signing the ICF.
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States, European Union [EU] Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.
3. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from signing the ICF, and

must agree to continue using such precautions through Day 296 of the study; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

- a. Females of childbearing potential are defined as those who are not surgically sterile (ie, have not undergone bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause).
  - b. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in [Table 4.1.2-1](#).
4. Nonsterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see [Table 4.1.2-1](#)) from Day 1 through Day 296.
  5. Body weight  $\geq$  40 kg.
  6. Fulfill American-European Consensus Group (AECG) criteria for pSS (see [Appendix 3](#)).
  7. ESSDAI score  $\geq$  6.
  8. Positive anti-SS-A and/or anti-SS-B autoantibodies AND at least one of the following laboratory abnormalities:
    - a. IgG > 13 g/L
    - b. RF level > upper limit of normal (ULN)
    - c. Positive test for cryoglobulins
  9. Willingness to undergo protocol-required minor salivary gland biopsies.
  10. Meet all of the following tuberculosis (TB) criteria:
    - a. No signs or symptoms suggestive of active TB upon medical history or physical examination
    - b. Negative diagnostic TB test during screening (defined as a negative interferon-gamma release assay [IGRA] test for TB at screening) OR a confirmed indeterminate IGRA test for TB obtained during the screening period (those with confirmed indeterminate IGRA test will have repeat IGRA test at Days 99 and 197).
    - c. A chest x-ray with no evidence of current active infection (eg, TB) or old active TB, malignancy, or clinically significant abnormalities (unless due to pSS) obtained during the screening period or anytime within 90 days prior to signing the ICF.
  11. Immunization up to date as determined by local standard of care.



**Table 4.1.2-1 Highly Effective Methods of Contraception**

Barrier Methods	Hormonal Methods
<ul style="list-style-type: none"> <li>• Male condom plus spermicide</li> <li>• Copper T intrauterine device</li> <li>• Levonorgestrel-releasing intrauterine system (eg, Mirena<sup>®</sup>)<sup>a</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Implants</li> <li>• Hormone shot or injection</li> <li>• Combined pill</li> <li>• Minipill</li> <li>• Patch</li> </ul>

<sup>a</sup> This is also considered a hormonal method.

### 4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.
2. Concurrent enrollment in another clinical study involving an investigational treatment.
3. Previous treatment with AMG 557/MEDI5872.
4. Evidence of signs or symptoms of a viral, bacterial, or systemic fungal infection within 2 weeks (14 days) prior to randomization (Day 1) according to the assessment of the investigator; any infection requiring IV antibiotic or antiviral treatment within 8 weeks of randomization (Day 1); history of herpes zoster within 3 months prior to randomization (Day 1).
5. History of ethanol or drug abuse within 1 year prior to signing informed consent.
6. Evidence of significant renal insufficiency, defined by estimated glomerular filtration rate (eGFR) < 30 mL/minute/1.73m<sup>2</sup>.
7. Positive test at screening for either hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody.
8. During screening and prior to randomization (Day 1), any of the following:
  - a. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × ULN or total bilirubin > 2 × ULN (unless due to Gilbert’s disease) or evidence of chronic liver disease;
  - b. Total white blood cell count < 1,500 × 10<sup>6</sup>/L;
  - c. Neutrophil count < 1,000 × 10<sup>6</sup>/L;
  - d. Platelet count < 50,000 × 10<sup>6</sup>/L;
  - e. Hemoglobin < 8 g/dL.
9. Poorly controlled hypertension as judged by the Principal Investigator and confirmed by repeat assessment during the screening period.
10. Poorly controlled diabetes (hemoglobin A1c > 8%).
11. History of malignancy, except for basal or squamous cell carcinoma of the skin or cervical carcinoma in situ (cervical intraepithelial neoplasia Grade 3) treated with documented success of curative therapy.

12. Underlying condition (other than SS) that predisposes the subject to infections (eg, history of splenectomy).
13. History of anaphylaxis to any biological therapy.
14. A known history of allergy or reaction to any component of the investigational product formulation or history of severe reaction to any human gamma globulin therapy.
15. History of serum sickness.
16. Prior administration of any of the following:
  - a. Belimumab in the past 6 months prior to randomization (Day 1);
  - b. Rituximab in the past 12 months or CD19+ B cells  $< 5/\mu\text{L}$  if rituximab treatment was more than 12 months prior to randomization (Day 1);
  - c. Abatacept in the past 6 months prior to randomization (Day 1);
  - d. Tumor necrosis factor inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab) in the past 3 months prior to randomization (Day 1);
  - e. Tocilizumab in the past 3 months prior to randomization (Day 1);
  - f. Cyclophosphamide (or any other alkylating agent) in the past 6 months prior to randomization (Day 1); cyclosporine (except for eye drops), tacrolimus, sirolimus, mycophenolate mofetil, azathioprine, or leflunomide in the past 3 months prior to randomization (Day 1).
17. Participation in an investigational drug or device trial within 30 days or 5 half-lives, whichever time period is longer, prior to randomization (Day 1).
18. Any live or attenuated vaccine within 4 weeks prior to signing the ICF (administration of killed vaccines is acceptable).
19. Planned or ongoing pregnancy (a negative urine pregnancy test is required during screening and at study visits specified in the schedule of assessments) or lactation.
20. Receiving any of the following:
  - a. Corticosteroids:
    - i.  $> 10$  mg/day oral prednisone (or equivalent);
    - ii. Any change or initiation of new dose of oral corticosteroids within 4 weeks prior to signing the ICF through randomization (Day 1);
    - iii. Intramuscular, IV, or intra-articular corticosteroids within 4 weeks prior to signing the ICF through randomization (Day 1);
    - iv. Any change or initiation of new dose of topical corticosteroids within 2 weeks prior to signing the ICF through randomization (Day 1);
  - b. Antimalarials: any increase or initiation of new dose of antimalarials (eg, chloroquine, hydroxychloroquine, quinacrine) within 12 weeks prior to signing the ICF through randomization (Day 1).
  - c. Methotrexate:
    - i.  $> 20$  mg/week methotrexate;
    - ii. Any change or initiation of new dose of methotrexate within 4 weeks prior to signing the ICF through randomization (Day 1);
    - iii. Any change in route of administration.

- d. Any increase or initiation of new dose of regularly scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) within 2 weeks prior to signing the ICF through randomization (Day 1).
- e. Any increase or initiation of new doses of cevimeline or pilocarpine and cyclosporine eye drops (Restasis) within 2 weeks prior to signing the ICF through randomization (Day 1).

#### **4.1.4 Subject Enrollment and Randomization**

Study participation begins (ie, a subject is “enrolled”) once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system [IVRS/IWRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

Subjects will be randomized at a 1:1 ratio to receive either AMG 557/MEDI5872 or placebo as described in [Table 3.1.2-1](#). Randomization will be stratified by screening cellular immunophenotyping abnormalities (elevated TFH or elevated PB/PC vs normal values for both parameters).

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) and are rescreened will receive a new SID number. Subjects can be rescreened with medical monitor approval.

#### **4.1.5 Withdrawal from the Study**

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up; questionnaires (eg, for patient-reported outcomes [PROs]) should be returned by the subject. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

#### 4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occurs in the subject in question:

1. Withdrawal of consent from further treatment with investigational product or lost to follow-up
2. An AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing
3. Any Grade  $\geq 3$  TEAE (based on Common Terminology Criteria for Adverse Events [CTCAE; Version 4.0]) that is considered to be related to investigational product by the investigator, unless in the opinion of the investigator, the event(s) are manifestations of SS (eg, within the definitions included in the ESSDAI). Isolated Grade  $\geq 3$  laboratory abnormalities without a clinical event meeting the above criteria will not automatically lead to discontinuation of investigational product. Grade  $\geq 3$  neutropenia requiring a therapeutic intervention to increase neutrophil counts will lead to discontinuation of investigational product even in the absence of any other clinical event (eg, fever) regardless of the relatedness to investigational product.
4. At the medical monitor's discretion, subjects may be withdrawn if it is determined that eligibility criteria had been violated at the time of enrollment or subjects are noncompliant with study procedures
5. The investigator or the medical monitor deems withdrawal as being in the subject's best interest
6. Pregnancy
7. Any of the following liver function abnormalities:
  - a. ALT or AST  $> 8 \times$  ULN;
  - b. ALT or AST  $> 5 \times$  ULN for more than 2 weeks;
  - c. ALT or AST  $> 3 \times$  ULN and bilirubin  $> 2 \times$  ULN or international normalized ratio (INR)  $> 1.5$ ; see Section 5.6.2 for additional details regarding reporting of subjects with ALT or AST  $> 3 \times$  ULN and bilirubin  $> 2 \times$  ULN with unknown etiology (ie, Hy's law cases);
  - d. ALT or AST  $> 3 \times$  ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $> 5\%$ ).
8. Active TB or latent TB defined as a confirmed positive IGRA test.
9. The use of any of the medications/treatments listed in Section 4.7.2 (Prohibited Concomitant Medications) at any time during the treatment period.

Subjects who are permanently discontinued from receiving investigational product will enter the follow-up period and be followed for safety and have protocol-specified assessments performed including follow up of any AEs unless consent is withdrawn specifically from further study participation (Section 4.1.5), the subject is lost to follow-up or the subject is enrolled in another clinical study.

#### **4.1.7 Replacement of Subjects**

Subjects who receive at least one dose of investigational product will not be replaced.

#### **4.1.8 Withdrawal of Informed Consent for Data and Biological Samples**

##### **Biological Samples Obtained for the Main Study**

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

##### **Samples Obtained for Future Research**

Samples obtained for future research will be labeled with a sample identification number. If the subject withdraws consent for participating in the future research, the Sponsor will locate the subject's sample and destroy it.

If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the Sponsor with similar sample(s) from other subjects at a secure central laboratory. The subject's sample(s) will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the Sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the Sponsor for future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the Sponsor for future research, the Sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number(s) has been removed and the subject can no longer be linked to any sample(s). However, if the subject's sample(s) have already been used for research, the Sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

## 4.2 Schedule of Study Procedures

### 4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at screening. Assessments should be performed in the order shown in the table, whenever feasible.

**Table 4.2.1-1 Schedule of Screening Procedures**

Study Period	Screening
Visit Number	V1
Procedure / Study Day	Day -28 to Day -1
Written informed consent/assignment of SID number	X
Subject Global Assessment of Disease Activity	X
ESSPRI	X
Medical history	X
Physical examination	X
Vital signs (BP, HR, RR and temp)	X
Body height	X
Body weight	X
Sjogren's Classification Worksheet	X
ESSDAI	X
Physician Global Assessment of Disease Activity	X
28-joint count	X
Safety laboratory tests (hematology, chemistry, and urinalysis)	X
Coagulation tests	X
Hemoglobin A1c	X
Serum $\beta$ -hCG pregnancy test <sup>a</sup>	X
Autoantibody panel <sup>b</sup>	X
Exploratory autoantibody panel <sup>c</sup>	X
Immune panel <sup>d</sup>	X
Infectious disease panel <sup>e</sup>	X
Immunophenotyping assay	X
Chest X-ray <sup>f</sup>	X
ECG <sup>g</sup>	X
Inflammatory markers <sup>h</sup>	X
Exploratory biomarker sample (serum)	X
Optional biomarker repository sample (serum)	X
Optional biomarker repository sample (plasma)	X
Biopsy of salivary gland	X
Assessment of AEs/SAEs	X
Concomitant medications	X

**Table 4.2.1-1 Schedule of Screening Procedures**

Study Period	Screening
Visit Number	V1
Procedure / Study Day	Day -28 to Day -1
Verify eligibility criteria	X

AE = adverse event; ANA = anti-nuclear antibody; PA = posteroanterior; B-2 microglobulin = beta-2 microglobulin;  $\beta$ hCG = beta-human chorionic gonadotropin; BP = blood pressure; CRP = C-reactive protein; ECG = electrocardiogram; ENA = extractable nuclear antigens; 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; HIV = human immunodeficiency virus; HR = heart rate; IgG = immunoglobulin G; IgM = immunoglobulin M; IGRA = interferon-gamma release assay; LIPS = Luciferase Immunoprecipitation Systems; RR = respiratory rate; SAE = serious adverse event; SID = subject identification; temp = temperature; V = visit

- <sup>a</sup> Female subjects, unless surgically sterile or 1 year postmenopausal
- <sup>b</sup> Autoantibody panel includes ANA, ENA (anti-SS-A, anti-SS-B, anti-Smith/anti-ribonuclear protein), rheumatoid factor (at minimum, IgG and IgM)
- <sup>c</sup> Exploratory autoantibody panel includes assessment of anti-SS-A and anti-SS-B by LIPS assay
- <sup>d</sup> Immune panel includes complements C3 and C4, cryoglobulins, quantitative immunoglobulins, and immunofixation electrophoresis
- <sup>e</sup> Infectious disease panel includes HIV, hepatitis B and C, IGRA
- <sup>f</sup> A PA and lateral chest x-ray will be performed at screening, if not performed within the previous 3 months
- <sup>g</sup> Standard 12-lead ECG
- <sup>h</sup> Inflammatory markers include hypergammaglobulinemia, B-2 microglobulin, ESR, and CRP

**4.2.2 Active Treatment Period**

Table 4.2.2-1 shows all procedures to be conducted during the active treatment period. Assessments should be performed in the order shown in the table, whenever feasible.

All blood, saliva, and biopsy samples should be collected prior to investigational product administration; the time of collection for these samples should be recorded in source documentation.



