**Official Title:** A Phase II, Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Assess the Efficacy and Safety of MSTT1041A in Patients With Moderate to Severe Atopic Dermatitis

**NCT Number:** NCT03747575

**Document Date:** Protocol Version 1: 31-August-2018

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF MSTT1041A IN PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS** |
| **PROTOCOL NUMBER:** | GS40965 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2018-003429-27 |
| **IND NUMBER:** | 140186 |
| **TEST PRODUCT:** | MSTT1041A (RO7187807) |
| **MEDICAL MONITOR:** | [redacted], M.D. |
| **SPONSOR:** | Genentech, Inc. |
| **DATE FINAL:** | See electronic date stamp below. |

## FINAL PROTOCOL APPROVAL

| Approver's Name | Title | Date and Time (UTC) |
|---|---|---|
| [redacted] | Company Signatory | 31-Aug-2018 16:41:39 |

## TABLE OF CONTENTS


PROTOCOL ACCEPTANCE FORM ..... 8

PROTOCOL SYNOPSIS ..... 9

1. BACKGROUND ..... 19
   - 1.1 Background on Atopic dermatitls ..... 19
   - 1.2 Background on MSTT1041A ..... 20
   - 1.3 Study Rationale and Benefit-Risk Assessment ..... 20

2. OBJECTIVES AND ENDPOINTS ..... 22
   - 2.1 Efficacy Objectives ..... 22
   - 2.1.1 Primary Efficacy Objective ..... 22
   - 2.1.2 Secondary Efficacy Objective ..... 22
   - [redacted] [redacted] 22
   - 2.2 Safety Objective ..... 23
   - 2.3 Pharmacokinetic Objectives ..... 23
   - 2.4 Immunogenicity Objective ..... 23
   - 2.5 Biomarker Objective ..... 23

3. STUDY DESIGN ..... 24
   - 3.1 Description of the Study ..... 24
   - 3.1.1 Internal Monitoring Committee ..... 25
   - 3.2 End of Study and Length of Study ..... 26
   - 3.3 Rationale for Study Design ..... 26
   - [redacted] [redacted] 26
   - 3.3.2 Rationale for Patient Population ..... 27
   - 3.3.3 Rationale for Control Group ..... 27
   - 3.3.4 Rationale for Biomarker Assessments ..... 27

4. MATERIALS AND METHODS ..... 27
   - 4.1 Patients ..... 27
   - 4.1.1 Inclusion Criteria ..... 27
   - 4.1.2 Exclusion Criteria ..... 29
   - 4.2 Method of Treatment Assignment and Blinding ..... 33
   - 4.3 Study Treatment and Other Treatments Relevant to the Study Design ..... 33
   - 4.3.1 Study Treatment Formulation, Packaging, and Handling ..... 34

4.3.1.1 MSTT1041A and Placebo ..... 34
4.3.2 Study Treatment Dosage, Administration, and Compliance ..... 34
4.3.2.1 MSTT1041A and Placebo ..... 34
4.3.3 Background Treatment ..... 35
4.3.4 Rescue Treatment ..... 35
4.3.5 Investigational Medicinal Product Accountability ..... 36
4.3.6 Continued Access to MSTT1041A ..... 36
4.4 Concomitant Therapy, Prohibited Therapy, and Additional Restrictions ..... 36
4.4.1 Cautionary Therapy ..... 36
4.4.1.1 Herbal Therapies ..... 36
4.4.2 Prohibited Therapy ..... 37
4.4.3 Additional Restrictions ..... 37
4.5 Study Assessments ..... 37
4.5.1 Informed Consent Forms and Screening Log ..... 38
4.5.2 Medical History, Concomitant Medication, and Demographic Data ..... 38
4.5.3 Atopy Status ..... 38
4.5.4 Physical Examinations ..... 38
4.5.5 Vital Signs ..... 39
4.5.6 Laboratory, Biomarker, and Other Biological Samples ..... 39
4.5.7 Electrocardiograms ..... 41
4.5.8 Chest X-Rays ..... 41
4.5.9 Clinician-Reported and Patient-Reported Outcomes ..... 42
4.5.9.1 Eczema Area and Severity Index ..... 42
4.5.9.2 SCORing Atopic Dermatitis, Clinician Reported ..... 42
4.5.9.3 Investigator Global Assessment ..... 43
[redacted] [redacted] 43
[redacted] [redacted] 43
[redacted] [redacted] 43
[redacted] [redacted] 43
[redacted] [redacted] 44
[redacted] [redacted] 44
[redacted] [redacted] 44

[redacted] [redacted] 45
[redacted] [redacted] 45
[redacted] [redacted] 46
4.6 Treatment, Patient, Study, and Site Discontinuation ..... 46
4.6.1 Study Treatment Discontinuation ..... 46
4.6.2 Patient Discontinuation from Study ..... 46
4.6.3 Study Discontinuation ..... 47
4.6.4 Site Discontinuation ..... 47
5. ASSESSMENT OF SAFETY ..... 47
5.1 Safety Plan ..... 47
5.1.1 Risks Associated with MSTT1041A ..... 48
5.1.1.1 Immunogenicity ..... 48
5.1.1.2 Hypersensitivity Reactions and Anaphylaxis/Hypersensitivity-Like Reactions ..... 48
5.1.1.3 Injection-Site Reactions ..... 49
5.1.1.4 Infection ..... 49
5.1.1.5 Exacerbation of Cardiovascular Disease ..... 50
5.1.2 Management of Patients Who Experience Adverse Events ..... 50
5.1.2.1 Treatment Interruption ..... 50
5.1.2.2 Management Guidelines ..... 51
5.1.2.3 Management of Increases in QT Interval ..... 52
5.1.2.4 Anaphylaxis ..... 52
5.2 Safety Parameters and Definitions ..... 53
5.2.1 Adverse Events ..... 53
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) ..... 53
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) ..... 54
5.3 Methods and Timing for Capturing and Assessing Safety Parameters ..... 55
5.3.1 Adverse Event Reporting Period ..... 55
5.3.2 Eliciting Adverse Event Information ..... 55
5.3.3 Assessment of Severity of Adverse Events ..... 55
5.3.4 Assessment of Causality of Adverse Events ..... 56
5.3.5 Procedures for Recording Adverse Events ..... 57

5.3.5.1 Injection Reactions ..... 57
5.3.5.2 Major Adverse Cardiac Events ..... 57
5.3.5.3 Diagnosis versus Signs and Symptoms ..... 58
5.3.5.4 Adverse Events That Are Secondary to Other Events ..... 58
5.3.5.5 Persistent or Recurrent Adverse Events ..... 58
5.3.5.6 Abnormal Laboratory Values ..... 59
5.3.5.7 Abnormal Vital Sign Values ..... 59
5.3.5.8 Abnormal Liver Function Tests ..... 60
5.3.5.9 Deaths ..... 60
5.3.5.10 Preexisting Medical Conditions ..... 61
5.3.5.11 Lack of Efficacy or Worsening of Atopic Dermatitis ..... 61
5.3.5.12 Hospitalization or Prolonged Hospitalization ..... 61
5.3.5.13 Safety Biomarker Data ..... 62
5.4 Immediate Reporting Requirements from Investigator to Sponsor ..... 62
5.4.1 Emergency Medical Contacts ..... 62
5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest ..... 63
5.4.2.1 Events That Occur prior to Study Drug Initiation ..... 63
5.4.2.2 Events That Occur after Study Drug Initiation ..... 63
5.4.3 Reporting Requirements for Pregnancies ..... 63
5.4.3.1 Pregnancies in Female Patients ..... 63
5.4.3.2 Pregnancies in Female Partners of Male Patients ..... 64
5.4.3.3 Congenital Anomalies/Birth Defects and Abortions ..... 64
5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error ..... 65
5.5 Follow-Up of Patients after Adverse Events ..... 66
5.5.1 Investigator Follow-Up ..... 66
5.5.2 Sponsor Follow-Up ..... 66
5.6 Adverse Events That Occur after the Adverse Event Reporting Period ..... 66
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees ..... 67
6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN ..... 67
6.1 Determination of Sample Size ..... 67
6.2 Summaries of Conduct of Study ..... 68

6.3 Summaries of Treatment Group Comparability....68
6.4 Efficacy Analyses....68
6.4.1 Primary Efficacy Endpoint....68
6.4.2 Secondary Efficacy Endpoints....69
[redacted] [redacted] 69
6.5 Safety Analyses....69
6.6 Pharmacokinetic Analyses....69
6.7 Immunogenicity Analyses....70
6.8 Biomarker Analyses....70
6.9 Sensitivity analysis....71
7. DATA COLLECTION AND MANAGEMENT....71
7.1 Data Quality Assurance....71
7.2 Electronic Case Report Forms....71
7.3 Electronic Patient- and Clinician- Reported Outcome Data....72
7.4 Source Data Documentation....72
7.5 Use of Computerized Systems....73
7.6 Retention of Records....73
8. ETHICAL CONSIDERATIONS....73
8.1 Compliance with Laws and Regulations....73
8.2 Informed Consent....74
8.3 Institutional Review Board or Ethics Committee....75
8.4 Confidentiality....75
8.5 Financial Disclosure....76
9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION....76
9.1 Study Documentation....76
9.2 Protocol Deviations....76
9.3 Site Inspections....76
9.4 Administrative Structure....77
9.5 Dissemination of Data and Protection of Trade Secrets....77
9.6 Protocol Amendments....78
10. REFERENCES....79

## LIST OF TABLES


Table 1 Guidelines for Treatment Interruption or Discontinuation for Patients Who Experience Hepatotoxicity ..... 51
Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale ..... 56
Table 3 Causal Attribution Guidance ..... 57


## LIST OF FIGURES


Figure 1 Study Schema ..... 25


## LIST OF APPENDICES


Appendix 1 Schedule of Activities ..... 82
Appendix 2 WHO Classification of Topical Corticosteroids ..... 87
Appendix 3 Hepatitis B Screening Flowchart ..... 88
Appendix 4 Eczema Area and Severity Index ..... 89
Appendix 5 SCORing Atopic Dermatitis ..... 90
Appendix 6 Investigator Global Assessment ..... 91
[redacted] [redacted] 92
Appendix 8 WHO Toxicity Grading Scale ..... 97

## PROTOCOL ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF MSTT1041A IN PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS** |
| **PROTOCOL NUMBER:** | GS40965 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2018-003429-27 |
| **IND NUMBER:** | 140186 |
| **TEST PRODUCT:** | MSTT1041A (RO7187807) |
| **MEDICAL MONITOR:** | [redacted], M.D. |
| **SPONSOR:** | Genentech, Inc. |

**I agree to conduct the study in accordance with the current protocol.**

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF MSTT1041A IN PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS** |
| **PROTOCOL NUMBER:** | GS40965 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2018-003429-27 |
| **IND NUMBER:** | 140186 |
| **TEST PRODUCT:** | MSTT1041A (RO7187807) |
| **PHASE:** | Phase II |
| **INDICATION:** | Moderate to severe atopic dermatitis |
| **SPONSOR:** | Genentech, Inc. |

**Objectives and Endpoints**

This study will evaluate the efficacy, safety, and pharmacokinetics of MSTT1041A compared with placebo in patients with moderate to severe atopic dermatitis (AD). Specific objectives and corresponding endpoints for the study are outlined below.

**Primary Efficacy Objective**

The primary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo on the basis of the following endpoint:

- Percent change from baseline to Week 16 of total Eczema Area and Severity Index (EASI) score

**Secondary Efficacy Objective**

The secondary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo on the basis of the following endpoints:

- Proportion of patients who achieve Investigator's Global Assessment (IGA) response of 0 or 1 (clear or almost clear) at Week 16
- Proportion of patients who achieve EASI-75 (≥75% reduction from baseline in EASI score) at Week 16
- Percent change in pruritus from baseline to Week 16, as assessed by a Numeric Rating Scale (NRS)
- Percent change in body surface area (BSA) with AD involvement from baseline to Week 16
- Percent change in disease severity from baseline to Week 16, as assessed by SCORing Atopic Dermatitis (SCORAD)

[redacted]

[redacted]

**Safety Objective**

The safety objective for this study is to evaluate the safety of MSTT1041A compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the WHO toxicity scale
- Change from randomization visit in vital signs, ECGs, and clinical laboratory results

**Pharmacokinetic Objectives**

The pharmacokinetic (PK) objective for this study is to characterize the MSTT1041A PK profile on the basis of the following endpoint:

- Serum concentration of MSTT1041A at specified timepoints

The exploratory PK objective is as follows:

- To evaluate potential relationships between drug exposure and MSTT1041A efficacy, safety, and biomarker endpoints

**Immunogenicity Objective**

The immunogenicity objective for this study is to evaluate the immune response to MSTT1041A on the basis of the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs) during the study
- Potential impact of ADA status on efficacy, safety, and PK endpoints

**Biomarker Objective**

The exploratory biomarker objective for this study is to identify biomarkers that may provide evidence of MSTT1041A activity, or may increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Relative change from randomization (Day 1) visit in biomarker levels in blood at Weeks 1, 4, 8, 16, and 24

[redacted]

## Study Design

**Description of Study**

This is a Phase II, randomized, double-blind, placebo-controlled multicenter study to assess the efficacy and safety of MSTT1041A in patients with moderate to severe AD. The study will consist of a screening period (Day –35 to –1), 16-week double-blind treatment period, and an 8-week follow-up period.

After providing informed consent, patients will be assessed for study eligibility during screening and at the randomization (Day 1) visit. Screening will be up to 35 days. During the screening period, patients must demonstrate EASI score ≥16, IGA score ≥3, pruritus NRS score for maximum itch intensity ≥3, and have a history of inadequate response to treatment with topical medications. Furthermore, patients will be required to apply moisturizers (emollients) at least twice daily and to refrain from topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) use for at least the 7 consecutive days immediately before randomization and throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each office visit. Patients who fail to meet eligibility criteria during screening will be permitted to re-screen once, unless the reason for the screen failure is because of not meeting any of the following:

- EASI score $\geq 16$ at screening and the randomization visit
- IGA score $\geq 3$ (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at screening and the randomization visit
- $\geq 10\%$ BSA of AD involvement at screening and the randomization visit
- Baseline pruritus NRS score for maximum itch intensity $\geq 3$ at screening and the randomization visit

Patients who fail to meet eligibility requirements and are eligible to be re-screened are required to repeat assessments as follows:

- If $\leq 35$ days after Informed Consent Form completion, repeat only the assessments that triggered screen failure.
- If $> 35$ days after Informed Consent Form completion, repeat the consent process and all screening assessments except tuberculosis (TB) screening and hepatitis serologies. TB screening and hepatitis serologies should be repeated if re-screening occurs $> 3$ months after initial Informed Consent Form completion.

At Day 1, patients will undergo further assessments to determine eligibility for randomization to the double-blind treatment period.

Approximately 90 patients will be randomized in a 1:1 ratio to receive MSTT1041A 490 mg SC or placebo SC every 4 weeks (Q4W). Randomization will be stratified by baseline disease severity IGA score (IGA = 3 vs. IGA = 4) and region. Patients will be given a loading dose of 245 mg SC MSTT1041A or placebo at the Week 1 visit to reduce the time required to achieve steady-state exposure of MSTT1041A.

During the double-blind treatment and follow-up period, laboratory tests and clinical assessments will be performed at the site (office visits). Additionally, telephone visits will be conducted to assess changes in health status, concomitant medications, and sleep and pruritus NRS score.

An Internal Monitoring Committee (IMC) will monitor data on safety and study conduct on an ongoing basis. Members of the IMC will be unblinded and will include representatives from Clinical Science and Drug Safety who are not directly involved in the study and representatives from Biostatistics and Statistical Programming and Analysis.

The IMC will review cumulative data at regular intervals of approximately every 3 months from the time of randomization of the first patient. Ad hoc meetings may be held at the request of the IMC or Sponsor at any time to address potential safety concerns. The data to be reviewed will include demographics, concomitant medications, study drug administration, adverse events, serious adverse events, adverse events of special interest, ECGs, and relevant laboratory data.

**Number of Patients**

Approximately 90 patients will be enrolled in this study.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form

- Age 18-75 years at time of signing Informed Consent Form
- Body mass index of 18–40 kg/m$^2$ and weight $\geq$40 kg at screening
- Ability to comply with the study protocol, in the investigator's judgment
- Ability to understand and complete study-related questionnaires
- Chronic AD, (according to American Academy of Dermatology Consensus Criteria), that has been present for at least 3 years before the screening visit
- EASI score $\geq$16 at screening and the randomization (Day 1) visit
- IGA score $\geq$3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at screening and the randomization (Day 1) visit
- $\geq$10% BSA of AD involvement at screening and the randomization (Day 1) visit
- Pruritus NRS score for maximum itch intensity $\geq$3 at screening and the randomization (Day 1) visit
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks)

  Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency ($\pm$ TCI as appropriate), applied for at least 4 weeks or for the maximum duration recommended by the product prescribing information (e.g., 2 weeks for ultra-high potent TCS), whichever is shorter.

  Patients with documented systemic treatment (e.g., oral, IV) for AD at any point during the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for the study after appropriate washout.

  Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the patient's treating physician.

  Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician. If documentation is inadequate, potential patients may be re-screened after such documentation is obtained (e.g., patients are shown to fail a 4-week course of mid-to-higher potency TCS [$\pm$TCI]).
- Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the randomization visit.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive method and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 12 weeks after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 12 weeks after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 weeks after the final dose of study drug

  Women of childbearing potential must have a negative serum pregnancy test result during the screening period and a negative urine pregnancy test at the randomization visit
- Prior treatment with MSTT1041A
- Use of any of the following:

  Treatment with any investigational therapy (with the exception of biologics) within 8 weeks or within 5 half-lives (if known), whichever is longer, before screening

  Treatment with immunomodulatory, immunosuppressive (e.g., systemic corticosteroids, methotrexate, mycophenolate-mofetil, interferon-γ, Janus kinase inhibitors, cyclosporine, azathioprine, etc.) within 4 weeks before screening or any condition (e.g., severe asthma) that, in the opinion of the investigator, is likely to require such treatment during the course of the study

  Treatment with investigational or licensed biologics as follows:

  – Any cell-depleting agents including but not limited to rituximab: within 6 months before screening, or until lymphocyte count returns to normal, whichever is longer
  – Other biologics: within 3 months or 5 half-lives (if known) before screening, whichever is longer
- Use of any of the following treatments within 2 weeks before screening, or any condition that, in the opinion of the investigator, is likely to require such treatment during the course of the study:

  Regular use (more than 2 visits per week) of a tanning booth/parlor

  Phototherapy
- Treatment with TCS or TCIs within 1 week before the randomization (Day 1) visit
- Initiation of treatment for AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products within 1 week before the randomization (Day 1) visit
- Initiation of or change in allergen immunotherapy within 12 weeks before screening
- Use of any of the following treatments within 4 weeks before screening, or any condition that, in the opinion of the investigator, is likely to require such treatment during the course of the study:

  Treatment with immunoglobulin or blood products

  Treatment with any live, attenuated vaccine
- Acute or chronic infection requiring either surgical intervention (e.g., drainage) or medical therapy (e.g., antibiotics, antiviral, antiparasitics, antifungal, or antiprotozoals) within 2 weeks before screening or superficial skin infections within 1 week before the randomization visit.

  Note: Patients may be rescreened after infection resolves.

- Positive test for TB during screening, defined as either a positive purified protein derivative (PPD) ($\geq$ 5 mm of induration 48–72 hours after injection) or a positive QuantiFERON TB-Gold® (QFT) test

  Patients with a history of Bacille Calmette-Guérin vaccination should be screened using the QFT only; the following criteria for the QFT apply:

  An indeterminate QFT should be repeated

  A positive QFT or two successive indeterminate QFT results should be considered a positive diagnostic TB test

  An indeterminate QFT followed by a negative QFT test, should be considered a negative diagnostic TB test

  Patients with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or patients with a positive QFT (see criteria above) are eligible if they meet all of the following criteria:

  No symptoms consistent with TB (see TB worksheet provided by Genentech)

  Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB per the treatment options as stated in the WHO guideline) before screening

  No known exposure to a case of active TB after most recent prophylaxis

  No evidence of active TB on chest X-ray within 3 months before screening
- History of any known immunodeficiency disorder, including but not limited to HIV infection
- Positive hepatitis C virus (HCV) antibody test result at screening
- Ineligible test results for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) total at screening as defined below:

  If HBsAg testing is positive, patient is not eligible. For patients with a negative HBsAg testing, following criteria apply:

  If HBsAb testing is negative and HBcAb is positive, patient is not eligible.

  If HBsAb testing is positive and HBcAb is negative, patient is eligible.

  If HBsAb testing is negative and HBcAb is negative, patient is eligible.

  If HBsAb testing is positive and HBcAb is positive, patient must undergo further testing for hepatitis B virus DNA (HBV DNA):

  – Patient is not eligible, if HBV DNA test value is $\geq$ 20 IU/mL or test cannot be performed.

  – Patient is eligible, if HBV DNA test value is $<$ 20 IU/mL.
- Evidence of active liver disease, including jaundice or AST, ALT, total bilirubin, or ALP $> 2 \times$ upper limit of normal (ULN) at screening
- History of anaphylaxis, hypersensitivity to a biologic agent, or known hypersensitivity to any component of the MSTT1041A or placebo injection
- Neutrophil count $\leq 0.5 \times 10^3$/µL at screening
- Platelet count $\leq 50 \times 10^3$/µL at screening
- Presence of skin comorbidities that may interfere with study assessments, in the opinion of the investigator
- Active malignancy, including cutaneous basal or squamous cell carcinoma or melanoma
- History of malignancy within 5 years before screening, except for cases of cervical carcinoma in situ or breast ductal carcinoma in situ that have been treated and considered cured
- Helminthic parasitic infection diagnosed within 6 months before screening that has not been treated or has not responded to standard-of-care therapy or exposure to water-born parasites within 6 weeks before screening

- History or evidence of substance abuse that would pose a risk to patient safety, interfere with the conduct of the study, have an impact on the study results, or affect the patient's ability to participate in the study, in the opinion of the investigator
- Hemoglobin A1c ($HbA_{1c}$) > 8.5% at screening or any other clinically significant finding that, in the opinion of the investigator, may define uncontrolled diabetes
- History of myocardial infarction, congestive heart failure NHYA Class III and IV, unstable angina pectoris, or stroke within 12 months before screening
- History or presence of complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction on ECG, or any abnormality that is clinically significant in the investigator's opinion
- QT interval corrected through use of Fridericia's formula (QTcF) > 450 ms, if patient is male, or QTcF > 470 ms, if patient is female
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as diagnosed structural heart disease (e.g., left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease, clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History or evidence of a medical condition or any clinically significant disorder, condition, or disease (e.g., psychiatric or other mental health disorder, renal failure, hypertension, liver disease, anemia) that is uncontrolled despite treatment or that is likely, in the opinion of the investigator, to require a change in therapy, pose a risk to patient safety, interfere with the conduct of the study, have an impact on the study results, or affect the patient's ability to participate in the study
- Planned surgical intervention during the course of the study
- Patient who is a member of the investigational team or his/her immediate family

**End of Study**

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur approximately 6 months after the last patient is enrolled.

**Length of Study**

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 17 months.

## Investigational Medicinal Products

**Test Product (Investigational Drug)**

The investigational medicinal products (IMPs) for this study are MSTT1041A and matching placebo. Patients who meet eligibility criteria during the screening period will be randomly allocated to receive treatment with MSTT1041A 490 mg Q4W or placebo. Additionally, patients in the active treatment arm will receive a loading dose of 245 mg at the Week 1 visit; patients in the placebo arm will receive placebo. Study drug administration must occur after all other procedures have been completed at each office visit, unless specifically indicated otherwise. Study drug will be administered at the study site by trained medical personnel. Except for the loading dose, each dose of study drug (MSTT1041A or placebo) will be administered as four SC injections (for a total of 7 mL), one in each quadrant of the abdomen. The loading dose (MSTT1041A or placebo) will be administered as two SC injections (for a total of 3.5 mL).

## Statistical Methods

**Primary Analysis**

Efficacy analyses will be based on the intent-to-treat (ITT) approach. All patients randomized (ITT population) will be included in the analysis, with patients grouped according to the treatment assigned at randomization. Hypothesis testing for the efficacy endpoints will be performed for each MSTT1041A dose level and the placebo group.

The primary efficacy endpoint for this study is percent change from baseline to Week 16 of total EASI score. A mixed-effect model for repeated measures (MMRM) model will be used, with percent change (post baseline change divided by baseline value) as the dependent variable.

The model will include baseline value of the EASI score, treatment arms, visits, treatment arm by visit interaction, and stratification factors. To account for repeated observations with patients, a random patient effect will be added to the model. The MMRM model will provide adjusted least-square means of percent change from baseline at Week 16 for each of the treatment arms with the corresponding standard error, 95% confidence interval and p-values.

**Determination of Sample Size**

Approximately 90 patients in total will be randomized in a 1:1 ratio to 490 mg MSTT1041A or placebo Q4W. The sample size provides at least 80% power to detect a difference of 34% in the percent change from baseline in EASI score at Week 16 between MSTT1041A- and placebo-treated patients, assuming a standard deviation of 40.6 for placebo-treated patients. The same number of patients can also provide at least 80% power to detect 1) a difference of 27% between MSTT1041A- and placebo-treated patients in the proportion of patients achieving IGA scores of 0 or 1 at Week 16, assuming the percentage is 2% in placebo-treated patients, respectively, 2) a difference of 32% between MSTT1041A- and placebo-treated patients in the proportion of patients achieving EASI-75 at Week 16, assuming the percentage is 13% in placebo-treated patients, and 3) a difference of 30% between MSTT1041A- and placebo-treated patients in percent change from baseline to Week 16 in pruritus NRS, assuming a standard deviation of 37.3 for placebo-treated patients. The sample size is calculated at a two-sided significance level of 0.05 and assumes 25% dropout.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AD | atopic dermatitis |
| ADA | anti-drug antibody |
| [redacted] | [redacted] |
| BSA | body surface area |
| ClinRO | clinician-reported outcome |
| CRO | contract research organization |
| EASI | Eczema Area and Severity Index |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| $HbA_{1c}$ | hemoglobin $A_{1c}$ |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Council for Harmonisation |
| IFN-$\gamma$ | interferon-$\gamma$ |
| IGA | Investigator's Global Assessment |
| IL | interleukin |
| IMC | Internal Monitoring Committee |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IxRS | web-based response system |
| MACE | major adverse cardiac events |
| MMRM | mixed model repeated measures |
| NRS | Numeric Rating Scale |
| PD | pharmacodynamic |
| PK | pharmacokinetic |

| Abbreviation | Definition |
|---|---|
| PPD | purified protein derivative |
| PRO | patient-reported outcome |
| Q4W | every 4 weeks |
| QFT | QuantiFERON TB-Gold® (QFT) |
| QTcF | QT interval corrected through use of Fridericia's formula |
| [redacted] | [redacted] |
| SC | subcutaneous |
| SCORAD | SCORing Atopic Dermatitis |
| [redacted] | [redacted] |
| sST2 | soluble ST2 |
| TB | tuberculosis |
| TCI | topical calcineurin inhibitor |
| TCS | topical corticosteroids |
| Th1 | Type 1 helper |
| Th2 | Type 2 helper |
| TNF-α | tumor necrosis factor-α |
| ULN | upper limit of normal |
| WES | whole exome sequencing |
| WGS | whole genome sequencing |

# 1. BACKGROUND

## 1.1 BACKGROUND ON ATOPIC DERMATITIS

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing and intensely pruritic inflammatory skin disease. Clinically, AD is characterized by recurrent eczematous lesions (such as erythematous patches with exudation, blistering, and crusting at early stages and scaling fissuring and lichenification at later stages), which can lead to skin infections, sleep loss, and poor quality of life (Williams and Gallo 2015; Weidinger et al. 2018). AD affects 15%–20% of children and 1%–3% of adults; recent data suggest that the prevalence of AD is still increasing, especially in low-income countries. First manifestations of AD usually appear early in life and often precede other allergic diseases such as asthma or allergic rhinitis. AD poses a significant burden on health care resources and the quality of life (mainly because of sleep deprivation due to pruritus, employment loss, time to care, and financial costs) of patients (Nutten 2015).