**Table 4.2.2-1 Schedule of Study Procedures**

Visit Number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Study Day / Procedure	1	8 (±1)	15 (±1)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	85 (±3)	99 (±3)	106 (±1)	113 (±1)	127 (±3)	141 (±3)	155 (±3)	169 (±3)	183 (±3)	197 (±3)/ ETV
Subject Global Assessment of Disease Activity	X			X		X			X			X		X			X
ESSPRI	X			X		X			X			X		X			X
SF-36v2	X			X		X			X			X		X			X
PROFAD-SSI-SF	X			X		X			X			X		X			X
PGI-S	X			X		X			X			X		X			X
PGI-C	X			X		X			X			X		X			X
Physical examination	X		X	X		X			X		X			X			X
Vital signs (BP, HR, RR, temp)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight				X		X			X			X		X			X
Physician Global Assessment of Disease Activity	X			X		X			X			X		X			X
28-joint count	X			X		X			X			X		X			X
ESSDAI	X			X		X			X			X		X			X
Safety laboratory tests (hematology, chemistry, and urinalysis)	X		X	X		X			X		X			X			X
Coagulation tests									X								X
IGRA <sup>a</sup>									X								X
Urine pregnancy test <sup>b</sup>	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X
Autoantibody panel <sup>c</sup>	X			X		X			X			X		X			X
Exploratory autoantibody panel <sup>d</sup>	X			X		X			X			X		X			X
Immune panel <sup>e</sup>	X								X								X

**Table 4.2.2-1 Schedule of Study Procedures**

Visit Number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Study Day / Procedure	1	8 (±1)	15 (±1)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	85 (±3)	99 (±3)	106 (±1)	113 (±1)	127 (±3)	141 (±3)	155 (±3)	169 (±3)	183 (±3)	197 (±3)/ ETV
Anti-AMG 557/MEDI5872 antibodies sample	X			X		X			X			X					X
ECG <sup>f</sup>																	X
Inflammatory markers <sup>g</sup>	X								X								X
Exploratory biomarker sample (serum)	X			X		X			X			X		X			X
Exploratory biomarker sample (saliva)	X			X		X			X			X		X			X
Optional biomarker repository sample (serum)	X			X		X			X			X		X			X
Optional biomarker repository sample (plasma)	X			X		X			X			X		X			X
Optional biomarker repository sample (saliva)	X			X		X			X			X		X			X
Immunophenotyping assay	X			X		X			X								X
PK sample	X	X	X	X		X			X	X	X	X		X			X
PAXgene RNA	X		X	X		X			X			X		X			X
Oral evaluation (unstimulated and stimulated salivary flow)	X <sup>h</sup>			X		X			X			X		X			X
Ophthalmological evaluation (complete dry eye evaluation) <sup>i</sup>	X <sup>h</sup>								X								X
Cell pellet for DNA methylation	X								X								X
Biopsy of salivary gland <sup>j</sup>									X								
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

**Table 4.2.2-1 Schedule of Study Procedures**

Visit Number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Study Day / Procedure	1	8 (±1)	15 (±1)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	85 (±3)	99 (±3)	106 (±1)	113 (±1)	127 (±3)	141 (±3)	155 (±3)	169 (±3)	183 (±3)	197 (±3)/ ETV
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X																
Randomization	X																
<b>AMG 557/MEDI5872 or Placebo</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>								
<b>AMG 557/MEDI5872</b>									<b>X</b>	<b>X</b> <sup>k</sup>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>

AE = adverse event; ANA = anti-nuclear antibody; B-2 microglobulin = beta-2 microglobulin; BP = blood pressure; CRP = C-reactive protein; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ENA = extractable nuclear antigens; 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; ETV = Early Termination Visit; HR = heart rate; IgG = immunoglobulin G; IgM = immunoglobulin M; IGRA = interferon-gamma release assay; LIPS = Luciferase Immunoprecipitation Systems; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PI = Principal Investigator; PK = pharmacokinetic; PROFAD-SSI-SF = Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SF-36v2 = Short Form-36 version 2; temp = temperature; V = visit

Note: All assessments should take place prior to investigational product administration.

- <sup>a</sup> In subjects with confirmed indeterminate results at screening
- <sup>b</sup> Female subjects, unless surgically sterile or 1 year postmenopausal
- <sup>c</sup> Autoantibody panel includes ANA, ENA (anti-SS-A, anti-SS-B, anti-Smith/anti-ribonuclear protein), rheumatoid factor (at minimum, IgG and IgM)
- <sup>d</sup> Exploratory autoantibody panel includes assessment of anti-SS-A and anti-SS-B by LIPS assay
- <sup>e</sup> Immune panel includes complements C3 and C4, cryoglobulins, quantitative immunoglobulins, and immunofixation electrophoresis
- <sup>f</sup> Standard 12-lead ECG
- <sup>g</sup> Inflammatory markers include hypergammaglobulinemia, B-2 microglobulin, ESR, and CRP
- <sup>h</sup> Baseline oral and ophthalmological evaluations may be performed within 28 days prior to dosing on Visit 2
- <sup>i</sup> Ophthalmological evaluation includes Schirmer's test without anesthesia, van Bijsterveld score, and tear break-up time
- <sup>j</sup> Subjects who discontinue the study before Day 99 should only have the repeat biopsy of the salivary gland performed at the PI's discretion
- <sup>k</sup> Blinded placebo administration for subjects who received AMG 557/MEDI5872 from Days 1 to 85

### 4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the follow-up period. Assessments should be performed in the order shown in the table, whenever feasible.

**Table 4.2.3-1 Schedule of Follow-up Procedures**

Visit Number	V19	V20	V21	NA
Study Days / Procedure	225 (±7)	253 (±7)	296 /EOS (±7)	Unsch <sup>a</sup>
Subject Global Assessment of Disease Activity	X	X	X	X
ESSPRI	X	X	X	X
SF-36v2	X	X	X	X
PROFAD-SSI-SF	X	X	X	X
PGI-S			X	X
PGI-C			X	X
Physical examination	X	X	X	X
Vital signs (BP, HR, RR, temp)	X	X	X	X
Body weight	X	X	X	
Physician Global Assessment of Disease Activity	X	X	X	X
28-joint count	X	X	X	X
ESSDAI	X	X	X	X
Safety laboratory tests (hematology, chemistry, and urinalysis)	X	X	X	X
Coagulation tests			X	
Urine pregnancy test <sup>b</sup>	X	X	X	X
Autoantibody panel <sup>c</sup>			X	
Exploratory autoantibody panel <sup>d</sup>			X	
Immune panel <sup>e</sup>			X	X
Anti-AMG 557/MEDI5872 antibodies sample			X	X
Inflammatory markers <sup>f</sup>			X	
Exploratory biomarker sample (serum)			X	X
Exploratory biomarker sample (saliva)			X	X
Optional biomarker repository sample (serum)			X	X
Optional biomarker repository sample (plasma)			X	X
Optional biomarker repository sample (saliva)			X	X
Immunophenotyping assay			X	X
PK sample	X	X	X	X
PAXgene RNA			X	X
ECG <sup>g</sup>			X	X
Oral evaluation (unstimulated and stimulated salivary flow)	X	X	X	X

**Table 4.2.3-1 Schedule of Follow-up Procedures**

Visit Number	V19	V20	V21	NA
Study Days / Procedure	225 (±7)	253 (±7)	296 /EOS (±7)	Unsch <sup>a</sup>
Cell pellet collection for DNA methylation			X	
Ophthalmological evaluation <sup>h</sup> (complete dry eye evaluation)			X	X
Assessment of AEs/SAEs	X	X	X	X
Concomitant medications	X	X	X	X

AE = adverse event; ANA = anti-nuclear antibody; B-2 microglobulin = beta-2 microglobulin; BP = blood pressure; CRP = C-reactive protein; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; ENA = extractable nuclear antigens; 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; HR = heart rate; IgG = immunoglobulin G; IgM = immunoglobulin M; LIPS = Luciferase Immunoprecipitation Systems; NA = not applicable; PGI-S = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PI = Principal Investigator; PK = pharmacokinetic; PROFAD-SSI-SF = Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SF-36v2 = Short Form-36 version 2; temp = temperature; Unsch = unscheduled; V = visit

- <sup>a</sup> Unscheduled visit assessments are to be completed at the PI’s discretion
- <sup>b</sup> Female subjects, unless surgically sterile or 1 year postmenopausal
- <sup>c</sup> Autoantibody panel includes ANA, ENA (anti-SS-A, anti-SS-B, anti-Smith/anti-ribonuclear protein), and rheumatoid factor (at minimum, IgG and IgM)
- <sup>d</sup> Exploratory autoantibody panel includes assessment of anti-SS-A and anti-SS-B by LIPS assay
- <sup>e</sup> Immune panel includes complements C3 and C4, cryoglobulins, quantitative immunoglobulins, and immunofixation electrophoresis
- <sup>f</sup> Inflammatory markers include hypergammaglobulinemia, B-2 microglobulin, ESR, and CRP
- <sup>g</sup> Standard 12-lead ECG
- <sup>h</sup> Ophthalmological evaluation may be performed within 2 weeks prior to EOS, and includes Schirmer’s test without anesthesia, van Bijsterveld score, and tear break-up time

## 4.3 Description of Study Procedures

### 4.3.1 Efficacy

#### 4.3.1.1 European League Against Rheumatism Sjogren’s Syndrome Disease Activity Index

The ESSDAI is a validated consensus disease activity index with 12 domains (Constitutional, Lymphadenopathy, Glandular, Articular, Cutaneous, Pulmonary, Renal, Muscular, Peripheral Nervous System, Central Nervous System, Hematological, and Biological) that is able to capture changes in the severity of systemic manifestations of pSS. Each domain is weighted from 1 (Biologic domain) to 6 (Muscular domain) and has 3 or 4 levels of activity per domain, ranging from 0 (no activity) to 3 (high activity).

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

$$\begin{aligned}\text{Final Score} &= \text{Sum of all 12 domain scores} \\ \text{Domain score} &= \text{Activity level} \times \text{Domain weight}\end{aligned}$$

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.

Over the course of the study, the ESSDAI should be completed by the same MedImmune trained Principal Investigator, designated physician, or qualified site personnel whenever possible. If there is a change in site personnel over the course of the study, new Principal Investigators or site physicians/personnel must be trained prior to performing the ESSDAI.

A copy of the ESSDAI can be found in [Appendix 4](#).

#### **4.3.2 Patient-reported Outcomes**

Patient-reported outcomes instruments will be completed at the site on paper. Patient-reported outcomes assessments must be administered in a systematic way to ensure data integrity. The following best practice guidelines should be followed for all PRO assessments:

- Administer before other procedures
  - Always administer PRO instruments before other study procedures
- Provide the right environment
  - Provide a quiet and private location to complete the instrument
- No right or wrong answers
  - Remind subjects that there are no right or wrong answers and that we are asking them to complete these questionnaires because we're interested in hearing directly from them on how they feel
- Help with procedural questions
  - Make sure the subject understands how to complete the instrument. Instrument instructions are usually self-explanatory but staff may answer questions about procedural issues like what it means to "tick a box"
- Avoid bias: do not clarify the meaning of questions or responses
  - Sometimes subjects will ask center staff to clarify the meaning of a question or response. To avoid introducing any bias, politely tell the subject that you cannot

clarify items. Remind them that there are no right or wrong answers. Tell them that they should select the response that best answers the question as they understand it

- No time limits
  - Although most instruments require only a few minutes to complete, the subject should be given as much time as is needed
- Review for completeness
  - Prompt review of the questionnaire for completeness will minimize missing data and data queries. If an item is left blank, ask the subject if they intended to leave the item blank. Provide an opportunity for the subject to answer if they wish

#### **4.3.2.1 Subject Global Assessment of Disease Activity**

Subjects will be asked to complete the SGA. The SGA is a single-item question which asks subjects 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 physician and subject must complete the global assessments (MDGA and SGA, respectively) independently of each other. A copy of the SGA can be found in [Appendix 5](#).

#### **4.3.2.2 Short-form 36 Version 2**

The SF-36v2 [acute recall] is a 36-item, subject-completed, general health status assessment ([Ware et al, 2007](#)). 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 recall period for the acute version is one week (ie, “last week”). The instrument can be completed in approximately 10-18 minutes. A copy of the SF-36v2 can be found in [Appendix 6](#).

#### **4.3.2.3 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 instrument can be completed in approximately 5-8 minutes. A copy of the PROFAD-SSI-SF can be found in [Appendix 7](#).



#### **4.3.2.4 European League Against Rheumatism Sjogren's Syndrome Patient Reported Index**

The ESSPRI is a 3-item, subject-completed assessment of SS symptoms ([Seror et al, 2011](#)). 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. The instrument can be completed in approximately 1 minute. A copy of the ESSPRI can be found in [Appendix 8](#).

#### **4.3.2.5 Patient Global Impression of Change**

The 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 (much better, about the same, much worse). A copy of the PGI-C can be found in [Appendix 9](#).

#### **4.3.2.6 Patient Global Impression of Severity**

The PGI-S is a single item designed to capture the subject's perception of overall symptom severity at the time of assessment on a 5-point categorical response scale (no symptoms, very severe symptoms). A copy of the PGI-S can be found in [Appendix 10](#).

### **4.3.3 Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs**

#### **4.3.3.1 Medical History**

Complete medical history will include past and current medical conditions such as cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders. Medical history will be performed at screening and will be reviewed at Day 1; any changes in medical history since screening will be documented, if applicable.

#### **4.3.3.2 Physical Examination, Height, and Weight**

Physical examinations, including weight will be performed by a physician or qualified designee and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding will be recorded in the electronic case report form (eCRF). Physical examinations including weight will be performed at screening

and during the active treatment and follow-up periods as specified in the schedule of study procedures (see [Table 4.2.1-1](#), [Table 4.2.2-1](#), [Table 4.2.3-1](#)). Height will be measured at screening only.

#### **4.3.3.3 Vital Signs**

Vital signs (blood pressure, heart rate, respiratory rate, and tympanic body temperature) will be obtained at screening and during the active treatment and follow-up periods as specified in the schedule of study procedures (see [Table 4.2.1-1](#), [Table 4.2.2-1](#), [Table 4.2.3-1](#)). All vital sign measurements will be made with the subject in a sitting position having rested in this position for at least 5 minutes before each reading. Vital signs will be obtained immediately before investigational product administration (within 15 minutes of the beginning of SC injection), immediately after investigational product administration, and approximately 30 minutes after completion of investigational product administration. During the weekly administration periods (Days 1, 8, 15, 99, 106, and 113), vital signs will also be evaluated at approximately 60 minutes after completion of dose administration and until stable as judged by the investigator.

#### **4.3.3.4 Electrocardiogram**

Electrocardiogram (ECG) recordings will be obtained at screening and during the active treatment and follow-up periods as specified in the schedule of study procedures (see [Table 4.2.1-1](#), [Table 4.2.2-1](#) and [Table 4.2.3-1](#)). At the specified visits, 12-lead ECGs will be obtained after 10 minutes of supine rest. The following variables will be reported: heart rate, RR, PR, QRS and QT intervals from the primary lead of the digital 12-lead ECG. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

#### **4.3.4 Chest Radiograph**

A chest x-ray (posteroanterior and lateral views) will be obtained during the screening period or can be substituted with documentation of a previous chest x-ray performed anytime within 90 days of signing the ICF. A chest x-ray that has no evidence of current active infection (eg, TB) or old active TB, malignancy, or clinically significant abnormalities (unless due to pSS) is required to meet inclusion criteria.