The therapeutic approach to AD primarily consists of trigger avoidance, skin hydration with bathing, and use of emollients and anti-inflammatory therapies consisting predominantly of topical corticosteroids (TCS). In many patients, treatment with TCS provides some measure of symptomatic relief but does not adequately control their disease.

In those patients who have persistent moderate to severe disease not responding adequately to TCS, recent guidelines outline a number of step-up therapeutic options (Ring et al. 2012; Schneider et al. 2013, Wollenberg et al. 2016). The step-up options include topical calcineurin inhibitors (TCIs), phototherapy, and immunosuppressive agents such as oral corticosteroids, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Although these step-up therapies (including systemic immunosuppressants) used to treat patients with moderate to severe AD show evidence of modest to good efficacy, poor tolerability due to side effects limit their prolonged use.

In attempts to find novel therapies for moderate to severe AD with an acceptable benefit-risk profile, a number of biologic agents that specifically target inflammatory cells are being tested. So far, only dupilumab (a fully human monoclonal antibody against interleukin [IL]-4Rα that blocks both IL-4 and IL-13 signaling) has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of moderate to severe AD. However, on average, over half of the participants in the pivotal studies did not achieve Investigator's Global Assessment (IGA) 0 or 1. Published results suggest that dupilumab is mainly modulating the Type 2 helper (Th2) pathway. Yet, findings from molecular research and trials on targeted therapeutics demonstrate that AD is a heterogeneous disease that probably comprises many different endotypes with distinct pathological features and clinical implications (Weidinger et al. 2018). Thus, the identification and characterization of these disease subtypes as well as exploring novel treatment options will further help improve the efficacy of the therapy and quality of life of patients with AD. IL-33/ST2 signaling has been demonstrated to

associate with key features of AD including decrease in filaggrin expression (Seltmann et al. 2015), increased itch (Liu et al. 2016), and Type 1 helper (Th1) and Th2 inflammation (Ding et al. 2018). Therefore, targeting ST2 with MSTT1041A has the potential to address the unmet need in this disease.

## 1.2 BACKGROUND ON MSTT1041A

MSTT1041A is a first-in-class, fully human, IgG2 monoclonal antibody that binds to ST2, the receptor for IL-33, and inhibits human IL-33. Nonclinical testing confirms that the molecule has high receptor affinity and is non-activating.

Refer to the MSTT1041A Investigator's Brochure for details on nonclinical and clinical studies.

## 1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

MSTT1041A prevents the IL-33-induced signaling that galvanizes immune cells in inflammation. IL-33 is a member of the IL-1 family of cytokines. It is considered an ”alarmin” or a damage-associated molecular pattern molecule, that is constitutively expressed on epithelial cells and released upon cell injury or stress from exposure to such exogenous stimuli as allergens, toxins, or infections. IL-33 activates various immune cells through its receptor ST2, also known as IL-1RL1 (Nabe 2014). Recently, the IL-33/ST2 pathway has been found to play an important role in allergic diseases such as AD, asthma, and allergic rhinitis (Ding et al. 2018). Once released from these cells, typically in response to stress or damage, IL-33 signals through a receptor complex containing the primary binding receptor ST2 and the co-receptor IL-1RAcP. Intracellular signaling induced by this complex promotes the inflammatory actions of ST2-expressing cells. A secreted soluble form of ST2 (sST2) arises from alternative splicing, is elevated in settings of inflammation, and acts as a decoy to bind and inhibit released IL-33 (Hayakawa et al. 2007). Mice genetically deficient in ST2 (ST2–/–) are phenotypically normal and have been used as controls for mechanistic studies to demonstrate that IL-33-elicited responses in vivo are entirely dependent on ST2 (Kondo et al. 2008). ST2 is expressed on keratinocytes, endothelial cells, fibroblasts, and inflammatory cells (including Type 2 innate lymphoid cells, monocytes, natural killer cells, T lymphocytes, mast cells, basophils, and eosinophils) (Cevikbas and Steinhof 2012; Liew et al. 2016). Binding of IL-33 to ST2 can activate both Th1 and Th2 T-cell inflammation depending on the underlying milieu. Signaling via ST2 leads to release of multiple mediators including tumor necrosis factor (TNF)-$\alpha$, interferon (IFN)-$\gamma$, IL-5, IL-6, IL-9, amphiregulin, and IL-13 (Martin and Martin 2016; Griesenauer and Paczesny 2017).

Du et al. (2016) showed that IL-33 is expressed in keratinocytes, endothelial cells, and infiltrating mononuclear cells of AD skin lesions. ST2 is expressed in the stratum spinosum and was localized to the cytoplasm, cellular membrane, and intercellular space. ST2 is further expressed on dermal infiltrating cells, endothelial cells, and

neutrophils that infiltrated the epidermis (Du et al. 2016). Triggers such as allergens, irritants, and staphylococcal enterotoxin B increase expression of IL-33 and ST2 (Savinko et al. 2012). Furthermore, IL-33 has been shown to play a crucial role in activating Type 2 innate lymphoid cells and by this, contributing to development of allergic skin inflammation (Salimi et al. 2013). Moreover, IL-33 downregulates the expression of the skin barrier molecule filaggrin (Seltmann et al. 2015; Ryu et al. 2016; Nygaard et al. 2017) and the β-defensin 2 expression in human primary keratinocytes (Alase et al. 2012), thereby, exacerbating the defect in the barrier against allergen penetration and the susceptibility to bacterial superinfection in acute AD.

The inflammatory pathways in chronic AD are complex and involve both Th1 and Th2 immune responses. In vitro, IL-33 has been shown to influence both the Th1 and Th2 pathway. IL-33 expression is induced by TNF-α and IFN-γ in human dermal fibroblasts, HaCaT keratinocytes, macrophages, and human umbilical vein endothelial cells. IL-33-induced dendritic cells promote the differentiation from naive Th cells into Th2 cells and maintain memory Th2 cells, leading to the increased production of IL-5, IL-9, and IL-13. Meanwhile, Th1 cells respond to IL-33 and induce the release of IFN-γ, therefore driving skin inflammation towards chronic responses (Ding et al. 2018).

By targeting ST2, MSTT1041A has the capacity to block inflammation downstream of IL-33 activation. This is expected to translate into benefit in patients with AD. The ability to blunt inflammation across the broad population represents a significant therapeutic advance and addresses an important unmet medical need.

MSTT1041A was not associated with toxicity at doses of up to 300 mg/kg SC or IV (highest dose evaluated) in 28-day and 6-month cynomolgus monkey toxicology studies. In addition, there were no MSTT1041A-related cardiovascular findings in a single-dose safety pharmacology study or in repeat-dose toxicity studies. In an ex vivo human tissue cross-reactivity immunohistochemistry study, no specific staining in any human tissues was observed. At the no-observed-adverse-effect level (300 mg/kg SC or IV), there are significant exposure margins over human exposures.

As reported in the MSTT1041A Investigator's Brochure, there are no identified risks associated with MSTT1041A. In three completed Phase 1 studies, there were no serious adverse events or adverse events that led to treatment discontinuation in healthy subjects who received single ($n=70$, Study 20110235; $n=41$, Study 20130177) or multiple ($n=41$, Study 20110236) doses of MSTT1041A at SC doses ranging from 2.1 to 560 mg and IV doses ranging from 210 to 700 mg.

A Phase IIb study with MSTT1041A in patients with severe asthma is currently ongoing (502 patients were randomized into a 52-week double-blind treatment period and received blinded study treatment [70 mg, 210 mg, or 490 mg of MSTT1041A, or placebo]). Refer to the MSTT1041A Investigator's Brochure for a complete summary of safety information.

Thus, the favorable safety profile to date supports further development of MSTT1041A in patients with AD.

# 2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of MSTT1041A compared with placebo in patients with moderate to severe AD. Specific objectives and corresponding endpoints for the study are outlined below.

## 2.1 EFFICACY OBJECTIVES

### 2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo on the basis of the following endpoint:

- Percent change from baseline to Week 16 of total Eczema Area and Severity Index (EASI) score

### 2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo on the basis of the following endpoints:

- Proportion of patients who achieve IGA response of 0 or 1 (clear or almost clear) at Week 16
- Proportion of patients who achieve EASI-75 (≥75% reduction from baseline in EASI score) at Week 16
- Percent change in pruritus from baseline to Week 16, as assessed by a Numeric Rating Scale (NRS)
- Percent change in body surface area (BSA) with AD involvement from baseline to Week 16
- Percent change in disease severity from baseline to Week 16, as assessed by SCORing Atopic Dermatitis (SCORAD)

[redacted]

[redacted]

## 2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of MSTT1041A compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the WHO toxicity scale
- Change from randomization visit in vital signs, ECGs, and clinical laboratory results

## 2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the MSTT1041A PK profile on the basis of the following endpoint:

- Serum concentration of MSTT1041A at specified timepoints

The exploratory PK objective is as follows:

- To evaluate potential relationships between drug exposure and MSTT1041A efficacy, safety, and biomarker endpoints

## 2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to MSTT1041A on the basis of the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs) during the study
- Potential impact of ADA status on efficacy, safety, and PK endpoints

## 2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that may provide evidence of MSTT1041A activity, or may increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Relative change from randomization (Day 1) visit in biomarker levels in blood (see Section 4.5.6) at Weeks 1, 4, 8, 16, and 24

[redacted]

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

This is a Phase II, randomized, double-blind, placebo-controlled multicenter study to assess the efficacy and safety of MSTT1041A in patients with moderate to severe AD. The study will consist of a screening period (Day −35 to −1), 16-week double-blind treatment period, and an 8-week follow-up period.

After providing informed consent, patients will be assessed for study eligibility during screening and at the randomization (Day 1) visit. Screening will be up to 35 days. During the screening period, patients must demonstrate EASI score ≥ 16, IGA score ≥ 3, pruritus NRS score for maximum itch intensity ≥ 3, and have a history of inadequate response to treatment with topical medications. Furthermore, patients will be required to apply moisturizers (emollients) at least twice daily and to refrain from TCS or TCI use for at least the 7 consecutive days immediately before randomization and throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each office visit (see Sections 4.1.1 and 4.1.2 for details). Patients who fail to meet eligibility criteria during screening will be permitted to re-screen once, unless the reason for the screen failure is because of not meeting any of the following:

- EASI score ≥ 16 at screening and the randomization visit
- IGA score ≥ 3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at screening and the randomization visit
- ≥ 10% BSA of AD involvement at screening and the randomization visit
- Baseline pruritus NRS score for maximum itch intensity ≥ 3 at screening and the randomization visit

Patients who fail to meet eligibility requirements and are eligible to be re-screened are required to repeat assessments as follows:

- If ≤ 35 days after Informed Consent Form completion, repeat only the assessments that triggered screen failure.
- If > 35 days after Informed Consent Form completion, repeat the consent process and all screening assessments except tuberculosis (TB) screening and hepatitis serologies. TB screening and hepatitis serologies should be repeated if re-screening occurs > 3 months after initial Informed Consent Form completion.

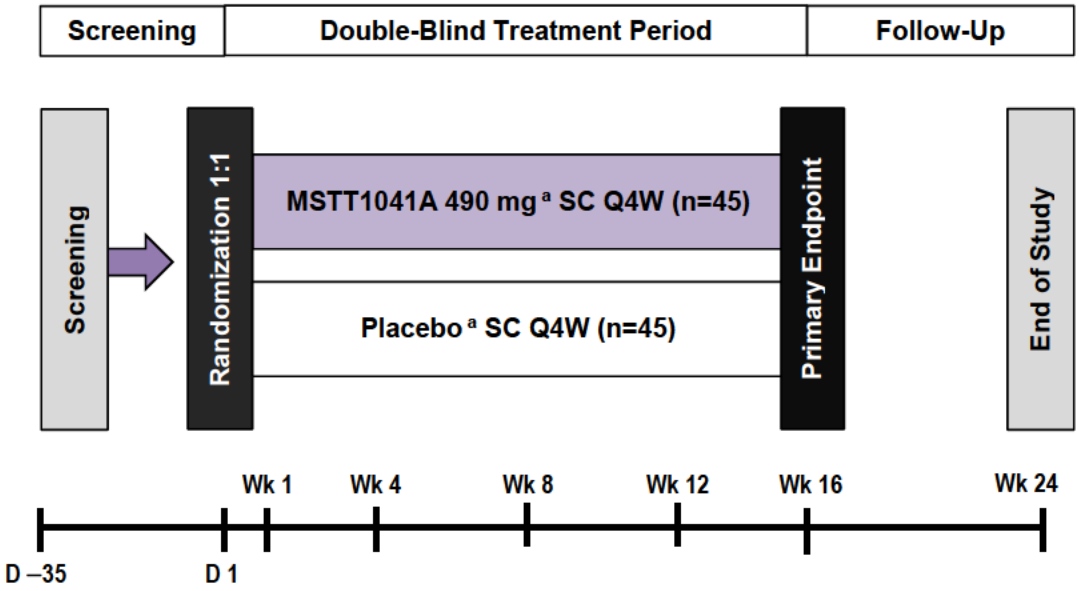
At Day 1, patients will undergo further assessments to determine eligibility for randomization to the double-blind treatment period.

Approximately 90 patients will be randomized in a 1:1 ratio to receive MSTT1041A 490 mg SC or placebo SC every 4 weeks (Q4W). Randomization will be stratified by baseline disease severity IGA score (IGA=3 vs. IGA=4) and region. Patients will be given a loading dose of 245 mg SC MSTT1041A or placebo at the Week 1 visit to reduce the time required to achieve steady-state exposure of MSTT1041A (see Section 4.3.2.1 for details).

During the double-blind treatment and follow-up period, laboratory tests and clinical assessments will be performed at the site (office visits). Additionally, telephone visits will be conducted to assess changes in health status, concomitant medications, and sleep and pruritus NRS score.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

**Figure 1 Study Schema**




D=day; Q4W=every 4 week; Wk=week.

[a] Additional loading dose on Week 1 of 245 mg MSTT1041A (or placebo) SC.

### 3.1.1 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor data on safety and study conduct on an ongoing basis. Members of the IMC will be unblinded and will include representatives from Clinical Science and Drug Safety who are not directly involved in the study and representatives from Biostatistics and Statistical Programming and Analysis. Further details regarding roles and responsibilities will be outlined in the IMC Charter.

The IMC will review cumulative data at regular intervals of approximately every 3 months from the time of randomization of the first patient. Ad hoc meetings may be held at the request of the IMC or Sponsor at any time to address potential safety concerns. The data to be reviewed will include demographics, concomitant medications, study drug administration, adverse events, serious adverse events, adverse events of special interest, ECGs, and relevant laboratory data.

At the time of each review, the IMC will make one of the following recommendations: the trial continues as planned, the trial is stopped for safety reasons, the protocol is amended, additional analyses need to be performed, or enrollment will be held pending further safety evaluations. Decisions will be made in consideration of the totality of the available data. Final decisions will rest with the Sponsor's study team.

Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Board (IRB) or Ethics Committee (EC).

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur approximately 6 months after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 17 months.

In addition, the Sponsor may decide to terminate the study at any time.

## 3.3 RATIONALE FOR STUDY DESIGN

[redacted]

[redacted]

### 3.3.2 Rationale for Patient Population

See Section 1 for details on the high unmet medical need for new therapies for patients with moderate to severe AD.

### 3.3.3 Rationale for Control Group

A placebo-treated control group will be used in this study to assess differences in efficacy and safety in patients who receive MSTT1041A compared with patients who receive placebo. The use of a control group is necessary given the inherent variability in self-reported symptoms and investigator assessments. All patients will continue to receive standard-of-care treatment in addition to study drug (MSTT1041A or placebo) throughout the study.

### 3.3.4 Rationale for Biomarker Assessments

Biomarker assessments, before and at various timepoints after treatment, will be used to provide evidence of the biologic activity of MSTT1041A in patients, identify biomarkers that may be predictive of response to MSTT1041A, define PK and/or pharmacodynamic (PD) relationships, advance the understanding of the mechanism of action of MSTT1041A in patients, support selection of a recommended dose regimen, and increase the knowledge and understanding of disease biology. [redacted]

[redacted]

## 4. MATERIALS AND METHODS

### 4.1 PATIENTS

Approximately 90 patients with moderate to severe AD will be enrolled in this study.

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years at time of signing Informed Consent Form
- Body mass index of 18–40 kg/m$^2$ and weight $\geq$ 40 kg at screening
- Ability to comply with the study protocol, in the investigator's judgment

- Ability to understand and complete study-related questionnaires
- Chronic AD, (according to American Academy of Dermatology Consensus Criteria [Eichenfield et al. 2014]), that has been present for at least 3 years before the screening visit
- EASI score ≥16 at screening and the randomization (Day 1) visit
- IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at screening and the randomization (Day 1) visit
- ≥10% BSA of AD involvement at screening and the randomization (Day 1) visit
- Pruritus NRS score for maximum itch intensity ≥3 at screening and the randomization (Day 1) visit
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks)

    Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 4 weeks or for the maximum duration recommended by the product prescribing information (e.g., 2 weeks for ultra-high potent TCS; see Appendix 2), whichever is shorter.

    Patients with documented systemic treatment (e.g., oral, IV) for AD at any point during the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for the study after appropriate washout.

    Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the patient's treating physician.

    Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician. If documentation is inadequate, potential patients may be re-screened after such documentation is obtained (e.g., patients are shown to fail a 4-week course of mid-to-higher potency TCS [±TCI]; see Appendix 2 for examples of TCS classified by potency).
- Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the randomization visit (see Section 4.1.2 for limitations regarding emollients).

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive method and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 12 weeks after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq 12$ continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 12 weeks after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

### 4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 weeks after the final dose of study drug

  Women of childbearing potential must have a negative serum pregnancy test result during the screening period and a negative urine pregnancy test at the randomization visit

- Prior treatment with MSTT1041A

- Use of any of the following:

  Treatment with any investigational therapy (with the exception of biologics) within 8 weeks or within 5 half-lives (if known), whichever is longer, before screening

  Treatment with immunomodulatory, immunosuppressive (e.g., systemic corticosteroids, methotrexate, mycophenolate-mofetil, IFN-$\gamma$, Janus kinase inhibitors, cyclosporine, azathioprine, etc.) within 4 weeks before screening or any condition (e.g., severe asthma) that, in the opinion of the investigator, is likely to require such treatment during the course of the study

  Treatment with investigational or licensed biologics as follows:

  – Any cell-depleting agents including but not limited to rituximab: within 6 months before screening, or until lymphocyte count returns to normal, whichever is longer
  – Other biologics: within 3 months or 5 half-lives (if known) before screening, whichever is longer
- Use of any of the following treatments within 2 weeks before screening, or any condition that, in the opinion of the investigator, is likely to require such treatment during the course of the study:

  Regular use (more than 2 visits per week) of a tanning booth/parlor

  Phototherapy
- Treatment with TCS or TCIs within 1 week before the randomization (Day 1) visit
- Initiation of treatment for AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products within 1 week before the randomization (Day 1) visit
- Initiation of or change in allergen immunotherapy within 12 weeks before screening
- Use of any of the following treatments within 4 weeks before screening, or any condition that, in the opinion of the investigator, is likely to require such treatment during the course of the study:

  Treatment with immunoglobulin or blood products

  Treatment with any live, attenuated vaccine
- Acute or chronic infection requiring either surgical intervention (e.g., drainage) or medical therapy (e.g., antibiotics, antiviral, antiparasitics, antifungal, or antiprotozoals) within 2 weeks before screening or superficial skin infections within 1 week before the randomization visit.

  Note: Patients may be rescreened after infection resolves.

- Positive test for TB during screening, defined as either a positive purified protein derivative (PPD) (≥ 5 mm of induration 48–72 hours after injection) or a positive QuantiFERON TB-Gold® (QFT) test

  Patients with a history of Bacille Calmette-Guérin vaccination should be screened using the QFT only; the following criteria for the QFT apply:

  An indeterminate QFT should be repeated

  A positive QFT or two successive indeterminate QFT results should be considered a positive diagnostic TB test

  An indeterminate QFT followed by a negative QFT test, should be considered a negative diagnostic TB test

  Patients with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or patients with a positive QFT (see criteria above) are eligible if they meet all of the following criteria:

  No symptoms consistent with TB (see TB worksheet provided by Genentech)

  Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB per the treatment options as stated in the WHO guideline) before screening

  No known exposure to a case of active TB after most recent prophylaxis

  No evidence of active TB on chest X-ray within 3 months before screening
- History of any known immunodeficiency disorder, including but not limited to HIV infection
- Positive hepatitis C virus (HCV) antibody test result at screening
- Ineligible test results for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) total at screening as defined below (see also Flowchart in Appendix 3):

  If HBsAg testing is positive, patient is not eligible. For patients with a negative HBsAg testing, following criteria apply:

  If HBsAb testing is negative and HBcAb is positive, patient is not eligible.

  If HBsAb testing is positive and HBcAb is negative, patient is eligible.

  If HBsAb testing is negative and HBcAb is negative, patient is eligible.

  If HBsAb testing is positive and HBcAb is positive, patient must undergo further testing for hepatitis B virus (HBV) DNA:

  – Patient is not eligible, if HBV DNA test value is ≥ 20 IU/mL or test cannot be performed.

  – Patient is eligible, if HBV DNA test value is < 20 IU/mL.
- Evidence of active liver disease, including jaundice or AST, ALT, total bilirubin, or ALP > 2 × upper limit of normal (ULN) at screening

- History of anaphylaxis, hypersensitivity to a biologic agent, or known hypersensitivity to any component of the MSTT1041A or placebo injection
- Neutrophil count $\leq 0.5 \times 10^3$/µL at screening
- Platelet count $\leq 50 \times 10^3$/µL at screening
- Presence of skin comorbidities that may interfere with study assessments, in the opinion of the investigator
- Active malignancy, including cutaneous basal or squamous cell carcinoma or melanoma
- History of malignancy within 5 years before screening, except for cases of cervical carcinoma in situ or breast ductal carcinoma in situ that have been treated and considered cured
- Helminthic parasitic infection diagnosed within 6 months before screening that has not been treated or has not responded to standard-of-care therapy or exposure to water-born parasites within 6 weeks before screening
- History or evidence of substance abuse that would pose a risk to patient safety, interfere with the conduct of the study, have an impact on the study results, or affect the patient's ability to participate in the study, in the opinion of the investigator
- Hemoglobin A1c ($HbA_{1c}$) $> 8.5\%$ at screening or any other clinically significant finding that, in the opinion of the investigator, may define uncontrolled diabetes
- History of myocardial infarction, congestive heart failure NHYA Class III and IV, unstable angina pectoris, or stroke within 12 months before screening
- History or presence of complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction on ECG, or any abnormality that is clinically significant in the investigator's opinion
- QT interval corrected through use of Fridericia's formula (QTcF) $>$ 450 ms, if patient is male, or QTcF $>$ 470 ms, if patient is female
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as diagnosed structural heart disease (e.g., left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease, clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History or evidence of a medical condition or any clinically significant disorder, condition, or disease (e.g., psychiatric or other mental health disorder, renal failure, hypertension, liver disease, anemia) that is uncontrolled despite treatment or that is likely, in the opinion of the investigator, to require a change in therapy, pose a risk to patient safety, interfere with the conduct of the study, have an impact on the study results, or affect the patient's ability to participate in the study
- Planned surgical intervention during the course of the study
- Patient who is a member of the investigational team or his/her immediate family

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients who meet all eligibility criteria will be randomized to one of the two treatment groups through the web-based response system (IxRS) on the first day of dosing. Patients will be randomized in a 1:1 ratio to receive 490 mg SC MSTT1041A Q4W or placebo, and stratified by baseline disease severity IGA score (IGA=3 vs. IGA=4) and region.

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of IxRS provider and prespecified personnel (e.g., IMC members).

While PK and ADA samples must be collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the placebo arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples will be analyzed for all patients. Postbaseline ADA samples from patients assigned to the placebo arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

## 4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are MSTT1041A and matching placebo.

### 4.3.1 Study Treatment Formulation, Packaging, and Handling

#### 4.3.1.1 MSTT1041A and Placebo

MSTT1041A or matching placebo will be supplied by the Sponsor as sterile, clear, and colorless to slightly yellow liquid in glass vials. For information on the formulation and handling of MSTT1041A, see the pharmacy manual and the MSTT1041A Investigator's Brochure.

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

No dose modifications should be performed in this study. Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.1.

#### 4.3.2.1 MSTT1041A and Placebo

Patients who meet eligibility criteria during the screening period will be randomly allocated to receive treatment with MSTT1041A 490 mg SC Q4W or placebo. Additionally, patients in the active treatment arm will receive a loading dose of 245 mg SC MSTT1041A at the Week 1 visit; patients in the placebo arm will receive placebo (see Appendix 1).

Study drug administration must occur after all other procedures have been completed at each office visit, unless specifically indicated otherwise. Study drug will be administered at the study site by trained medical personnel. Except for the loading dose, each dose of study drug (MSTT1041A or placebo) will be administered as four SC injections (for a total of 7 mL), one in each quadrant of the abdomen. The loading dose (MSTT1041A or placebo) will be administered as two SC injections (for a total of 3.5 mL). See the pharmacy manual for details on study drug preparation and administration.

All patients will be observed for at least 30 minutes after each dose and longer in the event of an injection-site reaction, approximately 60 minutes, as determined by the investigator. If a patient develops any signs or symptoms to suggest a systemic hypersensitivity reaction or anaphylactic event, longer observation may be warranted in the opinion of the investigator.

Patients who are unable to tolerate study drug will discontinue treatment but will be asked to continue with study assessments. Study drug may be resumed after the events resolve, if the investigator determines that the event was not related to study drug and the investigator and Medical Monitor agree that it is appropriate for the patient to resume

study drug. See Section 5.1.2 for specific guidelines for withholding or discontinuing study drug for patients who experience adverse events.

### 4.3.3 Background Treatment

All patients are required to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before the randomization visit and to continue throughout the study (all 24 weeks where applicable). However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each office visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products within 1 week before the randomization visit or after enrollment into the double-blind treatment period.
If prescription moisturizers containing these additives are initiated more than 1 week before the randomization visit, they are permitted. Patients should continue using stable doses of permitted moisturizers throughout the study.

### 4.3.4 Rescue Treatment

If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment for AD may be provided to patients at the discretion of the investigator. For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications (e.g., TCS). TCI may be used for rescue, but it should be reserved for problem areas only (e.g., face, neck, intertriginous, and genital areas, etc.). If possible, investigators should attempt to limit the first step of rescue therapy to topical medications and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. If a patient receives rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine), study treatment will be discontinued.

After systemic treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the Medical Monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

All patients will complete all study visits and assessments regardless of completion of study treatment and regardless of receipt of rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (e.g., disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

### 4.3.5 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (MSTT1041A and placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

### 4.3.6 Continued Access to MSTT1041A

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP MSTT1041A or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing MSTT1041A in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

## 4.4 CONCOMITANT THERAPY, PROHIBITED THERAPY, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements, emollients) used by a patient in addition to protocol-mandated treatment from 6 months before screening. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

### 4.4.1 Cautionary Therapy

#### 4.4.1.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies may be used during the study at the discretion of the investigator.

### 4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited at any time after enrollment in the double-blind treatment period, unless otherwise indicated as described below (see Sections 4.1.1 and 4.1.2 for inclusion and exclusion criteria):

- Investigational therapy (other than protocol-mandated study treatment)
- Treatment with TCS or TCIs
- Treatment with a licensed biologic agent
- Treatment with immunomodulatory/immunosuppressive (e.g., systemic corticosteroids, methotrexate, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, cyclosporine, azathioprine)
- Treatment with immunoglobulin or blood products
- Treatment with any live attenuated vaccines
- Initiation of or change in allergen immunotherapy
- Initiation of or change in treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products

  Note: Patients should continue using stable doses of such moisturizers if initiated at least 1 week before the randomization visit
- Initiation of therapy with bleach baths
- Regular use (more than 2 visits per week) of a tanning booth/parlor
- Phototherapy

### 4.4.3 Additional Restrictions

Patients will have to fast for at least 8 hours prior to collection of blood samples for fasted glucose and lipids for select visits (see Appendix 1 for timepoints). If patient has not fasted for 8 hours, the patient must return to the site for fasting blood draw.