In addition to screening for the presence of current active infection (eg, TB) or old active TB, malignancy, or clinically significant abnormalities (unless due to pSS), the chest x-ray will be used to document the presence of significant cardiac and pulmonary disease abnormalities as well as to provide the initial disease activity data (pulmonary involvement) needed for the

ESSDAI assessment on Day 1. A formal radiologic report of the chest x-ray should be available at the site. The report should allow the assessment of the following:

- No evidence of any active infection including TB
- No evidence of old active TB
- No evidence of malignancy
- No evidence of other clinically significant abnormalities unless felt secondary to pSS (these should be specified [eg, pleural effusion])

#### 4.3.5 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically significant abnormal laboratory results, which represent a change which may require an intervention, should be repeated as soon as possible (preferably within 24 to 48 hours from receipt of results) at the discretion of the Principal Investigator.

Clinical laboratory safety tests can be repeated at the Principal Investigator's discretion.

The following clinical laboratory tests will be performed (see [Table 4.2.1-1](#), [Table 4.2.2-1](#), [Table 4.2.3-1](#) for the schedule of tests):

#### Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- Cholesterol (including total, low-density lipoprotein, and high-density lipoprotein)
- Triglycerides
- Alkaline phosphatase (ALP)
- Total bilirubin and direct bilirubin
- Creatinine
- Blood urea nitrogen
- eGFR
- Glucose
- Albumin
- Total protein
- Uric acid
- Creatinine phosphokinase

**Note for serum chemistries:** Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

## Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Platelet count
- Hemoglobin

## Coagulation

- INR
- Prothrombin time
- Activated partial thromboplastin time

## Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy including WBC/high power field (HPF), RBC/HPF

## Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG)
- Serum beta-hCG (at screening only)

## Other Safety Tests

- Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody
- HIV antibody
- IGRA

## Other Tests

- Autoantibody panel: anti-nuclear antibody, extractable nuclear antigens (anti-SS-A, anti-SS-B, anti-Smith/anti-ribonuclear protein), RF (at minimum, IgG and IgM)
- Exploratory autoantibody panel: anti-SS-A and anti-SS-B by Luciferase Immunoprecipitation Systems assay
- Immune panel: complements C3 and C4, cryoglobulins, quantitative Igs, and immunofixation electrophoresis
- Inflammatory markers: beta-2 microglobulin, ESR, CRP
- Hemoglobin A1c

#### **4.3.6 Pharmacokinetic Evaluation and Methods**

Serum samples for AMG 557/MEDI5872 concentration determination will be collected at baseline prior to investigational product administration and also during the active treatment and follow-up periods of the study (see [Table 4.2.2-1](#) and [Table 4.2.3-1](#)).

AMG 557/MEDI5872 serum concentrations will be measured using a validated enzyme-linked immunosorbent assay developed at Amgen.

AMG 557/MEDI5872 plasma concentration will be measured prior to investigational product administration.

#### **4.3.7 Immunogenicity Evaluation and Methods**

Serum samples will be collected for the assessment of anti-AMG 557/MEDI5872 antibodies against AMG 557/MEDI5872 during the active treatment and follow-up periods of the study (see [Table 4.2.2-1](#) and [Table 4.2.3-1](#)). Serum will be measured for the presence of anti-AMG 557/MEDI5872 antibodies by Amgen using a validated immunoassay.

#### **4.3.8 Biomarker Evaluation and Methods**

Serum, plasma, whole blood, tissue, and saliva samples will be collected at various time points as outlined in [Table 4.2.1-1](#), [Table 4.2.2-1](#) and [Table 4.2.3-1](#). All biomarker analyses will be conducted to test hypotheses associated with the mechanism of action of AMG 557/MEDI5872, identify subsets of subjects responsive to AMG 557/MEDI5872, and to characterize the gene signatures. Detailed instructions on sample collection, processing and shipping will be provided in a separate laboratory manual.

##### **4.3.8.1 Biopsy of Salivary Gland**

A minor salivary gland biopsy will be performed during screening, after the subject signs the informed consent but before receiving investigational product, and at Day 99 (see [Table 4.2.1-1](#) and [Table 4.2.2-1](#)) for clinical evaluation and assessment of tissue biomarkers. Subjects who meet eligibility criteria after rescreening do not need to have a minor salivary gland biopsy during rescreening if a biopsy was done during their first screening period. The biopsy obtained during the first screening can be used as the baseline biopsy. The minor salivary glands are the most accessible glands located just under the mucosal surface in the lower lip. Using sterile technique, a shallow incision 1-2 cm in length should be made on either side of the midline of inner lip under local anesthesia. The screening and Day 99 biopsies will be taken from different sides of the lip. A minimum of 3 glands and a maximum of 6 glands should be obtained for analysis. Closure of the incision and selection of suture (eg, suture size and/or type [resorbable vs traditional]), as well as postoperative care and

follow-up, should be in accordance with local medical practice and in the judgment of the Principal Investigator. Simple analgesics are allowed in the postoperative period, as needed.

Minor salivary gland biopsies will be analyzed for 1) the focus score (a semi-quantitative assessment of focal lymphocytic sialoadenitis, which is defined as the presence of  $\geq 1$  dense aggregate of 50 or more lymphocytes in a 4 mm<sup>2</sup> area), 2) immunohistochemistry enumeration of TFH and PC (including PB) and 3) ribonucleic acid (RNA) isolation to evaluate gene signature biomarkers. Detailed instructions on sample collection, processing and shipping will be provided in a separate laboratory manual.

#### **4.3.8.2 Immunophenotyping Assay**

Blood samples for immunophenotyping (including but not limited to B-cell counts (eg, cells/ $\mu$ L) and B-cell subpopulations, including PB and PC, TFH counts, and ICOS levels on CD4+ T cells) will be collected at specified time points specified in [Table 4.2.1-1](#), [Table 4.2.2-1](#), [Table 4.2.3-1](#). Levels of TFH and PB/PC at screening will be used to stratify subjects (see Section 4.1.4 for more details). Detailed instructions on sample collection, processing and shipping will be provided in a separate laboratory manual.

#### **4.3.8.3 PAXgene Ribonucleic Acid**

Whole blood samples will be collected in PAXgene tubes for total RNA sample preparation. Ribonucleic acid will be used in the analyses of transcript expression using both Affymetrix U133+ microarrays and quantitative reverse-transcriptase polymerase chain reaction technologies and stored for future analyses as specified in the exploratory biomarker analysis plan (EBAP). Gene signatures measuring the presence of the following cell populations will be evaluated both pre- and post-dose and during the follow-up period at time points specified in [Table 4.2.2-1](#) and [Table 4.2.3-1](#): plasma cells, B cells, and TFH cells. Detailed instructions on sample collection, processing and shipping will be provided in a separate laboratory manual. These data will be analyzed using descriptive statistics and will not be included in the clinical study report (CSR).

#### **4.3.8.4 Cell Pellet for Deoxyribonucleic Acid Methylation**

The cell pellet will be collected and stored for a deoxyribonucleic acid (DNA) methylation assay at time points specified in [Table 4.2.2-1](#) and [Table 4.2.3-1](#). These samples will not be used for any genetic testing and will be destroyed at the end of the study. Detailed instructions on sample collection, processing and shipping will be provided in a separate laboratory manual. These data will be analyzed using descriptive statistics and will not be included in the CSR.

#### **4.3.8.5 Exploratory Biomarker Sample**

Serum and saliva samples will be collected for analyses of protein biomarkers, including, but not limited to SS-related cytokines (B-cell activating factor, interleukin [IL]-6, IL-21) and SS-related exploratory autoantibodies (parotid secretory protein, carbonic anhydrase 6, salivary gland protein 1) at time points specified in [Table 4.2.1-1](#), [Table 4.2.2-1](#) and [Table 4.2.3-1](#). Detailed instructions on sample collection, processing and shipping will be provided in a separate laboratory manual. These data will be analyzed using descriptive statistics and will not be included in the CSR.

#### **4.3.8.6 Optional Biomarker Repository Samples**

There is reason to believe that future scientific advancements may further the understanding of the pathophysiology in various disease states as they pertain to safety or efficacy. Collection of blood and saliva samples will allow the testing of as yet unknown hypotheses raised by these scientific advancements or as laboratory techniques advance. Deoxyribonucleic acid will not be extracted from samples collected in this study. As such, samples will only be used for research in pSS and not for current or future DNA testing, genotyping, or DNA analyses.

Sampling for biomarker repository at a given site is contingent upon the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of sampling for exploratory biomarker assessments. If a site's IRB/IEC does not approve the collection of samples for exploratory biomarker assessments, this section will not be applicable.

Samples (including serum, plasma, and saliva) for biomarker discovery and validation will only be collected from subjects who consent to biomarker sample collection. The subject may withdraw their consent to have their samples used for biomarker sample repository analyses at any time. Samples will be stored at MedImmune for up to a maximum of 25 years after the end of the main study at which time any remaining samples will be destroyed.

Detailed instructions on sample collection, processing, and shipping will be provided in a separate laboratory manual. These data will be analyzed using descriptive statistics and will not be included in the CSR.



### **4.3.9 Disease Evaluation and Methods**

#### **4.3.9.1 Training**

In order to maintain consistent evaluation of pSS disease activity across study sites, MedImmune will provide training to Principal Investigators and any designated site personnel who will be completing the following disease evaluation assessments:

- ESSDAI
- Joint count

The ESSDAI and joint count must be administered by the Principal Investigator or another qualified site personnel who, as per Principal Investigator discretion, are qualified to perform the assessments. Training will include printed training materials and formal presentations, as well as web-based training modules.

Over the course of the study, investigator assessments for a given subject should be completed by the same MedImmune trained Principal Investigator, designated physician, or qualified site personnel whenever possible. If there is a change in site personnel over the course of the study, new Principal Investigators or site physicians/personnel must be trained prior to performing the ESSDAI and joint count assessments.

It is expected that the Principal Investigator will ensure their site personnel have adequate experience and training qualifications to perform disease assessments. Documentation of all training will be maintained in the site's study file.

#### **4.3.9.2 Sjogren's Classification Worksheet**

To ensure that the correct subject population is enrolled (subjects with pSS) during screening, sites will be required to complete a Sjogren's Classification Worksheet for each screened subject ([Table 4.2.1-1](#)). The original copy should be maintained as a source document in the subject's study file.

The worksheet is based on the AECG SS Classification Criteria, which is broken down into three sections: 1) Inclusion Criteria; 2) Classification Rules; and 3) Exclusion Criteria.

The AECG SS Classification Criteria contains 6 inclusion criteria, including 2 criteria that require subjects to answer questions regarding ocular and oral dryness; objective confirmation of ocular involvement with ocular dyeing tests; histopathologic findings based on minor salivary gland biopsy; and objective confirmation of salivary gland involvement through salivary flow tests, parotid sialography, and/or salivary scintigraphy.

The Classification Rules provides 3 distinct definitions for diagnosing pSS based on the inclusion criteria. A definition for sSS is also included.

The AECG SS Classification Criteria also includes 7 exclusion criteria, including: 1) past head and neck radiation treatment; 2) hepatitis C infection; 3) acquired immunodeficiency syndrome; 4) pre-existing lymphoma; 5) sarcoidosis; 6) graft versus host disease; and 7) use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug).

#### **4.3.9.3 Physician Global Assessment of Disease Activity**

A qualified investigator will complete the MDGA at the time points specified in [Table 4.2.1-1](#), [Table 4.2.2-1](#), and [Table 4.2.3-1](#). The MDGA represents the investigator's overall assessment of pSS disease severity on a 0 to 10 Likert scale, with 0 indicating 'inactive disease' and 10 indicating 'very highly active disease.' Every attempt should be made to have the same investigator complete the MDGA for each subject throughout their study participation.

#### **4.3.9.4 28-joint Count**

A trained investigator will assess 28-joint count at the time points specified in [Table 4.2.1-1](#), [Table 4.2.2-1](#), and [Table 4.2.3-1](#). The swollen and tender joint count is based on left and right shoulder, elbow, wrist, metacarpophalangeal (MCP)1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP)1, PIP2, PIP3, PIP4, PIP5 joints of the upper extremities, and left and right knee of the lower extremities. Each of the 28 joints will be evaluated for the presence of synovitis. Subjects will be queried at the start of the 28-joint count (prior to assessment of tenderness and swelling) as to whether they have experienced or are experiencing pain in any of the 28 joints.

#### **4.3.9.5 Oral Evaluation**

An oral evaluation, including the unstimulated whole saliva flow rate and collection, and stimulated whole saliva flow rate and collection, will be performed at the time points specified in [Table 4.2.2-1](#) and [Table 4.2.3-1](#).

The unstimulated salivary flow assessment should be performed before the stimulated flow rate and collection. Subjects receiving standard of care for xerostomia at screening must discontinue use of pilocarpine or cevimeline for at least 12 hours and artificial saliva for at least 3 hours prior to the collection of saliva. Subjects should be prohibited from eating or drinking for at least 90 minutes prior to the collection of saliva. To minimize diurnal variation, every attempt should be made to collect saliva at the same time of the day as the Day 1 assessment across all subsequent visits.

During the unstimulated salivary flow assessment, subjects will be asked to refrain from swallowing or speaking. Subjects should refrain from speaking or swallowing, with the exception of a single swallow, immediately prior to the initiation of the procedure. The entire duration of the procedure is expected to be approximately 5 minutes, during which subjects will be asked to allow saliva to accumulate in the oral cavity for a period of 60 seconds prior to emptying into a pre-weighed container; this is to be repeated a total of 5 times during the test.

Stimulated salivary flow rate and collection should always be performed after unstimulated salivary flow and collection. Subjects may be offered a single rinse with water between the procedures. For stimulated saliva measurements, the same procedures are followed as for the unstimulated collections, except that stimulus with 2% citric acid directly to both sides of the posterior lateral tongue will be applied for 5 seconds every 30 seconds for 2 minutes prior to the first stimulated collection. The weight of the collection vial is to be determined and recorded before and after the collection, with the difference representing the saliva volume.