## 4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and available laboratory test values are acceptable.

All assessments must be performed on the day of the specified visit unless otherwise specified in the schedule of activities (see Appendix 1). As much as feasible, the disease severity assessments (EASI, IGA, and SCORAD) for each patient should be administered by the same assessor throughout the study. The assessments should

be performed by the investigator but may be administered by other site staff who are qualified and trained to perform the assessment, if approved by the Sponsor.

### 4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history, reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements, emollients) used by the patient within 6 months before screening will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

### 4.5.3 Atopy Status

The patient's atopy status (atopic or non-atopic) will be assessed during screening on the basis of historical documentation (e.g., patient's medical records). A patient is considered atopic if he or she has a positive result to any allergen demonstrated via historical allergy test (e.g., skin prick [wheal diameter $\geq$3 mm and documented negative control]), ImmunoCAP®, or other specific IgE test. Regardless of atopy status, total and specific IgE testing will be performed as specified in Appendix 1.

### 4.5.4 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities

should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, ideally while the patient is in a seated position, and temperature.

### 4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis or analyzed at point of care:

- Urine pregnancy test for all women of childbearing potential

  Urine pregnancy tests will be performed at the site prior to each administration of study drug and at other specified visits after treatment discontinuation. If a local urine pregnancy test result is positive, it must be reported immediately, and study drug will not be administered that day. The positive urine pregnancy result must be confirmed by a serum pregnancy test (conducted by the central laboratory). Refer to Section 5.4.3.1 for management of a patient with a positive pregnancy test.
- TB tests: PPD or QFT (QFT may be conducted by the central laboratory, per Sponsor agreement with site)

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST
- Fasting lipids: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
- Fasting glucose
- $HbA_{1c}$
- N-terminal pro B-type natriuretic peptide
- Serum pregnancy test
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)

- Viral serology: HBsAb, HBsAg, HBcAb, HCV antibody

  If HBsAb testing is positive and HBcAb is positive, patient must undergo further testing for HBV DNA.

Blood samples will be collected to evaluate the pharmacokinetics of MSTT1041A in serum as noted in the schedule of activities (see Appendix 1). Serum concentrations of MSTT1041A will be determined using validated analytical procedures.

The following samples will be sent to the Sponsor or a designee for analysis:

- Serum samples for MSTT1041A PK analysis
- Serum samples for immunogenicity analysis
- Serum samples for specific IgE, and total IgE, and other biomarkers; mandatory blood [redacted]

[redacted]

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for [redacted] biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood [redacted] research will be destroyed no later than 10 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

### 4.5.7 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at central ECG laboratory, and the data will be sent to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data. Any clinically significant morphologic waveform changes or other ECG abnormalities must be documented on the appropriate eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The same procedure should be repeated approximately 30 minutes after QTcF has stabilized on two successive ECGs of the first measurement. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.2.3. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

### 4.5.8 Chest X-Rays

Patients with a positive PPD (without a history of Bacillus Calmette-Guérin vaccination) or a positive or indeterminate QFT will require a chest X-ray to review for evidence of active TB, including posteroanterior and lateral views, unless a chest X-ray has been

performed within 3 months before screening and the report is available for review. A chest computed tomography scan may substitute for a chest X-ray. Chest X-rays should only be performed if patients first meet all other study eligibility criteria. All imaging should be read by a radiologist or per local requirements.

### 4.5.9 Clinician-Reported and Patient-Reported Outcomes

Clinician-reported outcome (ClinRO) and patient-reported outcome (PRO) data will be collected via questionnaires to document the treatment benefit of MSTT1041A. The questionnaires, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self- or interviewer-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. Adverse event reports will not be derived from PRO or ClinRO data by the Sponsor, and safety analyses will not be performed using PRO or ClinRO data. All adverse events should be recorded as described in Section 5.

Patients and clinicians will use an electronic device to capture PRO and ClinRO data. The electronic device and/or instructions for completing the questionnaires electronically will be provided by site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

#### 4.5.9.1 Eczema Area and Severity Index

EASI is a clinician-reported comprehensive measure of disease that is composed of individual components (i.e., body region involvement, severity) that can be separated and evaluated independently or in combination to provide a more complete assessment of the patient (see Appendix 4). EASI evaluates four anatomical regions (head/neck, upper limbs, trunk, lower limbs) for both the affected BSA and severity of key disease signs (erythema, induration, excoriation, lichenification).

#### 4.5.9.2 SCORing Atopic Dermatitis, Clinician Reported

The SCORAD has clinician-reported and patient-reported assessments. The clinician-reported assessments require physician-assessed intensity ratings for six signs/symptoms of AD (erythema, edema/papulation, oozing/crust, excoriation, lichenification, and dryness), which are each weighted by the percentage of the BSA affected. This clinician-rated score is augmented with patient-reported assessments ranging from 0–10 of both pruritus and sleep loss.

The patient-reported symptom components of SCORAD are single-item assessments of itch and sleep that use a 3-day recall period. They can be found in Appendix 5.

#### 4.5.9.3 Investigator Global Assessment

The IGA is a clinician-reported assessment using a 0–4 point scale to capture the IGA of AD (see Appendix 6). The IGA severity scale will be dichotomized to success or failure, with success defined as a score of clear (0) or almost clear (1) with at least two grades reduction from baseline score.

[redacted]

[redacted]

[redacted]

[redacted]

## 4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Every effort should be made to retain patients in the study. All patients will be asked to complete all study visits and assessments regardless of discontinuation of study treatment. Patients who discontinue study treatment prematurely will not be replaced.

### 4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Any patient that the investigator or Sponsor considers lost to follow up

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient is unable to complete all study visits and assessments (see Section 4.6.1), the patient should be asked to return to the clinic for an early termination visit. This visit should occur approximately 4 weeks after the final dose of study drug (see Appendix 1, for study assessment details).

### 4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

### 4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

## 5. ASSESSMENT OF SAFETY

### 5.1 SAFETY PLAN

MSTT1041A is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with MSTT1041A in completed Phase I studies and an ongoing Phase IIb study. As reported in the MSTT1041A Investigator's Brochure, there are no identified risks associated with MSTT1041A and there were no serious adverse events or adverse events that led to treatment discontinuation in healthy subjects who received single (n=79) or multiple (n=31) SC doses of MSTT1041A ranging from 2.1 to 560 mg and IV doses ranging from

210 to 700 mg, or in patients with atopic asthma (n = 2) who received a single 700 mg IV dose of MSTT1041A.

To date, a Phase IIb study with MSTT1041A in patients with severe asthma is currently ongoing. In this study, 502 patients were randomized to a 52-week double-blind treatment period and received blinded study treatment (70 mg, 210 mg, 490 mg of MSTT1041A, or placebo). Refer to the MSTT1041A Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

### 5.1.1 Risks Associated with MSTT1041A

#### 5.1.1.1 Immunogenicity

As with administration of any exogenous protein, there is potential risk for development of ADAs. Such antibodies can be neutralizing with potential for reduced therapeutic effect of the drug and/or sensitizing with potential for adverse events.

Serum samples will be collected at protocol-defined intervals to monitor for the development of ADAs. Patients who have clinical sequelae that are considered potentially related to an ADA response may also be asked to return for additional follow-up testing.

Refer to the MSTT1041A Investigator's Brochure for details on immunogenicity.

#### 5.1.1.2 Hypersensitivity Reactions and Anaphylaxis/Hypersensitivity-Like Reactions

Hypersensitivity reactions and anaphylaxis have been described with SC administration of monoclonal antibodies (Corominas et al. 2014). Signs and symptoms may include acute onset (minutes to several hours) of one or more of the following: respiratory compromise, reduced blood pressure, skin-mucosal involvement, or gastrointestinal symptoms (Sampson et al. 2006).

The potential for hypersensitivity to MSTT1041A in humans is unknown. However, as with any large-molecule therapeutic, administration of MSTT1041A may result in systemic reactions. Systemic reactions to large-molecule therapeutics can be IgE or non-IgE mediated or due to the release of cytokines and are generally characterized by signs and symptoms such as skin rash, urticaria, pruritus, local or diffuse erythema, angioedema, fever, chills, cough, dyspnea, wheezing, bronchospasm, nausea, vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can be

severe or life threatening. Effects typically occur during or within several hours after drug administration, but they may be delayed. Patients with a history of anaphylaxis, hypersensitivities to a biologic agent, or known hypersensitivity to any component of the MSTT1041A or placebo injection will be excluded from the study (see Section 4.1.2).

Investigators and health care professionals administering MSTT1041A should monitor patients after drug administration as described in Section 4.3.2.1. Investigators and staff should recognize and manage the signs and symptoms of such reactions and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006). All potential cases of anaphylaxis should be captured on the appropriate eCRF as instructed in Section 5.2 and Section 5.3. Investigators and health care professionals should accurately report these events immediately to the Sponsor as serious adverse events if appropriate. Health care professionals should also instruct patients on how to recognize the symptoms of any such events and to contact a health care provider or seek emergency care in case of any such symptoms.

Refer to the MSTT1041A Investigator's Brochure for details on hypersensitivity reactions and anaphylaxis/hypersensitivity-like reactions.

#### 5.1.1.3 Injection-Site Reactions

Injection-site reactions have been described with SC administration of monoclonal antibodies (Corominas et al. 2014). Signs and symptoms may include pain, itching, erythema, and swelling at the injection site. The reaction may be immediate, although it usually appears within 24–48 hours with variable incidence according to the drug administered.

No clinically significant injection-site reactions associated with MSTT1041A were observed following single or repeat doses in cynomolgus monkeys or healthy volunteers. However, as with any large-molecule therapeutic, administration of MSTT1041A may result in local reactions. Local reactions may include signs and symptoms such as redness, tenderness or pain, bruising, warmth, swelling, pruritus, or infection.

During the study, all injection-site events should be accurately reported on the appropriate eCRF.

Refer to the MSTT1041A Investigator's Brochure for details on injection-site reactions.

#### 5.1.1.4 Infection

The intended mechanism of action of MSTT1041A suggests inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of a decrease in the protective response to infection, particularly helminthic infections (Molofsky et al. 2015). All study participants will be monitored for signs and symptoms suggestive of infection by collection of vital signs, clinical laboratory tests, and adverse events.

Refer to the MSTT1041A Investigator's Brochure for details on infections.

#### 5.1.1.5 Exacerbation of Cardiovascular Disease

Published studies involving mouse models of cardiovascular disease or in vitro culture systems describe potential cardioprotective and atheroprotective roles of the IL-33/ST2 axis (Sanada et al. 2007; Miller et al. 2008; Seki et al. 2009; McLaren et al. 2010; Wasserman et al. 2012). For example, after experimentally induced acute left ventricular pressure overload, which could be relevant to clinical scenarios involving increased afterload (e.g., left-sided congestive heart failure or acute hypertension), ST2 mice had more left ventricular hypertrophy, more fibrosis, and impaired survival relative to their wild-type littermates (Sanada et al. 2007). However, the translatability of these findings remains uncertain. In addition, studies with conflicting data exist (Abston et al. 2012; Demyanets et al. 2013; Martin et al. 2015). In nonclinical toxicology and safety pharmacology studies with cynomolgus monkeys, including a 28-day and 6-month, repeat-dose toxicology study as well as a single-dose, cardiovascular safety study in telemetrized animals, no biologically significant changes were exhibited by MSTT1041A.

Evidence has shown that the ST2 receptor is a prognostic biomarker of cardiovascular disease outcome (Sabatine et al. 2008; Shah et al. 2009; Weir et al. 2010). Although published findings suggest a possible risk of exacerbation of existing cardiovascular disease in humans, there are no identified cardiovascular risks associated with inhibiting the IL-33/ST2 axis in humans.

Patients with active or unstable recent cardiovascular disease will be excluded from the study. Cardiac safety will be evaluated with monitoring of vital signs, ECG assessments, the collection of relevant adverse events, and other assessments described in the protocol. To monitor other factors that may affect cardiovascular risk, $HbA_{1c}$, fasting glucose, and lipid panels will be monitored to observe for indication of possible atherogenic and metabolic effects of MSTT1041A exposure.

During the study, all major adverse cardiac events (MACE) should be accurately reported on the appropriate eCRF. MACE include death due to cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack, unstable angina, or chest pain requiring hospitalization, coronary revascularization, and congestive heart failure requiring hospitalization.

Refer to the MSTT1041A Investigator's Brochure for details on cardiovascular disease.

### 5.1.2 Management of Patients Who Experience Adverse Events

#### 5.1.2.1 Treatment Interruption

MSTT1041A treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If MSTT1041A has been withheld for two or more consecutive dosing visits because of toxicity, the patient should be discontinued from MSTT1041A, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. MSTT1041A treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval.

The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Note: For treatment interruption because of rescue treatment, see Section 4.3.4.

#### 5.1.2.2 Management Guidelines

Table 1 provides specific guidelines for withholding or discontinuing study drug for patients who experience hepatotoxicity.

**Table 1 Guidelines for Treatment Interruption or Discontinuation for Patients Who Experience Hepatotoxicity**

| Event | Action to Be Taken |
|---|---|
| **Hepatotoxicity** | |
| ALT or AST increase that meets Hy's Law criteria: ALT or AST $>3\times$ ULN in combination with TBILI $>2\times$ ULN or clinical jaundice ruling out other medical sequels to explain the combination of increased aminotransferase and serum total bilirubin. | Discontinue MSTT1041A. |
| If abnormal liver tests, but the criteria for Hy's Law are not met: ALT or AST increase that meets at least one of the following criteria:<br>• $>8\times$ ULN<br>• $>5\times$ ULN for $\geq 2$ weeks<br>• $>3\times$ ULN with clinical signs or symptoms that are consistent with hepatitis (e.g., right upper quadrant pain or tenderness, fever, nausea, vomiting, jaundice) | Withhold MSTT1041A. Treatment may be resumed if an alternative cause is identified and laboratory values have resolved to those at the randomization visit. If signs or symptoms recur, permanently discontinue MSTT1041A. |
| If abnormal liver tests, but the criteria for Hy's Law are not met: TBILI $>3\times$ ULN | Consider withholding MSTT1041A. Treatment may be resumed if an alternative cause is identified and laboratory values have resolved to those at the randomization visit. If signs or symptoms recur, permanently discontinue MSTT1041A. |
| ALP $>3\times$ ULN | Consider withholding MSTT1041A. Treatment may be resumed if an alternative cause is identified and laboratory values have resolved to those at the randomization (Day 1) visit. If signs or symptoms recur, permanently discontinue MSTT1041A. |

TBILI = total bilirubin; ULN = upper limit of normal.

#### 5.1.2.3 Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements $>30$ minutes apart) QTcF that is $>500$ ms and $>60$ ms longer than the baseline value
- Sustained absolute QTcF that is $>515$ ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended to help in the management of such patients.

In rare circumstances, it may be acceptable to resume study drug at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

#### 5.1.2.4 Anaphylaxis

Anaphylaxis should be promptly assessed and treated per local standard of care. For current guidelines, refer to Campbell et al. 2014:

https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Anaphylaxis-Practice-Parameter-2014.pdf

In accordance with the current guidelines, the measurement of tryptase (serum or plasma) and histamine (plasma) levels should be considered to support a diagnosis of anaphylaxis, although clinicians should treat anaphylaxis regardless of the availability of the results of these tests.

During the study, all anaphylaxis events should be accurately reported on the appropriate eCRF.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

### 5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- 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
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, severe, or life-threatening according to WHO Adverse Drug Reaction Terminology; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### 5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Anaphylaxis, anaphylactoid, and hypersensitivity reactions
- MACE, including death due to cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack, unstable angina, or chest pain requiring hospitalization, coronary revascularization, and congestive heart failure requiring hospitalization

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### 5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 12 weeks after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

### 5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last office visit?"

"Have you had any new or changed health problems since you were last here?"

### 5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 8) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

**Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale**

| Grade | Severity |
|---|---|
| 1 | Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required |
| 2 | Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required |
| 3 | Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible |
| 4 | Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable |

Notes: Developed by the Division of Microbiology and Infectious Diseases.
Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

**Table 3 Causal Attribution Guidance**

| Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment? | |
|---|---|
| YES | There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge. |
| NO | An adverse event will be considered related, unless it fulfills the criteria specified below.<br>Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug). |

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

### 5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### 5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated eCRF. Refer to the eCRF completion guideline for details.

#### 5.3.5.2 Major Adverse Cardiac Events

MACE (including death due to cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack, unstable angina or chest pain requiring hospitalization, coronary revascularization, and congestive heart failure requiring hospitalization) should be recorded on the Adverse Event eCRF. Associated details should be recorded on the appropriate MACE CRF.

#### 5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### 5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

#### 5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any changes in severity, increases or decreases, will be captured on Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from

"non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

#### 5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

#### 5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

#### 5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

#### 5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

#### 5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

#### 5.3.5.11 Lack of Efficacy or Worsening of Atopic Dermatitis

Medical occurrences or symptoms of deterioration that are anticipated as part of AD should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of AD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of atopic dermatitis").

#### 5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

#### 5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from exploratory safety biomarker data by the Sponsor, and exploratory safety biomarker data will not be included in the formal safety analyses for this study. In addition, exploratory safety biomarker data will not inform decisions on patient management.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Accidental overdoses or medication errors (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information**

Contract research organization (CRO) Name Medical Monitor contact information:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted] (USA)

Alternate Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D.

Telephone Nos.: [redacted] (USA)

[redacted] (USA)

### 5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

#### 5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 12 weeks after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 12 weeks after the final dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 12 weeks after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy

should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 12 weeks after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### 5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or

elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

### 5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For MSTT1041A or placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with MSTT1041A or placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 12 weeks after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

## 5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- MSTT1041A Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of the data from the double-blind treatment period will be performed when all patients have either completed the end of the treatment visit (Week 16) or discontinued early from the study.

The analysis of complete data for the study, including data from the double-blind treatment period and 8-week safety follow-up period, will be performed when all patients have either completed the double-blind treatment period and 8-week safety follow-up period or discontinued early from the study, all data from the study are in the database, and the database is locked.

Personnel who perform the blinded-efficacy assessments will remain blinded to individual treatment assignment until after the study is completed (after all patients have either completed the double-blind treatment period and 8-week safety follow-up period or discontinued early from the study), all data from the study are in the database, and the database is locked.

## 6.1 DETERMINATION OF SAMPLE SIZE

Approximately 90 patients in total will be randomized in a 1:1 ratio to 490 mg SC MSTT1041A or placebo Q4W. The sample size provides at least 80% power to detect a difference of 34% in the percent change from baseline in EASI score at Week 16 between MSTT1041A- and placebo-treated patients, assuming a standard deviation of 40.6 for placebo-treated patients. The same number of patients can also provide at least 80% power to detect 1) a difference of 27% between MSTT1041A- and

placebo-treated patients in the proportion of patients achieving IGA scores of 0 or 1 at Week 16, assuming the percentage is 2% in placebo-treated patients, respectively, 2) a difference of 32% between MSTT1041A- and placebo-treated patients in the proportion of patients achieving EASI-75 at Week 16, assuming the percentage is 13% in placebo-treated patients, and 3) a difference of 30% between MSTT1041A- and placebo-treated patients in percent change from baseline to Week 16 in pruritus NRS, assuming a standard deviation of 37.3 for placebo-treated patients. The sample size is calculated at a two-sided significance level of 0.05 and assumes 25% dropout.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for treatment discontinuation and premature study withdrawal, as well as treatment failure, will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. Exposure to study treatment (number of study drug treatments and duration of treatment) will be summarized. All summaries will be presented according to randomized treatment assignment.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including age, sex, race/ethnicity, concomitant AD medication use, and comorbid illnesses) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

## 6.4 EFFICACY ANALYSES

Efficacy analyses will be based on the intent-to-treat (ITT) approach. All patients randomized (ITT population) will be included in the analysis, with patients grouped according to the treatment assigned at randomization. Hypothesis testing for the efficacy endpoints will be performed for each MSTT1041A dose level and the placebo group.

### 6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is percent change from baseline to Week 16 of total EASI score. A mixed-effect model for repeated measures (MMRM) model will be used, with percent change (post baseline change divided by baseline value) as the dependent variable. The model will include baseline value of the EASI score, treatment arms, visits, treatment arm by visit interaction, and stratification factors as listed in Section 3.1. To account for repeated observations with patients, a random patient effect will be added to the model. The MMRM model will provide adjusted least-square means of percent change from baseline at Week 16 for each of the treatment arms with the corresponding standard error, 95% CI and p-values.

### 6.4.2 Secondary Efficacy Endpoints

All secondary endpoints involving binary outcome measures will be analyzed using the Cochran-Mantel-Haenszel chi-square test. Patients with missing results at Week 16 will be considered non-responders for the corresponding endpoint.

Percent and absolute change from baseline for (approximately) continuous endpoints will be analyzed using a MMRM model as described for primary endpoint in Section 6.4.1. The MMRM model will provide adjusted least-square means of percent change from baseline at Week 16 for each of the treatment arms with the corresponding standard error, 95% CI and p-values.

Summary statistics of the (approximately) continuous endpoints will be calculated for each treatment arm in absolute changes and raw values. Mean, standard deviations, medians, and lower and upper quartiles, as well as minimum and maximum will be reported. For all summaries involving change from baseline, patients without baseline values will be excluded from the analyses.

[redacted]

## 6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to actual treatment received.

Safety will be assessed by adverse events, clinical laboratory evaluations, vital signs, and ECGs. All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to the WHO toxicity grading. The incidence of mapped adverse events will be summarized by treatment arm. A treatment emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. Treatment emergent adverse event will be summarized by treatment arm. Clinical laboratory data (hematology and serum chemistry), vital signs, and ECGs will be summarized by descriptive statistics by treatment groups at each visit. In addition, separate summaries will be generated for serious adverse events, adverse events of special interest, deaths, pregnancies, malignancies, adverse events leading to discontinuation from the study, and adverse events leading to discontinuation of study drug.

## 6.6 PHARMACOKINETIC ANALYSES

Serum concentration data for MSTT1041A will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, standard

deviation, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyze the concentration-time data of MSTT1041A. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as area under the concentration–time curve, maximum concentration, and trough serum concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately from the Clinical Study Report. Additional analyses such as assessment of potential relationships between drug exposure and MSTT1041A efficacy, safety, and biomarker endpoints, will be conducted as appropriate and may be reported separately from the Clinical Study Report.

## 6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported via descriptive statistics.

## 6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

- PD biomarkers ([redacted]) may be assessed to determine pharmacological activity and mechanism of action of MSTT1041A in patients with AD. Data will be summarized by absolute levels of the biomarker, as well as absolute and relative changes from levels at randomization visit, for each treatment group. Additional PD analyses will be conducted as appropriate.

### 6.9 SENSITIVITY ANALYSIS

Sensitivity analyses will be performed to evaluate the robustness of primary and secondary analyses. The details of the sensitivity analyses will be specified in the Data Analysis Plan.

## 7. DATA COLLECTION AND MANAGEMENT

### 7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory and ECG data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO and ClinRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

### 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

## 7.3 ELECTRONIC PATIENT- AND CLINICIAN- REPORTED OUTCOME DATA

An electronic device will be used to capture PRO and ClinRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure method. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

## 7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the trial monitoring plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

### 7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

### 7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ClinRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Genentech will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

## 8. ETHICAL CONSIDERATIONS

### 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

## 8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a

separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on germline mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

### 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

## 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

### 9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

### 9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

### 9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

## 9.4 ADMINISTRATIVE STRUCTURE

Genentech, a member of the Roche group, is the Sponsor of this study. A CRO may provide clinical operations oversight, including, but not limited to, project management, medical monitoring, site management, data quality support, safety reporting, and regulatory activities as specified in the study management plans. Genentech will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. An IMC will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and safety scientist. EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into the study through use of a dynamic hierarchical algorithm, and manage site drug supply. A central laboratory will be used for sample management and storage until shipment to specialty laboratories or Genentech for analysis.

## 9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the EMA, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

## 9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

## 10. REFERENCES


Abston ED, Barin JG, Cihakova D, et al. IL-33 independently induces eosinphillic pericarditis and cardiac dilation: ST2 improves cardiac function. Circ Heart Fail 2012;5:366–75.

Alase A, Seltmann J, Werfel T, et al. Interleukin-33 modulates the expression of human β-defensin 2 in human primary keratinocytes and may influence the susceptibility to bacterial superinfection in acute atopic dermatitis. Br J Dermatol 2012;167:1386–9.

Campbell RL, Li JTC, Nicklas RA, et al. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol 2014;113:599–608.

Cevikbas F, Steinhof M. IL-33: a novel danger signal system in atopic dermatitis. J Invest Dermatol 2012;132:1326–9.

Corominas M, Gastaminza G, Lobera T. Hypersensitivity reactions to biological drugs. J Investig Allergol Clin Immunol 2014;24:212–25.

Demyanets S, Kaun C, Pentz R, et al. Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature. J Mol Cell Cardiol 2013;60:16–26.

Ding W, Zou GL, Zhang W, et al. Interleukin-33: its emerging role in allergic diseases. Molecules 2018;23:E1665.

Du HY, Fu HY, Li DN, et al. The expression and regulation of interleukin-33 in human epidermal keratinocytes: a new mediator of atopic dermatitis and its possible signaling pathway. J Interferon Cytokine Res 2016;36:552–62.

Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338–51.

Griesenauer B, Paczesny S. The ST2/IL-33 axis in immune cells during inflammatory diseases front. Front Immunol 2017;8:475.

Hayakawa H, Hayakawa M, Kume A, et al. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. J Biol Chem 2007;282:26369–80.

Liew FY, Girard JP, Turnquist HR. Interleukin-33 in health and disease. Nat Rev Immunol 2016;16:676–89.

Liu B, Tai Y, Achanta S, et al. IL-33/ST2 signaling excites sensory neurons and mediates itch response in a mouse model of poison ivy contact allergy. Proc Natl Acad Sci U S A 2016;113:E7572–9.

Kondo Y, Yoshimoto T, Yasuda K, et al. Administration of IL-33 induces airway hyperresponsiveness and goblet cell hyperplasia in the lungs in the absence of adaptive immune system. Int Immunol 2008;20:791–800.

Martin NT, Martin MU. Interleukin 33 is a guardian of barriers and a local alarmin. Nat Immunol 2016;17:122–31.

Martin P, Palmer G, Rodriguez E, et al. Atherosclerosis severity is not affected by a deficiency in IL-33/ST2 signaling. Immun Inflamm Dis 2015;3:239–46.

McLaren JE, Michael DR, Salter RC, et al. IL-33 reduces macrophage foam cell formation. J Immunol 2010;185:1222–9.

Miller AM, Xu D, Asquith DL, et al. IL-33 reduces the development of atherosclerosis. J Exp Med 2008;205:339–46.

Molofsky AB, Savage AK, Locksley RM. Interleukin-33 in tissue homeostasis, injury, and infalmmation. Immunity 2015;42:1005–19.

Nabe T. Interleukin (IL)-33: new therapeutic target for atopic diseases. J Pharmacol Sci 2014;126:85–91.

Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab 2015;66(Suppl 1):8–16.

Nygaard U, van den Bogaard EH, Niehues H, et al. The "Alarmins" HMBG1 and IL-33 downregulate structural skin barrier proteins and impair epidermal growth. Acta Derm Venereol 2017;97:305–12.

Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. J Eur Acad Dermatol Venereol 2012;26:1176–93.

Ryu WI, Lee H, Bae HC, et al. IL-33 down-regulates filaggrin expression by inducing STAT3 and ERK phosphorylation in human keratinocytes. J Dermatol Sci 2016;82:131–4.

Sabatine MS, Morrow DA, Higgins LJ, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation 2008;117:1936–44.

Salimi M, Barlow JL, Saunders SP, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. J Exp Med 2013;210:2939–50.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

Sanada S, Hakuno D, Higgins LJ, et al. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007;117:1538–49.