#### 4.3.9.6 Ophthalmological Evaluation

A dry eye exam will be performed by an ophthalmologist or a trained professional at the time points specified in [Table 4.2.2-1](#) and [Table 4.2.3-1](#). At a minimum, it will include a Schirmer’s test without local anesthesia, corneal and conjunctival staining (van Bijsterveld score), and the assessment of tear break-up time. These assessments will be performed according to local standard of care procedures. Other clinically indicated examinations may be performed as clinically indicated at the discretion of the ophthalmologist or a trained professional.

#### 4.3.10 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject at each visit (and across all visits) from screening through Day 296 is presented in [Table 4.3.10-1](#). If repeats of any blood tests are required, the volume of blood collection will increase accordingly.

**Table 4.3.10-1 Estimate of Blood Volume to be Collected**

Visit Day	Estimated Blood Volume (mL)
Day -28 to Day -1	65
Day 1	77
Day 8	5
Day 15	15
Day 29	54
Day 43	0

**Table 4.3.10-1 Estimate of Blood Volume to be Collected**

Visit Day	Estimated Blood Volume (mL)
Day 57	54
Day 71	0
Day 85	0
Day 99	80
Day 106	5
Day 113	12
Day 127	44
Day 141	0
Day 155	34
Day 169	0
Day 183	0
Day 197/Early Termination Visit	80
Day 225	12
Day 253	12
Day 296/End of Study Visit	77
Unscheduled Visit	variable <sup>a</sup>
<b>Total</b>	<b>626</b>

<sup>a</sup> The amount of blood taken at the unscheduled visit is estimated to be 15 mL.

#### 4.4 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects. Study treatment will be suspended if any of the following events occur in this study:
  - a. Any death that that is considered to be related to investigational product by the investigator
  - b. Any Grade 4 TEAE (based on CTCAE [Version 4.0]) that is considered to be related to investigational product by the investigator, with the exception of anaphylactic reaction
  - c. If 2 subjects have TEAEs in the same organ system of Grade  $\geq 3$  (based on CTCAE [Version 4]) that are considered to be related to investigational product by the investigator, unless in the opinion of the investigator, the events are manifestations of SS (eg, within the definitions included in the ESSDAI). Isolated Grade  $\geq 3$  laboratory abnormalities without a clinical event meeting the above criteria will not automatically trigger suspension of the study.

In these cases, study treatment will be suspended, the subject data will be unblinded, and the data will be reviewed by MedImmune Patient Safety. Based upon this review, MedImmune Patient Safety will determine if the dosing may resume or if the study will be terminated.

2. Subject enrollment is unsatisfactory
3. Non-compliance that might significantly jeopardize the validity or integrity of the study
4. Sponsor decision to terminate development
5. Sponsor decision to terminate the study based on a futility analysis

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs, when applicable) will be obtained prior to resuming the study.

## 4.5 Investigational Products

### 4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

**Table 4.5.1-1 Identification of Investigational Products**

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
AMG 557/MEDI5872	Amgen	[REDACTED]
Placebo	Amgen	Supplied as frozen liquid containing [REDACTED]

w/v = weight/volume

Investigational product will be supplied to the site in vials with identical appearances in blinded, coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). Each carton is labeled with a unique number range that corresponds to the labeled number series of the vials within the carton. Refer to Section 4.6.2 for information on methods for ensuring blinding.

#### **4.5.1.1 Investigational Product Dose Preparation**

The investigational product manager will select the kit assigned by the IVRS/IWRS to prepare the subject's dose.

#### **4.5.1.2 Investigational Product Inspection**

Each vial selected for dose preparation should be inspected. AMG 557/MEDI5872 and placebo are supplied as frozen liquid drug product. Instructions for thawing investigational product are described in Section 4.5.1.3.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.7) for further instructions.

#### **4.5.1.3 Investigational Product Thawing Instructions**

The pharmacist or qualified designee will thaw 4 vials of investigational product for each dose.

- The pharmacist or qualified designee should not remove the vials from the assigned kit. The vials can remain in the kit during the thaw process.

### **Thawing**

Remove the vials from the freezer and thaw in the dark in one of two ways:

1. Thaw undisturbed at room temperature (20°C to 40°C) for up to 1 hour.
2. Thaw undisturbed at refrigerated temperature (2°C to 8°C) for up to 12 hours.

During the thaw:

1. Leave vials undisturbed, except to gently swirl to check for completion of thaw.
2. Protect from light by thawing in a darkened refrigerator or in a secondary container (ie, covered box)
3. Never shake vials vigorously, especially during the thawing process



- Carefully check the vial for cracks (see below instructions).

### **After Thawing**

- Once completely thawed, vials should be warmed to room temperature for up to 1 hour before administration.
- Gently swirl the vial to ensure the contents are mixed to a clear, homogeneous solution.
- Carefully check the vial for damage (eg, cracks). Vials should be free of any external moisture or condensation during inspection. If necessary, wipe the vial with a clean, lint-free wipe to remove moisture. Quarantine damaged vials and notify the investigator and site monitor to report compromised investigational product and obtain further instructions for destruction and reporting.

### **Storage of Thawed Investigational Product**

- Unopened vials may be kept refrigerated (2°C to 8°C), protected from light, for a maximum time of 7 days from the time the investigational product was removed from frozen storage.
- Unopened vials may be kept at room temperature (20°C to 40°C), protected from light, for a maximum time of 8 hours from the time the investigational product was removed from frozen or refrigerated storage. Any time used for room temperature storage is also counted against the refrigerated storage.
- Unopened vials may be moved between refrigerated storage and room temperature storage as needed within the maximum time limits for each temperature.

PLEASE NOTE:

- Do not re-freeze the vials once set up for thaw.
- Do not use opened and dispensed vials for subsequent dosing.
- Storage times and temperatures must be strictly adhered to (see [Table 4.5.1.3-1](#)).

**Table 4.5.1.3-1 Allowable Time and Temperatures for Investigational Product Thawing**

Temperature	Maximum Storage Time of Vial Post-thaw	Timing of IP Administration
Room 20°C to 40°C (68°F to 104°F)	8 hours	IP should be administered within 8 hours after the vial is initially placed at room temperature.
Refrigerated 2°C to 8°C (36°F to 46°F)	7 days	IP should be equilibrated at room temperature for at least 1 hour before administration. IP should be administered within 8 hours after the vial is initially



**Table 4.5.1.3-1 Allowable Time and Temperatures for Investigational Product Thawing**

Temperature	Maximum Storage Time of Vial Post-thaw	Timing of IP Administration
		placed at room temperature (ie, from the start of equilibrium at room temperature).

IP = investigational product

Thawed vials of the investigational product may be maintained at 2°C to 8°C for a total of 7 days. The investigational product not used for study administration within this time duration must be discarded. Once completely thawed, vials should be transferred to room temperature and gently swirled to ensure the vial contents are adequately mixed. Do not shake or refreeze investigational product after thawed. Mixing may result in the formation of small bubbles, which is normal. Preparation of the clinical supplies should be performed using aseptic techniques and under sterile conditions. Prolonged exposure of the IP to light should be avoided. Before administration, the thawed investigational product should be warmed to room temperature, if necessary, for a minimum of 1 hour, but should not be kept at room temperature more than 8 hours. The investigational product not used for study administration within this time duration must be discarded.

**4.5.1.4 Dose Preparation Steps**

No incompatibilities between AMG 557/MEDI5872 and plastics passing compatibility tests have been observed.

AMG 557/MEDI5872 and placebo do not contain preservatives and any unused portion must be discarded. Preparation of investigational product is to be performed aseptically. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new dose must be prepared from new vials.

Each dose of investigational product will be administered by two injections (see [Table 4.5.1.4-1](#)) and must be prepared using plastic disposable syringes and aseptic technique.

<b>Table 4.5.1.4-1 Preparation of Investigational Product Dose</b>		
<b>Vials Required</b>	<b>Dose Preparation Instructions</b>	<b>Syringe Size</b>
4 vials (placebo or AMG 557/MEDI5872)	Step 1: <ul style="list-style-type: none"> <li>• Withdraw 0.5 mL of investigational product using a 3-mL syringe with a 19-gauge needle</li> <li>• Remove the 19-gauge needle</li> <li>• Replace with another 19-gauge needle and cap</li> <li>• Set vial aside and do not reuse</li> </ul>	3 mL
	Step 2: <ul style="list-style-type: none"> <li>• With the same syringe used in Step 1, withdraw 1 mL of investigational product for a total volume of 1.5 mL</li> <li>• Remove the 19-gauge needle</li> <li>• Replace with a 25- or 27-gauge 1/2-inch needle and cap syringe until administration</li> <li>• Set vial aside and do not reuse</li> </ul>	3 mL
	Step 3: <ul style="list-style-type: none"> <li>• Repeat Steps 1 and 2 for remaining 2 investigational product vials using a fresh syringe and needles for the second dose</li> </ul>	3 mL

#### **4.5.1.5 Treatment Administration**

The first day of dosing is considered Day 1.

Each dose of AMG 557/MEDI5872 or placebo should be administered using the following guidelines:

- Female subjects, unless surgically sterile or 1 year postmenopausal, must have a negative urine pregnancy test prior to receiving AMG 557/MEDI5872 or placebo

#### **4.5.1.6 Monitoring of Dose Administration**

Subjects should be observed for at least 1 hour following the administration of investigational product during the weekly treatment visits (ie, Days 1, 8, 15, 99, 106, and 113) and at least 30 minutes following the administration of investigational product at all other treatment visits. Sites should follow local guidelines if they require longer observation periods. Treatment for injection-site reactions, hypersensitivity reactions, and/or anaphylaxis is at the discretion of the Principal Investigator and should reflect local standard of care.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

#### **4.5.1.7 Reporting Product Complaints**

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: [productcomplaints@medimmune.com](mailto:productcomplaints@medimmune.com)

Phone: +1-301-398-2105  
+1-877-MEDI-411 (+1-877-633-4411)

Fax: +1-301-398-8800

Mail: MedImmune, LLC  
Attn: Product Complaint Department  
One MedImmune Way  
Gaithersburg, MD 20878 USA

#### **4.5.2 Labeling**

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

#### **4.5.3 Storage**

Storage of investigational product is summarized in [Table 4.5.3-1](#).

**Table 4.5.3-1 Storage of Investigational Product**

Freezer Median Temperature	Acceptable Variation	Acceptable Range
-30°C or -70°C	-30 (±10)°C or -70 (±10)°C	-20°C to -40°C or -60°C to -80°C

Thawing temperature requirements can be found in Section 4.5.1.3.

#### **4.5.4 Treatment Compliance**

Investigational product is administered by study site personnel, who will monitor compliance.

#### **4.5.5 Accountability**

The investigator’s or site’s designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

### **4.6 Treatment Assignment and Blinding**

#### **4.6.1 Methods for Assigning Treatment Groups**

An IVRS/IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IVRS/IWRS that the subject meets eligibility criteria and the IVRS/IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized at a 1:1 ratio to receive either AMG 557/MEDI5872 or placebo as described in Table 3.1.2-1. Randomization will be stratified by screening cellular immunophenotyping abnormalities (elevated TFH or elevated PB/PC vs normal values for both parameters).

Investigational product (AMG 557/MEDI5872 or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

## **4.6.2 Methods for Ensuring Blinding**

This is a double-blind study in which AMG 557/MEDI5872 and placebo are identically labeled and indistinguishable in appearance. As such, neither the subject/legal representative nor any of the investigational site staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation [ICH] E9).

Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will also be unaware of the treatment received from the start of the study until all subjects have reached Day 99 or withdrawn from the study. After this time, Sponsor staff may be unblinded, as described in Section 4.6.3.2.

In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the Sponsor must be notified *immediately*.

## **4.6.3 Methods for Unblinding**

### **4.6.3.1 Unblinding in the Event of a Medical Emergency**

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. At minimum, an attempt must be made by the investigator to *immediately* contact the medical monitor prior to unblinding. Instructions for unblinding an individual subject's investigational product allocation, including the requirement to immediately contact the medical monitor prior to unblinding, are contained in the IVRS/IWRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Such unblinding does not on its own require the subject to be discontinued from investigational product.

### **4.6.3.2 Unblinding for the Primary Analyses**

Planned analyses are described in Section 4.8.7. The primary analysis will be performed after all subjects have completed Day 99 or have withdrawn from the study. 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 or follow-up phases of the study until these subjects have completed the study.

#### **4.7 Restrictions During the Study and Concomitant Treatment(s)**

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

##### **4.7.1 Permitted Concomitant Medications**

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” as listed in Section 4.7.2.

Protocol permitted medications for pSS include oral corticosteroids, anti-malarials, methotrexate, NSAIDs, as well as, cevimeline, pilocarpine and cyclosporine eye drops for dry mouth and eyes, respectively.

Those subjects who are receiving protocol permitted medications for pSS must be maintained on a stable regimen (and for methotrexate, route of administration) throughout the treatment period.

Subjects should also receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

##### **4.7.2 Prohibited Concomitant Medications**

Subjects are not permitted to receive any of the following while receiving investigational product:

- Belimumab
- Rituximab
- Abatacept

- Tumor necrosis factor inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab)
- Tocilizumab
- Cyclophosphamide (or any other alkylating agent), cyclosporine (except for eye drops), tacrolimus, sirolimus, mycophenolate mofetil, azathioprine, or leflunomide
- Unstable doses of antimalarials (eg, chloroquine, hydroxychloroquine, quinacrine)
- Corticosteroids: > 10 mg/day oral prednisone (or equivalent) or any form of parental (IV, intramuscular, or intra-articular) corticosteroids
- Methotrexate: > 20 mg/week
- Increase in the doses of regularly scheduled NSAIDs
- Increase in the doses of cevimeline or pilocarpine and cyclosporine eye drops (Restasis)
- Any live or attenuated vaccine (administration of killed vaccines is acceptable)

Other than the medications described above, use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc from screening through Day 296/End of Study (EOS) is discouraged. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

## **4.8 Statistical Evaluation**

### **4.8.1 General Considerations**

Tabular summaries will be presented by treatment group. 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. Baseline values will be defined as the last assessment prior to the first administration of investigational product. Additional details of statistical analyses will be described in the statistical analysis plan.

The intent-to-treat (ITT) Population is defined as all subjects who are randomized and treated with investigational product and will be analyzed according to the initial randomization.

The as-treated Population is defined as all subjects who receive any investigational product and will be analyzed according to the actual treatment received.

Missing data will be imputed using the last-observation-carried-forward approach through the end of the double-blind, placebo-controlled treatment period.



Further details will be provided in the statistical analysis plan.

#### **4.8.2 Sample Size and Power Calculations**

The planned sample size of 42 subjects (21 subjects per arm) will provide 80% power to detect a difference in mean change in ESSDAI of 4 (assumed standard deviation 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 PC from tissue under assumption of coefficient of variation (CV) of 0.5. It should be noted that a smaller CV has been observed in blood from a previous study by Amgen (Study 20060169), which could result in higher statistical power. The sample size was calculated by using nQuery Advisor 7.0.

#### **4.8.3 Efficacy**

##### **4.8.3.1 Primary Analysis**

Changes in ESSDAI score from baseline to Day 99 will be compared between AMG 557/MEDI5872 group and placebo group using an analysis of covariance (ANCOVA) adjusting for ESSDAI score at baseline, randomization stratum, and treatment group. The analysis will be conducted using the ITT Population.. The significance of treatment effect will be tested by using a two-sided test at significance level  $\alpha$  of 0.1. The analysis will be conducted using the ITT Population.

To assess the effect of AMG 557/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.

##### **4.8.3.2 Secondary Analyses**

The number and proportion of ESSDAI[3] and ESSDAI[4] responders will be summarized by treatment and visit. The proportion of AMG 557/MEDI5872 and placebo subjects with an ESSDAI[3] and ESSDAI[4] response at Day 99 will be compared using Fisher's Exact test.

Relative change in biomarker levels in the peripheral blood and minor salivary gland tissue, and change in focus score, will be compared between AMG 557/MEDI5872 and placebo groups in a similar way to the primary endpoint, with log-transformation prior to analysis. In the minor salivary gland tissue, TFH and PC levels will be calculated as the number of the marker positive cells per unit area or among ICOS+ cells. In the peripheral blood, TFH levels will be calculated as the percent of CD45RO+CXCR5+ICOS+PD-1+ among CD3+CD4+ lymphocytes and as the absolute number (eg, cells/ $\mu$ L) of

CD3+CD4+CD45RO+CXCR5+ICOS+PD-1+ lymphocytes. Also, in the peripheral blood, the combined PB/PC levels will be calculated as the percent of CD20dimCD27+CD38++ among CD19+ lymphocytes and as the absolute number (eg, cells/ $\mu$ L) of CD19+CD20dimCD27+CD38++ lymphocytes. Secondary biomarker endpoints are presented in Section 2.2.2.

#### **4.8.3.3 Exploratory Analyses**

Relative change in TFH, PB, and PC levels (and other exploratory immunophenotyping parameters) from baseline to Day 99 in peripheral blood will be log-transformed and compared between AMG 557/MEDI5872 and placebo groups using ANCOVA, adjusting for log (TFH, PB, or PC levels at baseline), randomization stratum, and treatment group. The PC gene signature is described by [Streicher et al, 2014](#). The TFH gene signature is currently under development at MedImmune using a similar approach to the PC gene signature. The analysis will be conducted using the ITT Population. Exploratory biomarker endpoints are presented in Section 2.2.3.

A detailed description of exploratory biomarker analyses will be specified in the EBAP.

#### **4.8.4 Safety**

##### **4.8.4.1 Analysis of Adverse Events**

Treatment-emergent adverse events and TESAEs will be coded by the most updated Medical Dictionary for Regulatory Activities (MedDRA) version and the type, incidence, severity, and relationship to investigational product will be summarized by MedDRA 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. In addition, AESIs and laboratory abnormalities will be summarized. The safety analyses will be conducted using the as-treated Population.

##### **4.8.4.2 Analysis of Clinical Laboratory Parameters**

The laboratory measurements, and the change from baseline, will be summarized by treatment and time point.

##### **4.8.4.3 Other Safety and Tolerability Endpoints**

Vital signs, and the change from baseline, will be summarized by dose and time point. The number and percentage of subjects with normal and abnormal ECG findings will be summarized by dose and time point.

## **4.8.5 Patient-Reported Outcomes**

### **4.8.5.1 Analysis of ESSPRI**

Change in ESSPRI score from baseline to Day 99 will be compared between AMG 557/MEDI5872 and placebo groups using ANCOVA, adjusting for ESSPRI score at baseline, randomization stratum, and treatment group. The analysis will be conducted using the ITT Population. To assess the effect of AMG 557/MEDI5872 on changes in ESSPRI over time, a longitudinal mixed effects analysis of variance model will be fitted for the change from baseline in ESSPRI, for the ITT population.

The number and proportion of ESSPRI responders will be summarized by treatment and visit. The proportion of AMG 557/MEDI5872 and placebo subjects with an ESSPRI response at Day 99 will be compared using Fisher's Exact test.

### **4.8.5.2 Analysis of PROFAD-SSI-SF**

Change in the PROFAD-SSI-SF domain scores over time will be evaluated using a method similar to that used for the ESSPRI:

- 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 (female subjects only)
- 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

The analysis will be conducted using the ITT Population.

### **4.8.5.3 Analysis of SF-36v2**

Change in the following SF-36v2 scores over time will be evaluated using a method similar to that used for the ESSPRI:

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

The analysis will be conducted using the ITT Population.

#### **4.8.5.4 Analysis of Subject Global Assessment of Disease Activity**

Change in SGA score from baseline over time will be evaluated using a method similar to that used for the ESSPRI.

The analysis will be conducted using the ITT Population.

#### **4.8.5.5 Patient Global Impression of Severity**

Descriptive statistics for each visit where a PGI-S assessment is completed will be calculated.

#### **4.8.5.6 Patient Global Impression of Change**

The proportion of AMG 557/MEDI5872 and placebo subjects with improvement at Day 99 will be compared using a Chi-squared test.

The analysis will be conducted using the ITT Population.

#### **4.8.6 Analysis of Immunogenicity/Pharmacokinetics**

The number and percentage of subjects who are anti-AMG 557/MEDI5872-antibody positive will be summarized by dose. The impact of anti-AMG 557/MEDI5872-antibodies on PK and the association with TEAEs and TESAEs will be assessed.

AMG 557/MEDI5872 serum trough concentrations will be summarized by treatment group at each time point using descriptive statistics.

#### **4.8.7 Planned Analyses**

The primary analysis will be performed when all subjects have completed Day 99 (ie, at the end of the double-blind treatment phase). The primary analysis will include all assessments performed 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 treatment and safety follow-up periods or have withdrawn from the study.

### **5 ASSESSMENT OF SAFETY**

#### **5.1 Definition of Adverse Events**

The ICH Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

An untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A non-TEAE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

## **5.2 Definition of Serious Adverse Events**

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

### **5.3 Definition of Adverse Events of Special Interest**

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the Sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the investigational product.

Adverse events of special interest for this study include:

- Hepatic function abnormality meeting the definition of Hy's law (see Section 5.6.2).
- New or reactivated TB infection
- Malignancy
- Hypersensitivity and anaphylactic reactions.

### **5.4 Recording of Adverse Events**

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 5.2 for the definition of SAEs and Appendix 2 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious", it will be reported on the SAE Report Form.

#### **5.4.1 Time Period for Collection of Adverse Events**

Adverse events will be collected from time of signature of informed consent, throughout the blinded and open-label treatment period, and including the follow-up period (through Day 296/EOS).

All SAEs will be recorded from the time of informed consent.

After submitting the initial SAE report to MedImmune Patient Safety, the investigator will be required to follow the subject proactively and provide MedImmune Patient Safety with further information regarding the subject's condition.

If at any time after completion of the study the investigator or qualified designee becomes aware of an SAE that is suspected to be related to investigational product, the event must be reported to MedImmune Patient Safety.

#### **5.4.2 Follow-up of Unresolved Adverse Events**

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The investigator is responsible for following all SAEs to resolution, until the subject returns to baseline status, or until the condition has stabilized, with the exception if a condition remains chronic, even if this extends beyond study participation.

#### **5.5 Reporting of Serious Adverse Events**

**Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety.**

MedImmune Patient Safety contact information:

Patient Safety  
MedImmune, LLC  
One MedImmune Way  
Gaithersburg, MD 20878 USA  
Fax: +1 301-398-4205

The Sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH guidelines and/or local regulatory requirements. The Sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the Sponsor as soon as it becomes available.



Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

## 5.6 Other Events Requiring Immediate Reporting

### 5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported *within 24 hours of knowledge of the event* to MedImmune Patient Safety using the SAE Report Form (see Section 5.5 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF (see Section 5.4). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 5.4 and Section 5.5). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

### 5.6.2 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the Sponsor are defined as any increase in ALT or AST to greater than  $3 \times \text{ULN}$  **and concurrent** increase in bilirubin to greater than  $2 \times \text{ULN}$  (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE.

Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as “hepatic function abnormal” ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be nonserious (see Section 5.5 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

- If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, dosing of the study subject should be permanently discontinued.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the Sponsor.

### **5.6.3 Pregnancy**

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE Report Form (see Section 5.5 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product and will be withdrawn from the study. If the subject requests to know which treatment she received, this information will be provided to her. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE Report Form (see Section 5.5 for contact information). The Sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

### **5.6.4 Adverse Events of Special Interest**

The reporting period for AESIs is the period immediately following the time that informed consent is obtained through the end of the subject’s participation in the study. An AESI (serious or nonserious), regardless of the presumed relationship to the investigational product, is required to be reported ***within 24 hours of knowledge of the event*** to

MedImmune Patient Safety using the SAE Report Form (see Section 5.5 for contact information).

## **6 STUDY AND DATA MANAGEMENT**

### **6.1 Training of Study Site Personnel**

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

### **6.2 Monitoring of the Study**

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

### **6.2.1 Source Data**

Refer to the Clinical Study Agreement for location of source data.

### **6.2.2 Study Agreements**

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

### **6.2.3 Archiving of Study Documents**

The Investigator follows the principles outlined in the Clinical Study Agreement.

## **6.3 Study Timetable and End of Study**

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5 and Section 4.1.6).

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

## **6.4 Data Management**

Data management will be performed by Cognizant Technology Solutions according to the data management plan.

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

## **6.5 Medical Monitor Coverage**

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

## **7 ETHICAL AND REGULATORY REQUIREMENTS**

### **7.1 Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

### **7.2 Subject Data Protection**

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Extra precautions are taken to preserve confidentiality and prevent data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune medical monitor or an investigator might know a subject's identity and also have access to his or her data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the files would remain physically separate.

### **7.3 Ethics and Regulatory Review**

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide Regulatory Authorities, IRB/IEC and Principal Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

Each Principal Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

### **7.4 Informed Consent**

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time

- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated ICF before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

## **7.5 Changes to the Protocol and Informed Consent Form**

Study procedures will not be changed without the mutual agreement of the Coordinating Investigator and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's ICF, MedImmune and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

## **7.6 Audits and Inspections**

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines



of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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## 9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

### **Protocol Amendment 4, 24Oct2017**

Text revisions resulting from this amendment are incorporated in the body of the Protocol Amendment 4. Major changes to the protocol are summarized below.

1. Title Page (Medical Monitor): Updated the title page of this protocol amendment to include the name and contact information of the new Medical Monitor, Dr. Marius Albuлесcu.
2. Protocol Synopsis (Secondary Objectives), Section 2.1.2 (Secondary Objectives): Added objective measures of overall disease activity to Secondary Objective 3, to include a secondary objective describing Secondary Endpoint 4, for which the text was amended and moved from Exploratory Endpoint 3 to Secondary Endpoint 4 in this protocol amendment (see text revision 3 below).
3. Protocol Synopsis (Study Endpoints), Section 2.2.3 (Secondary Endpoint[s]), Section 2.2.3 (Exploratory Endpoint[s]): Amended the definition of ESSDAI response in Exploratory Endpoint 3, to clarify the text, and moved Exploratory Endpoint 3 to Secondary Endpoint 4, to make this an endpoint of interest. Added ESSPRI response as a new Exploratory Endpoint 3, and MDGA as a new Exploratory Endpoint 9, as these endpoints were previously described in the protocol however not defined as study endpoints.
4. Table 4.2.3-1 (Schedule of Follow-up Procedures): Changed the window of +7 days to  $\pm 7$  days for Visit 21, Day 296/EOS, to amend a minor error in the table.
5. Section 4.6.2 (Methods for Ensuring Blinding): Rearranged and made minor edits to the text, to improve the readability and make the text consistent with other sections, respectively.
6. Section 4.6.3.1 (Unblinding in the Event of a Medical Emergency): Removed text specifying that subjects should be discontinued from investigational product if unblinded, to clarify that unblinding is not a reason to discontinue investigational product.
7. Section 4.6.3.2 (Unblinding for the Primary Analyses): Changed wording to enable results from the primary analysis to be presented publically before EOS, and to clarify that individual unblinded treatment assignments from subjects still ongoing in the study will not be shared with investigators until these subjects have completed the study.
8. Protocol Synopsis (Statistical Analysis Plan), Section 4.8.3.1 (Primary Analysis), Section 4.8.3.3 (Exploratory Analyses), Section 4.8.5.1 (Analysis of ESSPRI), Section 4.8.5.2 (Analysis of PROFAD-SSI-SF), Section 4.8.5.3 (Analysis of SF-36v2), Section 4.8.5.4 (Analysis of Subject Global Assessment of Disease Activity), Section 4.8.7 (Planned Analyses): Changed wording to clarify that randomization stratum will be included in the statistical analysis models, and that the endpoints will be analyzed over time using a longitudinal mixed effects model, to make minor changes in the planned statistical analyses.

9. Section 4.8.3.2 (Secondary Analyses): Added text to describe the analysis of ESSDAI response, to make minor changes in the planned statistical analyses.
10. Section 4.8.3.2 (Secondary Analyses), and Section 4.8.3.3 (Exploratory Analyses): Added text to clarify that the biomarkers will be log-transformed prior to statistical analysis, to make minor changes in the planned statistical analyses.
11. Section 4.8.5.1 (Analysis of ESSPRI): Added text to describe further the analysis of ESSPRI, to make minor changes in the planned statistical analyses.
12. Section 4.8.6 (Analysis of Immunogenicity/Pharmacokinetics): Changed wording describing the analysis of PK data so that only trough concentrations will be analyzed, to make minor changes in the planned statistical analyses.

### **Protocol Amendment 3, 17Feb2016**

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. Major changes to the protocol are summarized below.