Savinko T, Matikainen S, Saarialho-Kere U, et al. IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. J Invest Dermatol 2012;132:1392–400.

Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. J Allergy Clin Immunol 2013;131:295–9.

Seki K, Sanada S, Kudinova AY, et al. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. Circ Heart Fail 2009;2:684–91.

Seltmann J, Roesner LM, von Hesler FW, et al. IL-33 impacts on the skin barrier by downregulating the expression of filaggrin. J Allergy Clin Immunol 2015;135:1659–61.

Shah RV, Chen-Tournoux AA, Picard MH, et al. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. Circ Heart Fail 2009;2:311–9.

Wasserman A, Ben-Shoshan J, Entin-Meer M, et al. Interleukin-33 augments Treg cell levels: a flaw mechanism in atherosclerosis. Isr Med Assoc J 2012;14:620–3.

Weidinger S, Beck LA, Bieber T, et al. Atopic dermatitis. Nat Rev Dis Primers 2018;4:1.

Weir RA, Miller AM, Murphy GE, et al. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. J Am Coll Cardiol 2010;55:243–50.

Williams MR and Gallo RL. The role of the skin microbiome in atopic dermatitis. Curr Allergy Asthma Rep 2015;15:65.

Wollenberg A, Oranje A, Deleuran M, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. J Eur Acad Dermatol Venereol 2016;30:729–47.

# Appendix 1
# Schedule of Activities

| | SCR | Treatment Period | | | | | | | | | | FU | EOS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | | |
| Week | D −35 | | W1 | W2 | W4 | W6 | W8 | W10 | W12 | W14 | W16 | W20 | W24 | | |
| Day | to −1 | D1 | D8 | D15 | D29 | D43 | D57 | D71 | D85 | D99 | D113 | D141 | D169 | | |
| (Visit window in days) | | | (± 2) | (± 3) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 5) | (± 5) | ET [a] | UV [b] |
| Office/Phone visit | O | O | O | O or P | O | P | O | P | O | P | O | P | O | O | O |
| Informed consent [c] | x | | | | | | | | | | | | | | |
| Demographics | x | | | | | | | | | | | | | | |
| Medical history | x | | | | | | | | | | | | | | |
| Alcohol/Smoking/Substance use history | x | | | | | | | | | | | | | | |
| Atopy status | x | | | | | | | | | | | | | | |
| Complete physical examination [d] | x | | | | | | | | | | | | | | |
| Limited physical examination [e] | | x | | | x | | | | | | x | | x | x | x |
| Weight and height (height at screening only) | x | | | | | | | | | | x | | x | x | |
| [redacted] | | | | | | | | | | | | | | | |
| IGA | x | x | x | x [g] | x | | x | | x | | x | | x | x | x |
| EASI | x | x | x | x [g] | x | | x | | x | | x | | x | x | x |
| SCORAD [f] | x | x | x | x [g] | x | | x | | x | | x | | x | x | x |
| Pruritus and sleep NRS only [f] | | | | x [h] | | x | | x | | x | | x | | | |
| Emollient use status | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| [redacted] | | | | | | | | | | | | | | | |

**Appendix 1: Schedule of Activities**

| | SCR | Treatment Period | | | | | | | | | | FU | EOS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | | |
| Week | D –35 to –1 | | W1 | W2 | W4 | W6 | W8 | W10 | W12 | W14 | W16 | W20 | W24 | | |
| Day | | D1 | D8 | D15 | D29 | D43 | D57 | D71 | D85 | D99 | D113 | D141 | D169 | | |
| (Visit window in days) | | | (± 2) | (± 3) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 5) | (± 5) | ET [a] | UV [b] |
| Office/Phone visit | O | O | O | O or P | O | P | O | P | O | P | O | P | O | O | O |
| Vital signs [i] | x | x | x | | x | | x | | x | | x | | x | x | x |
| ECG (12-lead, single) | x | | | | | | x | | | | x | | x | x | x |
| Serum pregnancy test [j] | x | | | | | | | | | | | | | | x |
| Urine pregnancy test [j] | | x | x | | x | | x | | x | | x | | x | x | x |
| Hepatitis B/C serology | x | | | | | | | | | | | | | | |
| Hepatitis B DNA | x | | | | | | | | | | x | | | x | |
| TB test | x | | | | | | | | | | | | | | |
| Chest X-ray, TB worksheet [k] | x | | | | | | | | | | | | | | |
| Hematology [l] | x | x | x | | x | | x | | x | | x | | x | x | x |
| Chemistry [m] | x | x | | | x | | x | | x | | x | | x | x | x |
| NT-proBNP | | x | | | | | | | | | | | | | x [n] |
| Urinalysis [o] | x | x | | | | | | | | | x | | | x | |
| $HbA_{1C}$ | x | | | | | | | | | | x | | x | x | x |
| Fasted glucose and lipids [p] | | x | | | | | | | | | x | | x | x | x |
| Serum PK [q] | | x | x | | x | | x | | x | | x | | x | x | x |
| Serum specific IgE | | x | | | | | | | | | | | | | |

**Appendix 1: Schedule of Activities**

| | SCR | Treatment Period | | | | | | | | | | FU | EOS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | | |
| Week | D −35 to −1 | | W1 | W2 | W4 | W6 | W8 | W10 | W12 | W14 | W16 | W20 | W24 | | |
| Day | | D1 | D8 | D15 | D29 | D43 | D57 | D71 | D85 | D99 | D113 | D141 | D169 | | |
| (Visit window in days) | | | (± 2) | (± 3) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 4) | (± 5) | (± 5) | ET [a] | UV [b] |
| Office/Phone visit | O | O | O | O or P | O | P | O | P | O | P | O | P | O | O | O |
| Serum for biomarker (including total IgE) | x | x | x | | x | | x | | | | x | | x | x | |
| [redacted] | | | | | | | | | | | | | | | |
| Serum ADA [q] | | x | | | x | | | | | | x | | x | x | |
| [redacted] | | | | | | | | | | | | | | | |
| Randomization | | x | | | | | | | | | | | | | |
| Study drug administration [s] | | x | x | | x | | x | | x | | | | | | |
| Concomitant medications [t] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Adverse events [u] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

AD = atopic dermatitis; ADA = anti-drug antibody; [redacted] D = day; EASI = Eczema Area and Severity Index; eCRF = electronic Case Report Form; EOS = end of study visit; ET = early termination visit; FU = follow up; $HbA_{1c}$ = hemoglobin $A_{1c}$; IGA = Investigator's Global Assessment; NRS = Numeric Rating Scale; NT-proBNP = N-terminal pro B-type natriuretic peptide; O = office visit; P = phone visit; PK = pharmacokinetic; PPD = purified protein derivative; PRO = patient-reported outcome; QFT = QuantiFERON TB-Gold®; [redacted] SCORAD = SCORing Atopic Dermatitis; SCR = screening; [redacted] TB = tuberculosis; UV = unscheduled visit; V = visit; W = week.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Visit windows should be calculated relative to the randomization visit (Day 1).

[a] If a patient is unable to complete all study visits and assessments, the patient should be asked to return to the clinic for an early termination visit. This visit should occur approximately 4 weeks after the final dose of study drug (see Section 4.6.2).

[b] Any of the study procedures noted may be performed at an unscheduled visit, but not all are required.

[c] Informed consent must be documented before any study-specific screening procedure is performed.

[d] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[e] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Questionnaires ([redacted], pruritus and sleep NRS) will be self- or interviewer-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

[g] Assessment will be conducted only during an office visit (i.e., not at a telephone visit).

[h] Will only be conducted at a telephone visit. For the Week 2 visit, if the patient does not have an office visit (chooses a telephone visit), collect pruritus and sleep NRS.

[i] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure, ideally while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the appropriate eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be reported immediately, and study drug will not be administered that day. The positive urine pregnancy result must be confirmed by a serum pregnancy test. Refer to Section 5.4.3.1 for management of a patient with a positive pregnancy test.

[k] Patients with a positive PPD (without a history of Bacillus Calmette-Guérin vaccination) or a positive or indeterminate QFT will require a chest X-ray to review for evidence of active TB, including posteroanterior and lateral views, unless a chest X-ray has been performed within 3 months before screening and the report is available for review. A chest computed tomography scan may substitute for a chest X-ray. Chest X-rays should only be performed if patients first meet all other study eligibility criteria.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[m] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST.

[n] As clinically indicated.

[o] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[p] If patient has not fasted for 8 hours, the patient must return to the site for fasting blood draw only. All other visit assessments should be completed within the regular visit.

[q] PK and ADA samples to be collected prior to study drug administration.

[r] [redacted]

[s] Patients will receive 490 mg MSTT1041A or placebo at Day 1, Week 4, 8, and 12 visits administered as four SC injections (one in each quadrant of the abdomen). The dose at the Week 1 visit will be 245 mg MSTT1041A or placebo (loading dose) administered as two SC injections (see Section 4.3.2.1 for details).

[t] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements, emollients) used by a patient in addition to protocol-mandated treatment from 6 months before screening until 12 weeks after the final dose of study drug.

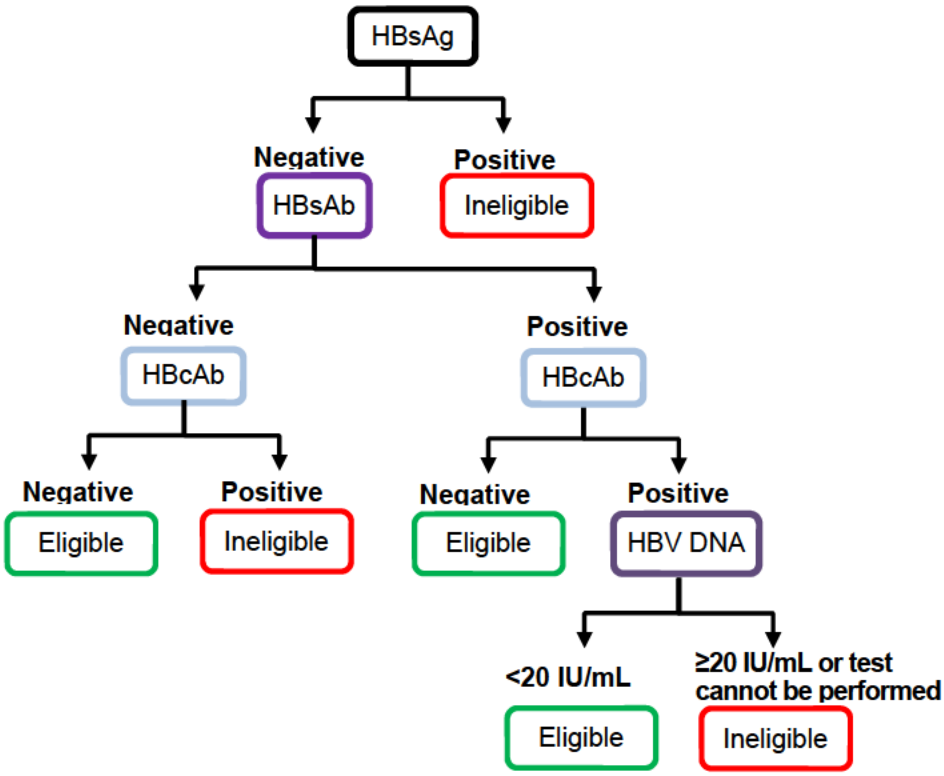
[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 12 weeks after the after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

# Appendix 2
# WHO Classification of Topical Corticosteroids

The following table provides a non-exhaustive list of examples of topical corticosteroids classified by potency (Source: http://apps.who.int/medicinedocs/en/d/Jh2918e/32.html).

| Potency | Class | Topical Corticosteroid | Formulation |
|---|---|---|---|
| Ultra High | I | Clobetasol propionate | Cream, 0.05% |
| | | Diflorasone diacetate | Ointment, 0.05% |
| High | II | Amcinonide | Ointment, 0.1% |
| | | Betamethasone dipropionate | Ointment, 0.05% |
| | | Desoximetasone | Cream or ointment, 0.025% |
| | | Fluocinonide | Cream, ointment or gel, 0.05% |
| | | Halcinonide | Cream, 0.1% |
| | III | Betamethasone dipropionate | Cream, 0.05% |
| | | Betamethasone valerate | Ointment, 0.1% |
| | | Diflorasone diacetate | Cream, 0.05% |
| | | Triamcinolone acetonide | Ointment, 0.1% |
| Moderate | IV | Desoximetasone | Cream, 0.05% |
| | | Fluocinolone acetonide | Ointment, 0.025% |
| | | Fludroxycortide | Ointment, 0.05% |
| | | Hydrocortisone valerate | Ointment, 0.2% |
| | | Triamcinolone acetonide | Cream, 0.1% |
| | V | Betamethasone dipropionate | Lotion, 0.02% |
| | | Betamethasone valerate | Cream, 0.1% |
| | | Fluocinolone acetonide | Cream, 0.025% |
| | | Fludroxycortide | Cream, 0.05% |
| | | Hydrocortisone butyrate | Cream, 0.1% |
| | | Hydrocortisone valerate | Cream, 0.2% |
| | | Triamcinolone acetonide | Lotion, 0.1% |
| Low | VI | Betamethasone valerate | Lotion, 0.05% |
| | | Desonide | Cream, 0.05% |
| | | Fluocinolone acetonide | Solution, 0.01% |
| | VII | Dexamethasone sodium phosphate | Cream, 0.1% |
| | | Hydrocortisone acetate | Cream, 1% |
| | | Methylprednisolone acetate | Cream, 0.25% |

# Appendix 3
# Hepatitis B Screening Flowchart




HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus DNA.

# Appendix 4
# Eczema Area and Severity Index

From: Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001;10 (1):11–8.

## Method

Four individual body regions are assessed: head and neck (H&N), upper limbs (UL; includes the external axillae and hands), trunk (includes the internal axillae and groin), and lower limbs (LL; includes the buttocks and feet).