1. Title Page (Medical Monitor): Updated the title page of this protocol amendment to include the name and contact information of the new Medical Monitor, Dr. Roberta Weiss.
2. Section 4.1.2 (Inclusion Criteria): Inclusion Criterion 1 has been changed to raise the age cap from 70 to 75 years to better reflect the age distribution of pSS; Inclusion Criterion 8 has been changed to lower the IgG requirement from 16g/dL to 13 g/dL, and to include a requirement for a positive test for cryoglobulins, to provide a broader definition of B-cell hyperactivity.
3. Section 4.1.3 (Exclusion Criteria): Exclusion Criterion 8 has been changed to lower the WBC count from  $2,000 \times 10^6/L$  to  $1,500 \times 10^6/L$  and to lower the neutrophil count requirement from  $1,500 \times 10^6/L$  to  $1,000 \times 10^6/L$  to allow SS-associated leukopenia/neutropenia. Exclusion Criterion 20e has been reworded for clarification.
4. Section 4.1.6 (Discontinuation of Investigational Product): Added specific language about severe neutropenia to mitigate any potential risk associated with lowering the neutrophil count for eligibility: “Grade  $\geq 3$  neutropenia requiring a therapeutic intervention to increase neutrophil counts will lead to discontinuation of investigational product even in the absence of any other clinical event (eg, fever) regardless of the relatedness to investigational product.”
5. Section 4.2.1 (Enrollment/Screening Period); Section 4.2.2 (Active Treatment Period); Section 4.2.3 (Follow-up Period): Added the words “whenever feasible” to allow flexibility in the order in which study assessments are performed.
6. Table 4.2.1-1 (Schedule of Screening Procedures): Corrected an error in footnote “f” by including posteroanterior chest x-ray assessment instead of the incorrect anteroposterior assessment.
7. Table 4.2.2-1 (Schedule of Study Procedures): Added footnote “h” to allow baseline oral and ophthalmological evaluations to be performed within 28 days prior to dosing on Visit 2 to accommodate the limited availability of ophthalmologists.



8. Table 4.2.3-1 (Schedule of Follow-up Procedures): Modified footnote “h” to allow ophthalmological evaluations to be performed within 2 weeks prior to EOS to accommodate the limited availability of ophthalmologists.
9. Section 4.3.4 (Chest Radiograph): Corrected an error by including posteroanterior chest x-ray assessment instead of the incorrect anteroposterior assessment.
10. Section 4.3.9.6 (Ophthalmological Evaluation): Whereas before the ophthalmological evaluation was to be performed by an ophthalmologist, now it may be performed by an ophthalmologist or a trained professional to reflect differences in local practices.
11. Table 4.5.1.4-1 (Preparation of Investigational Product Dose): Allowance has been added to use either a 25- or a 27-gauge needle for investigational product administration to accommodate differences in local practices.

## **Protocol Amendment 2, 28Aug2015**

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Major changes to the protocol are summarized below.

1. Protocol Synopsis (Study Design), Section 3.1.1 (Overview): Added the word “multiple” in the description of the study for clarification; increased the approximate number of study sites from 10 to 15 sites.
2. Protocol Synopsis (Study Endpoints), Section 2.2.3 (Exploratory Endpoint [s]): Modified wording in Exploratory Endpoint 10b (second sub-bullet of the last bullet point in the Protocol Synopsis) for consistency with wording in other endpoints.
3. Section 4.1.3 (Exclusion Criteria): Modified Exclusion Criterion 4 in order to exclude subjects with only systemic fungal infections and allow subjects with topical fungal infections, such as fungal nail infection or oral candidiasis; modified Exclusion Criterion 7 to clarify that subjects who tested positive for either hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or HIV antibody will be excluded from the study instead of subjects who tested positive for all 4; modified Exclusion Criterion 11 for clarification; modified Exclusion Criterion 13 to clarify that only subjects with a history of anaphylaxis to any biological therapy will be excluded from the study and not those with a history of anaphylaxis to unrelated allergens (eg, food, iodine, IV contrast agents); modified Exclusion Criterion 20a (ii) to clarify that any change or initiation of a new dose of oral corticosteroids within 4 weeks prior to signing the ICF through randomization will result in exclusion from the study.
4. Section 4.1.6 (Discontinuation of Investigational Product): Added new language in the last paragraph to clarify that subjects will be followed up for safety and protocol-specified assessments.
5. Section 4.1.8 (Withdrawal of Informed Consent for Data and Biological Samples): Modified language under “Samples Obtained for Future Research” for clarification.
6. Table 4.2.2-1 (Schedule of Study Procedures): Removed the 3-day window from Visit 2 as it is not needed and modified the study day window for Visits 11 and 12 for consistency with similar previous visits (Visits 3 and 4); added urine pregnancy testing at

Visits 4 and 12 for consistency with the urine pregnancy testing schedule in other visits in the study.

7. Section 4.3.2.6 (Patient Global Impression of Severity): Modified wording to clarify that the subject's perception of overall symptom severity will be captured at the time of the assessment instead of completion.
8. Section 4.3.8.1 (Biopsy of Salivary Gland): Added additional language to further clarify the salivary gland biopsy procedures.
9. Section 4.3.9.1 (Training): Removed MDGA from the list of assessments requiring training as no formal training beyond the instructions provided in the study reference manual is necessary or will be provided.
10. Section 4.3.9.3 (Physician Global Assessment of Disease Activity): Changed wording from "trained" to "qualified" as no formal training for MDGA beyond the instructions provided in the study reference manual is necessary or will be provided.
11. Section 4.3.9.6 (Ophthalmological Evaluation): Removed "with Lissamine green" to allow other types of stains to be used for the ophthalmological evaluation procedures.
12. Table 4.3.10-1 (Estimate of Blood Volume to be Collected): Modified the footnote to clarify that the amount of blood taken at the unscheduled visit is only an estimated volume.

### **Administrative Change 2, 11Jun2015**

1. Protocol Synopsis (Study Design), Section 3 (Study Design), Figure 3.1.1-1 (Study Flow Diagram), Section 4.1.2 (Inclusion Criteria), Table 4.2.3-1 (Schedule of Follow-up Procedures), Section 4.3.10 (Estimate of Volume of Blood to be Collected), Table 4.3.10-1 (Estimate of Blood Volume to Be Collected), Section 4.7.2 (Prohibited Concomitant Medications), Section 5.4.1 (Time Period for Collection of Adverse Events): Based on review of the PK modeling data, the duration of the follow-up period as well as the protocol-mandated duration of contraception has been increased from 98 days to 113 days. As a result of this change, the End of Study Visit has been changed from Day 281 to Day 296. This change has been applied globally throughout the protocol. The duration of follow up is guided by the non-linear PK of AMG 557/MEDI5872. Population PK modeling was used to determine that the PK concentration in the typical subject achieved a 96.8% reduction from the  $C_{max}$  value following the last dose of investigational product on Day 296. A 96.8% reduction in concentration is equivalent to that achieved using the 5 half-life standard used for drugs with linear PK. This corresponds to a follow-up duration of 113 days from the last dose of investigational product.
2. Protocol Synopsis (Study Design), Section 3 (Study Design): As a result of the changes mentioned above, the approximate number of weeks that the subjects will be in the study for has been changed from 44 weeks to 46 weeks.
3. Table 4.2.1-1 (Schedule of Screening Procedures): Corrected a typographical error by adding coagulation tests at the Screening visit (Visit 1) rather than the incorrect time point (Visit 2).

4. Table 4.2.2-1 (Schedule of Study Procedures): Corrected a typographical error that included coagulation tests at Visit 2 rather than the correct time point, Screening visit (Visit 1).
5. Table 4.2.3-1 (Schedule of Follow-up Procedures): Added urine pregnancy test to the follow-up visits for females of childbearing potential to confirm the absence of pregnancy after the last dose of investigational product.
6. Table 4.5.1-1 (Identification of Investigational Products): Corrected a typographical error that incorrectly specified polysorbate 80 as an excipient in the formulation of AMG 557/MEDI5872 and placebo rather than the correct excipient, polysorbate 20.

### **Administrative Change 1, 24Feb2015**

1. Section 4.1.6 (Discontinuation of Investigational Product): Added criterion for discontinuing investigational product in subjects who receive prohibited concomitant medications for consistency with language in Section 4.7.2 (Prohibited Concomitant Medications).
2. Table 4.2.1-1 (Schedule of Screening Procedures), Table 4.2.2-1 (Schedule of Study Procedures), Table 4.2.3-1 (Schedule of Follow-up Procedures): Clarified that the joint count assessments are “28-joint count”; removed footnote that limited joint count assessments in subjects with arthritis present at baseline to allow joint count assessments in subjects with new onset of arthritis.
3. Table 4.2.2-1 (Schedule of Study Procedures), Table 4.2.3-1 (Schedule of Follow-up Procedures): Specified in the footnote that the Schirmer’s test will be performed without anesthesia as most sites do not use anesthesia as a part of their dry eye assessment.
4. Section 4.3.9.4 (28-joint Count): Changed “joint count” to “28-joint count” for clarification and consistency with assessments in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.
5. Section 4.3.9.5 (Oral Evaluation): Corrected a typographical error that incorrectly specified stimulated parotid flow rate and collection rather than the correct stimulated whole saliva flow rate and collection.
6. Section 4.3.9.6 (Ophthalmological Evaluation): Specified that the Schirmer’s test will be performed without anesthesia as most sites do not use anesthesia as a part of their dry eye assessment.
7. Table 4.5.1-1 (Identification of Investigational Products): Removed a footnote about the investigational product storage conditions as the information was not as complete as that in Section 4.5.3 (Storage).
8. Section 4.5.1.1 (Investigational Product Dose Preparation): Corrected a typographical error to include selection of an investigational product kit instead of vials.
9. Section 4.5.1.3 (Investigational Product Thawing Instructions): Corrected a typographical error to include 4 vials of investigational product instead of 3 vials and corrected a typographical error that incorrectly used the word “box” rather than the corrected word “kit.”

10. Section 4.5.1.4 (Dose Preparation Steps): Included “placebo” in addition to AMG 557/MEDI5872 in the dose preparation steps. Revised the text describing the dose preparation steps for clarification.
11. Table 4.5.1.4-1 (Preparation of Investigational Product Dose): Removed the original table and replaced it with a table describing the dose preparation steps in detail.
12. Section 4.5.4 (Definition of Temperature Excursion): Removed section as all temperature deviations are routinely documented.
13. Section 4.7.1 (Permitted Concomitant Medications): Added background treatments for pSS that are permitted in the study as a clarification of text in the section on prohibited concomitant medications, and corrected a typographical error that incorrectly used the word “excluded” rather than the corrected word “prohibited.”

### **Protocol Amendment 1, 26Nov2014**

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below.

1. Section 4.1.6 (Discontinuation of Investigational Product): In response to a request from the United States Food and Drug Administration (US FDA), Criterion 3 was added to specify the number and type of AEs that would trigger either discontinuing investigational product in an individual subject or study stopping. An individual subject will not receive any further investigational product if any Grade  $\geq 3$  TEAE (based on CTC AE [Version 4.0]) occurs that is considered to be related to investigational product by the investigator, unless in the opinion of the investigator, the event(s) are a manifestations of SS (eg, within the definitions included in the ESSDAI). Isolated Grade  $\geq 3$  laboratory abnormalities without a clinical event meeting the above criteria will not automatically lead to discontinuation of investigational product.
2. Table 4.2.1-1 (Schedule of Screening Procedures): Added hemoglobin A1c to screening procedures, as poorly controlled diabetes (hemoglobin A1c  $> 8\%$ ) is considered exclusionary. Added coagulation tests. Removed IGRA from screening procedures, as this is assessed as part of the infectious disease panel.
3. Table 4.2.2-1 (Schedule of Study Procedures) and Table 4.2.3-1 (Schedule of Follow-up Procedures): Added time points for assessment of coagulation tests, which will be assessed at Day 1, Day 99, Day 197/ETV, and Day 281/EOS.
4. Section 4.3.5 (Clinical Laboratory Tests): Added creatinine phosphokinase to serum chemistry assessments, as subjects may have myositis. Added coagulation tests, including INR, prothrombin time, and activated partial thromboplastin time. Added hemoglobin A1c to other tests.
5. Section 4.3.9.3 (Physician Global Assessment of Disease Activity): Changed the description of the MDGA from “0 to 100 mm scale” to “0 to 10 Likert scale”, as the version of the MDGA that will be used in the study was changed.
6. Table 4.3.10-1 (Estimate of Blood Volume to be Collected): Estimated blood volumes were updated based on feedback received from the contract research organization and based on the addition of coagulation tests.

7. Section 4.4 (Study Suspension or Termination): In response to a request from the US FDA, Criterion 1 was modified to specify the number and type of AEs that would trigger either discontinuing investigational product in an individual subject or study stopping. Study treatment will be suspended if any of the following events occur in the study: a) any death that is considered to be related to investigational product by the investigator; b) any Grade 4 TEAE (based on CTCAE [Version 4.0]) that is considered to be related to investigational product by the investigator, with the exception of anaphylactic reaction; and c) if 2 subjects have TEAEs in the same organ system of Grade  $\geq 3$  (based on CTCAE [Version 4.0]) that are considered to be related to investigational product by the investigator, unless in the opinion of the investigator, the events are manifestations of SS (eg, within the definitions included in the ESSDAI). Isolated Grade  $\geq 3$  laboratory abnormalities without a clinical event meeting the above criteria will not automatically trigger suspension of the study. In these cases, study treatment will be suspended, the subject data will be unblinded, and the data will be reviewed by MedImmune Patient Safety. Based upon this review, MedImmune Patient Safety will determine if the dosing may resume or if the study will be terminated.
8. Section 4.6.2 (Methods for Ensuring Blinding): Clarified that Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will also be unaware of the treatment received from the start of the study until all subjects have reached Day 99 or withdrawn from the study. After this time, Sponsor staff may be unblinded.
9. Section 4.6.3.1 (Unblinding in the Event of a Medical Emergency): Clarified that, at minimum, the investigator should attempt to *immediately* contact the medical monitor prior to unblinding.
10. Section 4.6.3.2 (Unblinding for the Primary Analyses): Added section to describe that the Sponsor staff will be unblinded at the primary analysis (after Day 99). The data from the primary analysis will not be communicated to contract research organization staff, investigator staff, or enrolled subjects, until the study is complete.
11. Section 4.7.2 (Prohibited Concomitant Medications): Clarified that subjects are not permitted to receive methotrexate  $> 20$  mg/week.
12. Section 4.8.7 (Planned Analyses): Added section to describe that the primary analysis will be performed when all subjects have completed Day 99 (ie, at the end of the double-blind treatment phase). The primary analysis will include all assessments performed 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 treatment and safety follow-up periods or have withdrawn from the study. The analysis of the primary endpoint at Day 99 will not change at the final analysis, so no multiplicity adjustment will be applied.
13. Section 7.2 (Subject Data Protection): Removed “genetic” from the text, as there is no genetic testing in this study.



## **Appendix 1      Signatures**



**Sponsor Signature(s)**

A Phase 2a, Randomized, Placebo-controlled, Proof of Mechanism Study to Evaluate the Safety and Efficacy of AMG 557/MEDI5872 in Subjects with Primary Sjogren's Syndrome

I agree to the terms of this protocol and all amendments/administrative changes.

Signature and date: \_\_\_\_\_

Jorn Drappa, MD, Vice President, Clinical Development

Clinical Therapeutic Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: 301-398-1171

**Signature of International Coordinating Investigator**

A Phase 2a, Randomized, Placebo-controlled, Proof of Mechanism Study to Evaluate the Safety and Efficacy of AMG 557/MEDI5872 in Subjects with Primary Sjogren’s Syndrome

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the Sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the Sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the Sponsor immediately upon receipt.

Signature and date: \_\_\_\_\_

Name and title: \_\_\_\_\_

Address including postal code: \_\_\_\_\_

\_\_\_\_\_

Telephone number: \_\_\_\_\_

Site/Center number (if available): \_\_\_\_\_

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

**Signature of Principal or Coordinating Investigator**

A Phase 2a, Randomized, Placebo-controlled, Proof of Mechanism Study to Evaluate the Safety and Efficacy of AMG 557/MEDI5872 in Subjects with Primary Sjogren’s Syndrome

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

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## **Appendix 2      Additional Safety Guidance**

### **Assessment of Severity**

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grades 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

### **Assessment of Relationship**

#### **Relationship to Investigational Product**

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered “related” to use of the investigational product if the “not related” criteria are not met.

“Related” implies that the event is considered to be “associated with the use of the drug” meaning that there is “a reasonable possibility” that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

### Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes non TESAEs (ie, SAEs that occur prior to the administration of investigational product) as well as TESAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject’s medical record.

Not protocol related: The event is related to an etiology other than the procedure/intervention that was described in the protocol (the alternative etiology must be documented in the study subject’s medical record).

## Appendix 3 American European Consensus Group Criteria

**Table 2** Revised international classification criteria for Sjögren's syndrome

- I. Ocular symptoms: a positive response to at least one of the following questions:
  1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
  2. Do you have a recurrent sensation of sand or gravel in the eyes?
  3. Do you use tear substitutes more than 3 times a day?
- II. Oral symptoms: a positive response to at least one of the following questions:
  1. Have you had a daily feeling of dry mouth for more than 3 months?
  2. Have you had recurrently or persistently swollen salivary glands as an adult?
  3. Do you frequently drink liquids to aid in swallowing dry food?
- III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
  1. Schirmer's I test, performed without anaesthesia ( $\leq 5$  mm in 5 minutes)
  2. Rose bengal score or other ocular dye score ( $\geq 4$ , according to van Bijsterveld's scoring system)
- IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score  $\geq 1$ , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm<sup>2</sup> of glandular tissue<sup>16</sup>
- V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
  1. Unstimulated whole salivary flow ( $\leq 1.5$  ml in 15 minutes)
  2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts<sup>19</sup>
  3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer<sup>20</sup>
- VI. Autoantibodies: presence in the serum of the following autoantibodies:
  1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

**Table 3** Revised rules for classification

*For primary SS*

In patients without any potentially associated disease, primary SS may be defined as follows:

- a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
- b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
- c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

*For secondary SS*

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

*Exclusion criteria:*

- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency disease (AIDS)
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

Source: Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis.* 2002 Jun;61(6):554-8.

**Appendix 4**      **European League Against Rheumatism Sjogren's  
Syndrome Disease Activity Index**



### The ESSDAI: Domain and Item Definitions and Weights.

Domain [Weight]	Activity level	Description
<b>Constitutional [3]</b> <i>Exclusion of fever of infectious origin and voluntary weight loss</i>	No = 0 Low = 1 Moderate = 2	Absence of the following symptoms Mild or intermittent fever (37.5°-38.5°C) / night sweats and/or involuntary weight loss of 5 to 10% of body weight Severe fever (> 38.5°C) / night sweats and/or involuntary weight loss of > 10% of body weight
<b>Lymphadenopathy [4]</b> <i>Exclusion of infection</i>	No = 0 Low = 1 Moderate = 2 High = 3	Absence of the following features Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging) Current malignant B-cell proliferative disorder
<b>Glandular [2]</b> <i>Exclusion of stone or infection</i>	No = 0 Low = 1 Moderate = 2	Absence of glandular swelling Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular or lachrymal swelling Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling
<b>Articular [2]</b> <i>Exclusion of osteoarthritis</i>	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active articular involvement Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (> 30 minutes) 1 to 5 (of 28 total count) synovitis ≥ 6 (of 28 total count) synovitis
<b>Cutaneous [3]</b> <i>Rate as "No activity" stable long-lasting features related to damage</i>	No = 0 Low = 1 Moderate = 2	Absence of currently active cutaneous involvement Erythema multiforma Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
<b>Pulmonary [5]</b> <i>Rate as "No activity" stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc.)</i>	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active pulmonary involvement Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test. Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to: 70% > DL <sub>co</sub> ≥ 40% or 80% > FVC ≥ 60% Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NYHA III, IV) or with abnormal lung function tests: DL <sub>co</sub> < 40% or FVC < 60%
<b>Renal [5]</b> <i>Rate as "No activity" stable long-lasting features related to</i>	No = 0 Low = 1	Absence of currently active renal involvement with proteinuria < 0.5 g/d, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/d) and without hematuria or renal failure (GFR ≥ 60 mL/min)

<b>Domain [Weight]</b>	<b>Activity level</b>	<b>Description</b>
<b>Damage, and renal involvement not related to the disease.</b> <i>If biopsy has been performed, please rate activity based on histological features first</i>	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR < 60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/d and without hematuria or renal failure (GFR ≥ 60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria > 1.5 g/d or hematuria or renal failure (GFR < 60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
<b>Muscular [6]</b>	No = 0	Absence of currently active muscular involvement
<b>Exclusion of weakness due to corticosteroids</b>	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N < CK ≤ 2N)
	Moderate = 2	Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N < CK ≤ 4N).
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (> 4N)
<b>PNS [5]</b>	No = 0	Absence of currently active PNS involvement
<b>Rate as "No activity" stable long-lasting features related to damage or PNS involvement not related to the disease</b>	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia), Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High = 3	Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤ 3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤ 3/5 or severe ataxia
<b>CNS [5]</b>	No = 0	Absence of currently active CNS involvement
<b>Rate as "No activity" stable long-lasting features related to damage or CNS involvement not related to the disease</b>	Moderate = 2	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.
<b>Hematological [2]</b>	No = 0	Absence of auto-immune cytopenia
<b>For anemia, neutropenia, and thrombopenia, only</b>	Low = 1	Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm <sup>3</sup> ), and/or anemia (10 < hemoglobin < 12 g/dl), and /or thrombocytopenia ( 100,000 < platelets < 150,000/mm <sup>3</sup> )
		Or lymphopenia (500 < lymphocytes < 1000/mm <sup>3</sup> )

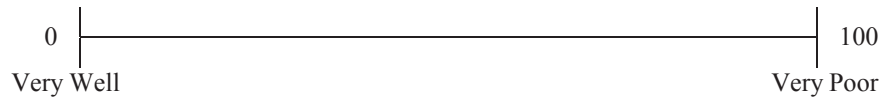


<b>Domain [Weight]</b>	<b>Activity level</b>	<b>Description</b>
<i>auto-immune cytopenia must be considered</i>	Moderate = 2	Cytopenia of auto-immune origin with neutropenia ( $500 \leq$ neutrophils $\leq 1000/\text{mm}^3$ ), and/or anemia ( $8 \leq$ hemoglobin $\leq 10$ g/dl), and/or thrombocytopenia ( $50,000 \leq$ platelets $\leq 100,000/\text{mm}^3$ ) Or lymphopenia ( $\leq 500/\text{mm}^3$ )
<i>Exclusion of vitamin or iron deficiency, drug-induced cytopenia</i>	High = 3	Cytopenia of auto-immune origin with neutropenia (neutrophils $< 500/\text{mm}^3$ ), and/or or anemia (hemoglobin $< 8$ g/dl) and/or thrombocytopenia (platelets $< 50,000/\text{mm}^3$ )
<b>Biological [1]</b>	No = 0	Absence of any of the following biological feature
	Low = 1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate = 2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level $> 20$ g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level ( $< 5$ g/L)

CIDP = chronic inflammatory demyelinating polyneuropathy; CK = creatine kinase; CNS = central nervous system; DLco = diffusing carbon monoxide capacity; EMG = electromyogram; ESSDAI = European League Against Rheumatism Sjogren's Syndrome Disease Activity Index; FVC = forced vital capacity; GFR = glomerular filtration rate; HRCT = high-resolution computed tomography; IgG = immunoglobulin G; min = minimum; N = normal; NCS= nerve conduction studies; NYHA = New York Heart Association classification; PNS = peripheral nervous system

## Appendix 5      Subject Global Assessment of Disease Activity

Considering all the ways that your illness affects you, how have you been doing over the previous 7 days?



## Appendix 6 Short-form 36 Version 2

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# Your Health and Well-Being

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This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an  in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

**3. The following questions are about activities you might do during a typical day.  
 Does your health now limit you in these activities? If so, how much?**

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

- a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports .....  1 .....  2 .....  3
- b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....  1 .....  2 .....  3
- c Lifting or carrying groceries .....  1 .....  2 .....  3
- d Climbing several flights of stairs .....  1 .....  2 .....  3
- e Climbing one flight of stairs .....  1 .....  2 .....  3
- f Bending, kneeling, or stooping .....  1 .....  2 .....  3
- g Walking more than a mile.....  1 .....  2 .....  3
- h Walking several hundred yards .....  1 .....  2 .....  3
- i Walking one hundred yards .....  1 .....  2 .....  3
- j Bathing or dressing yourself .....  1 .....  2 .....  3

**4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities.....  1.....  2.....  3.....  4.....  5
- b. Accomplished less than you would like .....  1.....  2.....  3.....  4.....  5
- c. Were limited in the kind of work or other activities .....  1.....  2.....  3.....  4.....  5
- d. Had difficulty performing the work or other activities (for example, it took extra effort).....  1.....  2.....  3.....  4.....  5

**5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities.....  1.....  2.....  3.....  4.....  5
- b. Accomplished less than you would like .....  1.....  2.....  3.....  4.....  5
- c. Did work or other activities less carefully than usual.....  1.....  2.....  3.....  4.....  5



6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past week?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Did you feel full of life? .....  1 .....  2 .....  3 .....  4 .....  5
- b. Have you been very nervous? .....  1 .....  2 .....  3 .....  4 .....  5
- c. Have you felt so down in the dumps that nothing could cheer you up? .....  1 .....  2 .....  3 .....  4 .....  5
- d. Have you felt calm and peaceful? .....  1 .....  2 .  3 .....  4 .....  5
- e. Did you have a lot of energy? .....  1 .....  2 .....  3 .....  4 .....  5
- f. Have you felt downhearted and depressed? .....  1 .....  2 .....  3 .....  4 .....  5
- g. Did you feel worn out? .....  1 .....  2 .....  3 .....  4 .....  5
- h. Have you been happy? .....  1 .....  2 .....  3 .....  4 .....  5
- i. Did you feel tired? .....  1 .....  2 .....  3 .....  4 .....  5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

**11. How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. I am as healthy as anybody I know .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. I expect my health to get worse.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. My health is excellent.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

***Thank you for completing these questions!***

## Appendix 7 Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form

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	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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6. The **worst** problem I've had in the last two weeks with **forgetting things** or **making mistakes**:

no such problem at all	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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**VISIT 1**

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	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

no problem at all	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

no problem at all	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

no problem at all	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	as bad as imaginable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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**VISIT 1**

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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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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	<b>0</b> <input type="checkbox"/>	<b>1</b> <input type="checkbox"/>	<b>2</b> <input type="checkbox"/>	<b>3</b> <input type="checkbox"/>	<b>4</b> <input type="checkbox"/>	<b>5</b> <input type="checkbox"/>	<b>6</b> <input type="checkbox"/>	<b>7</b> <input type="checkbox"/>	as bad as imaginable
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## Appendix 8      European League Against Rheumatism Sjogren's Syndrome Patient Reported Index

*The total score is the mean score of the 3 scales.*

1) How severe has your **dryness** been during the last 2 weeks?

No                  Maximal imaginable  
dryness      0    1    2    3    4    5    6    7    8    9    10      dryness

2) How severe has your **fatigue** been during the last 2 weeks?

No                  Maximal imaginable  
fatigue      0    1    2    3    4    5    6    7    8    9    10      fatigue

3) How severe has your **pain** (joint or muscular pains in your arms or legs)  
been during the last 2 weeks?

No                  Maximal imaginable  
pain      0    1    2    3    4    5    6    7    8    9    10      pain

## **Appendix 9 Patient Global Impression of Change**

Overall, how would you rate the change in your Sjogren's Syndrome symptoms since starting this study?

- Much better
- Moderately better
- A little better
- About the same
- A little worse
- Moderately worse
- Much worse

## **Appendix 10 Patient Global Impression of Severity**

Overall, how would you rate the severity of your Sjogren's Syndrome symptoms today?

- No symptoms
- Very mild
- Mild
- Moderate
- Severe
- Very Severe

## **Appendix 11      Guidance for Abnormal Liver Function Tests Management**

This guidance is based on the July 2009 Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

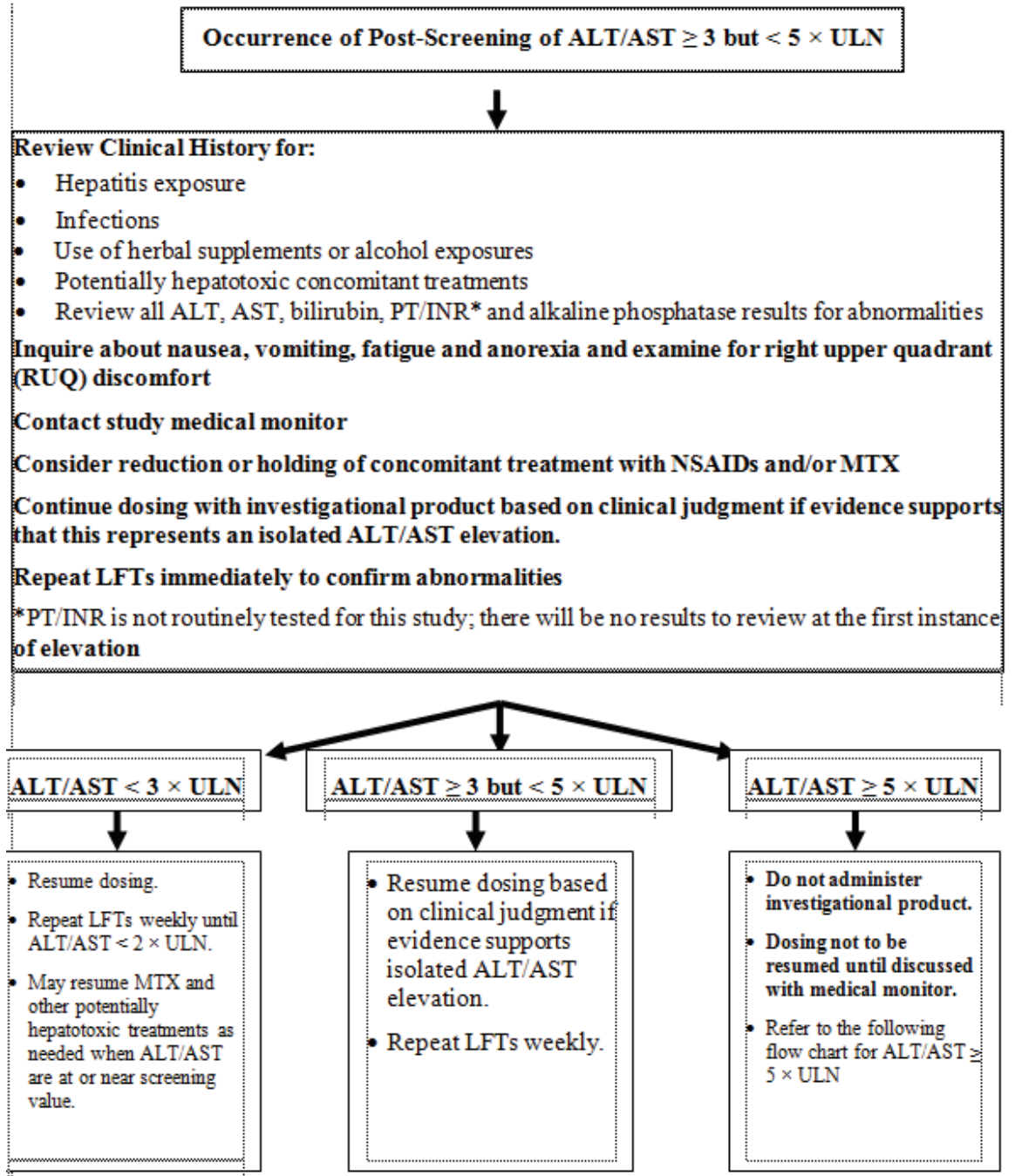
Section IV of the US FDA document deals with the clinical evaluation of and monitoring of drug-induced liver injury, and this protocol-specific guidance has adopted the recommendations on detection of drug-induced liver disease, confirmation of abnormal ALT/AST with regard to retesting, follow-up observation, advice on appropriate history gathering and advice on the need for obtaining additional laboratory tests and consultations as needed. MedImmune has adopted a conservative approach to holding administration of investigational product based on abnormal liver function tests (LFTs) until a full understanding of the event has been understood by the principle investigator and the medical monitor. This understanding is required so that the principle investigator, in consultation with the medical monitor, can reach a decision as to whether dosing can be continued or whether it is advisable to stop investigational product permanently. The US FDA document acknowledges there is no published consensus on how this decision should be made but this protocol-specific guidance requires involvement of the medical monitor at any early stage of clinically significant increases in ALT/AST to provide additional information on accumulating clinical experience of sifalimumab as well as input from the investigator regarding the nature of the subject and other factors that may be relevant. This approach will provide the balance necessary to permit learning about the investigational product while maximizing safety concerns to minimize the potential for functional liver impairment and damage. There are 2 separate parts to the guidance to detect clinically significant liver injury depending on whether the subject entered the study with normal or mildly elevated (up to  $2 \times \text{ULN}$ ) ALT/AST or on more severe abnormalities in subjects with  $\text{ALT/AST} > 2 \times \text{ULN}$  at baseline.

For the purpose of this document, LFTs will be AST, ALT, total bilirubin, and alkaline phosphatase.

The decision to include subjects in this clinical trial with baseline LFT abnormalities is supported by the US FDA guidance.

Copies of the document “Guidance of Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation” can be located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

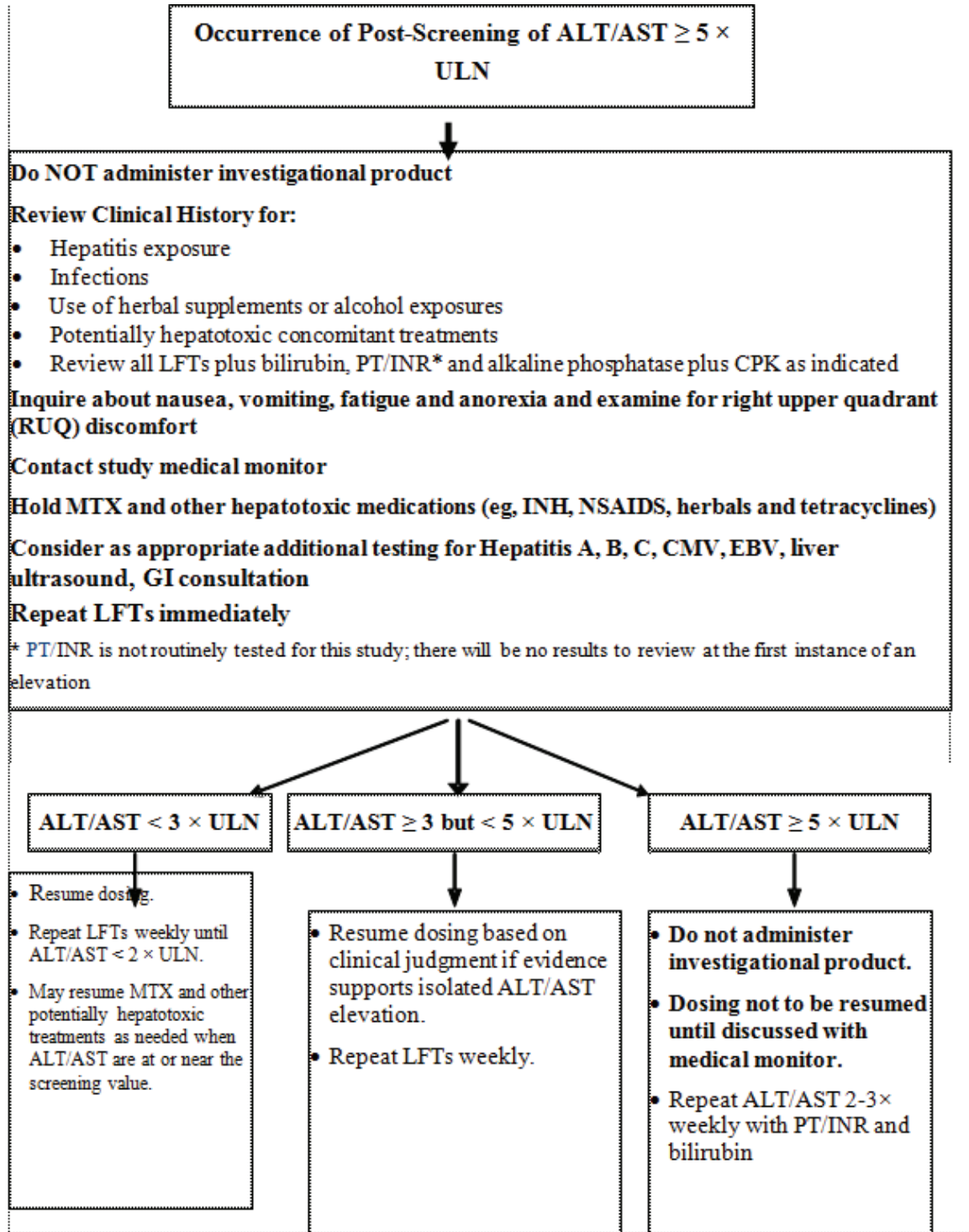
**Guidance for abnormal LFTs that develop post-screening in subjects with ALT/AST  $\leq 2 \times$  ULN at screening due to liver involvement by pSS in the opinion of the investigator:**



ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalization ratio; LFT = liver function test; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; pSS = primary Sjogren's syndrome; PT = prothrombin time; RUQ = right upper quadrant; ULN = upper limit of normal

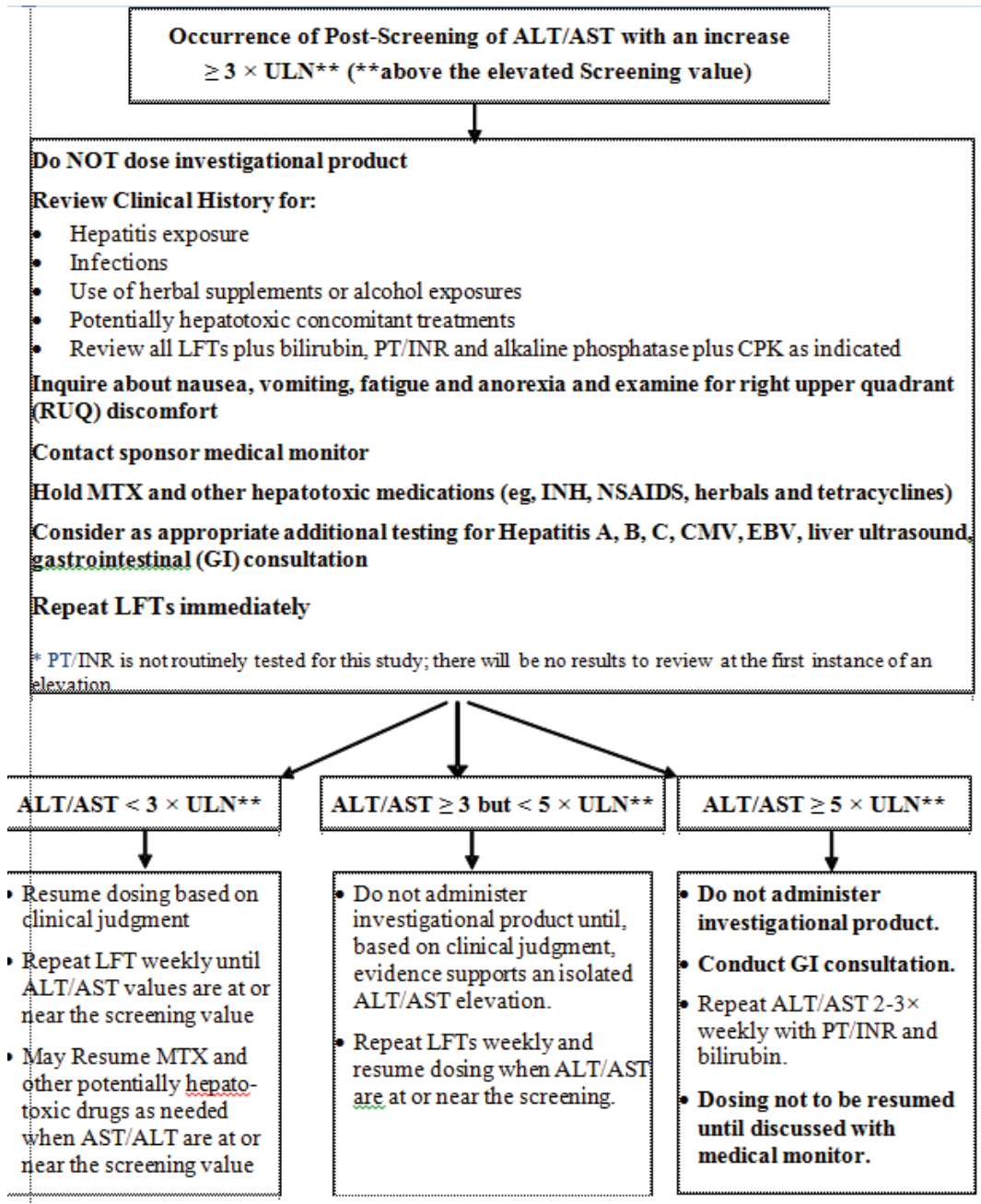


**Guidance for abnormal LFTs that develop post-screening in subjects with ALT/AST  $\leq 2 \times$  ULN at screening due to liver involvement by pSS in the opinion of the investigator:**



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; CPK = creatinine phosphokinase; EBV = Epstein-Barr virus; GI = gastrointestinal; INH = isoniazid; INR = international normalization ratio; LFT = liver function test; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; pSS = primary Sjogren's syndrome; PT = prothrombin time; RUQ = right upper quadrant; ULN = upper limit of normal

**Guidance for abnormal LFTs that develop post-screening in subjects with ALT/AST > 2 × ULN at screening due to liver involvement by pSS in the opinion of the investigator:**



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; CPK = creatinine phosphokinase; EBV = Epstein-Barr virus; GI = gastrointestinal; INH = isoniazid; INR = international normalization ratio; LFT = liver function test; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drugs; pSS = primary Sjogren’s syndrome; PT = prothrombin time; RUQ = right upper quadrant; ULN = upper limit of normal

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24-Oct-2017 14:58 GMT+0100	██████████	Biostatistics Approval	
24-Oct-2017 16:51 GMT+0100	██████████████████	Clinical Operations Approval	
24-Oct-2017 16:57 GMT+0100	██████████████████	Medical Monitor Approval	
31-Oct-2017 00:43 GMT+0000	██████████	Nonclinical Scientist Approval	
31-Oct-2017 18:21 GMT+0000	██████████	Clinical Development Approval	

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.