For each body region

- Assess the affected body surface area (BSA): score of 0 to 6 (see Table 1 footnote 3 below) assigned for the percentage of affected BSA (0%–100%)
- Individually rate the average degree of severity (0–3: none, mild, moderate, severe), with half steps allowed, for each of 4 clinical signs: erythema, induration-papulation, excoriations, and lichenification. A summed score of 0 to 12 is assigned to each body region
- Assign a total body region score: sum of the individual clinical signs score (maximum = 12) × affected area score (maximum = 6) × the body-region index (H&N–0.1, UL–0.2, trunk–0.3, LL–0.4)

Total score (0–72) = the sum of total scores for each of the 4 body region scores.

# Appendix 5
# SCORing Atopic Dermatitis

From: European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD Index (consensus report of the European Task Force on Atopic Dermatitis). Dermatology 1993;186:23–31.

Three aspects of disease severity are scored

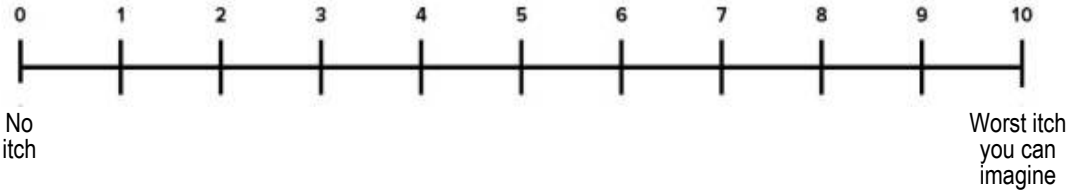
A. Extent (A): A sum of the affected (inflammation, not dryness) body areas as indicated in the figure (Total Score: 0–100)

B. Intensity (B): Six clinical signs, rated 0–3 for severity (absent, mild, moderate, severe): erythema, edema/papulation, oozing/crusting, excoriation, lichenification, and dryness (Total Score: 0–18)

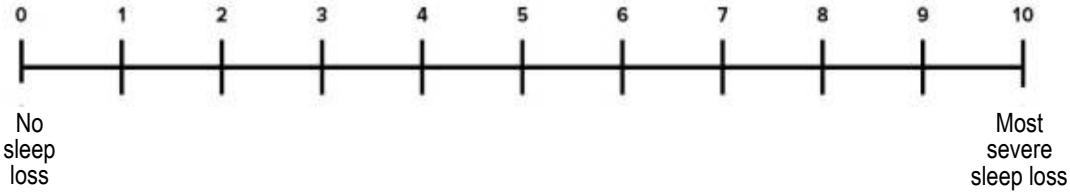
C. Subjective (C): Two patient-reported outcomes (PRO) are assessed by numeric rating scale (NRS) scored 0–10 i) Pruritus, ii) Sleep loss (Total PRO Score 0–20)

   The NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) and sleep loss during a recall period of 3 days. Patients will be asked the following questions:

   For average itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable,' how would you rate your itch overall (on average) during the previous 3 days?"



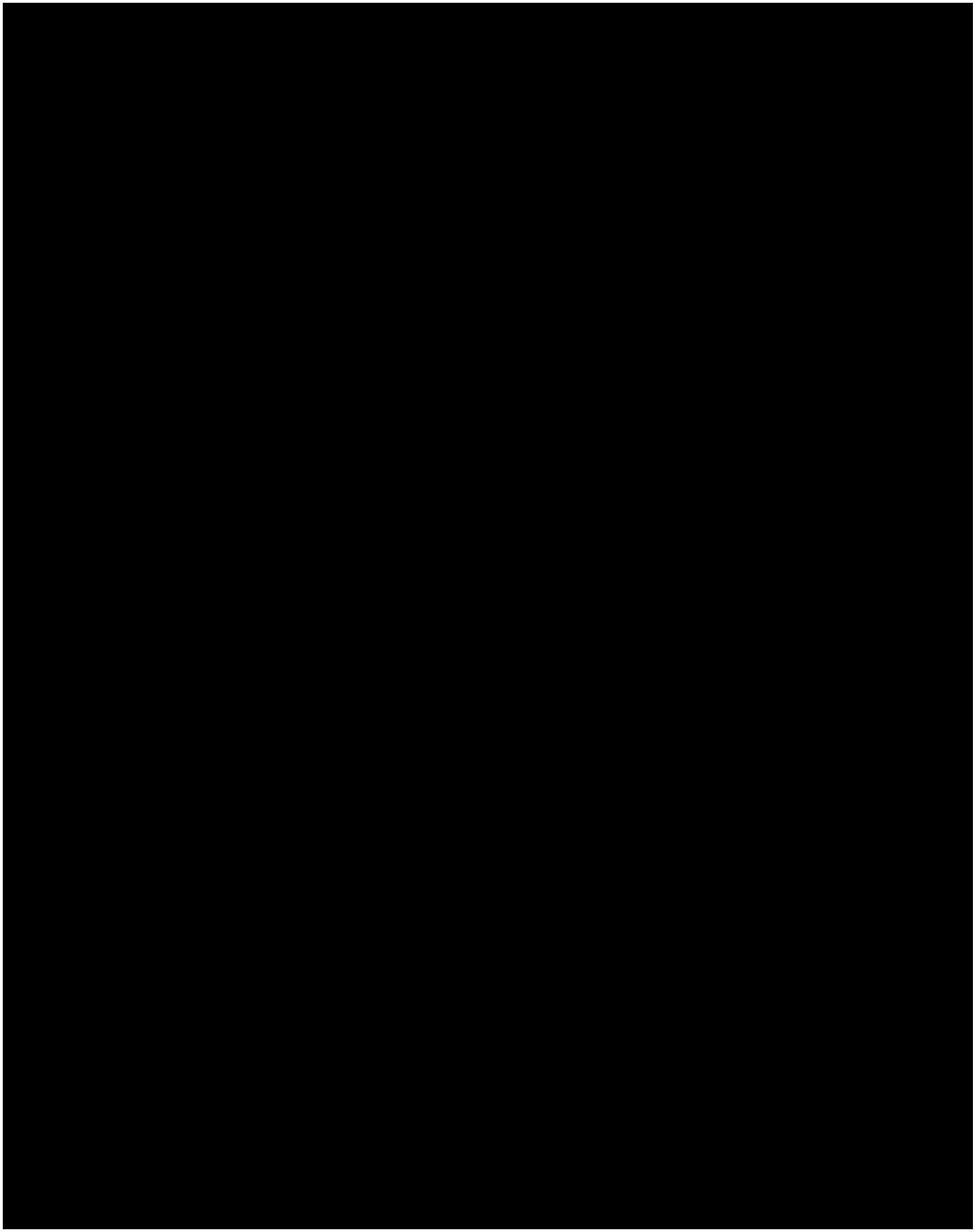

   For average sleep loss: "On a scale of 0 to 10, with 0 being 'no sleep loss' and 10 being the 'most severe loss', how would you rate your sleep loss overall (on average) during the previous 3 days?"

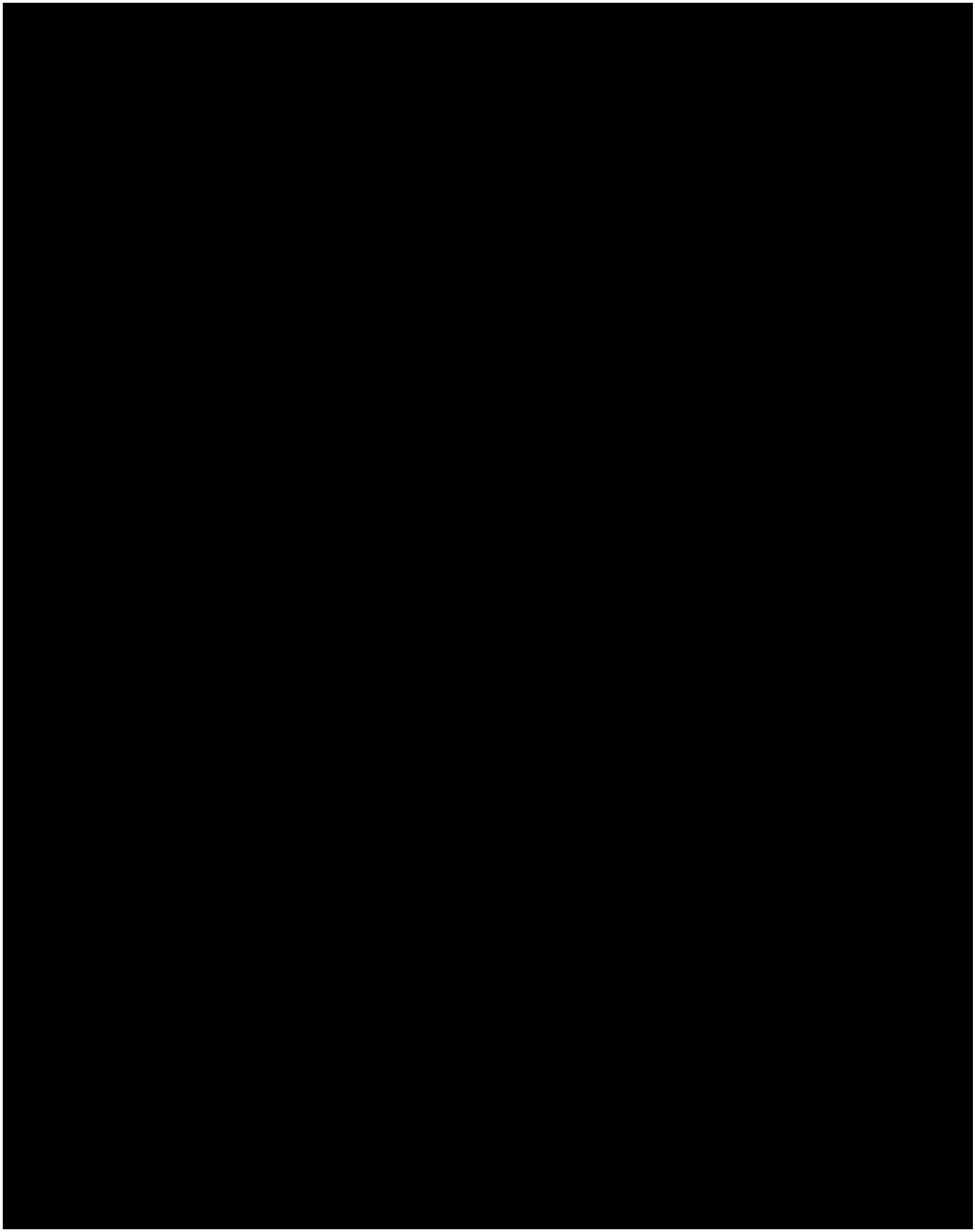


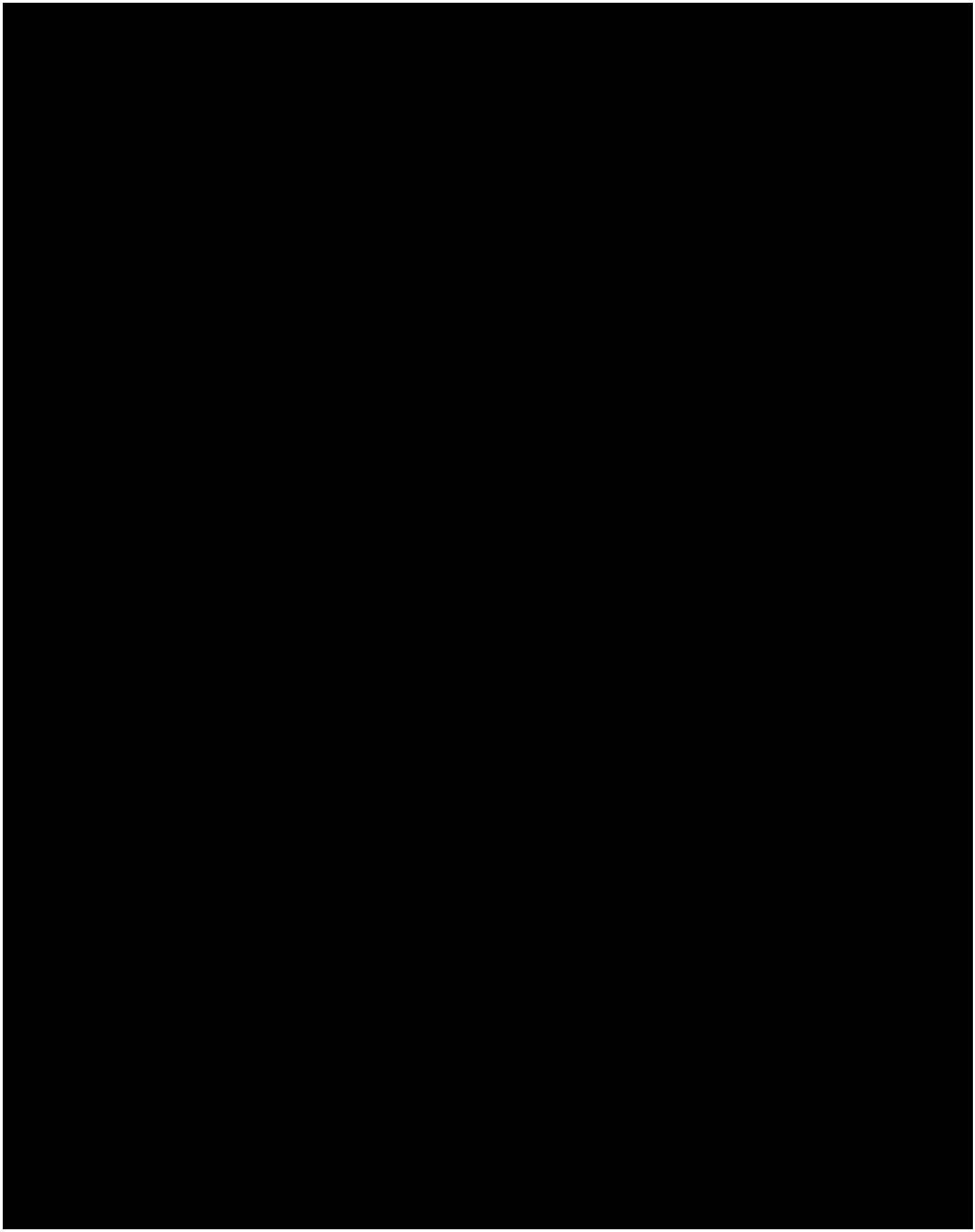

A total score (0–103) is calculated using the following formula: A/5 + (7B/2) + C.

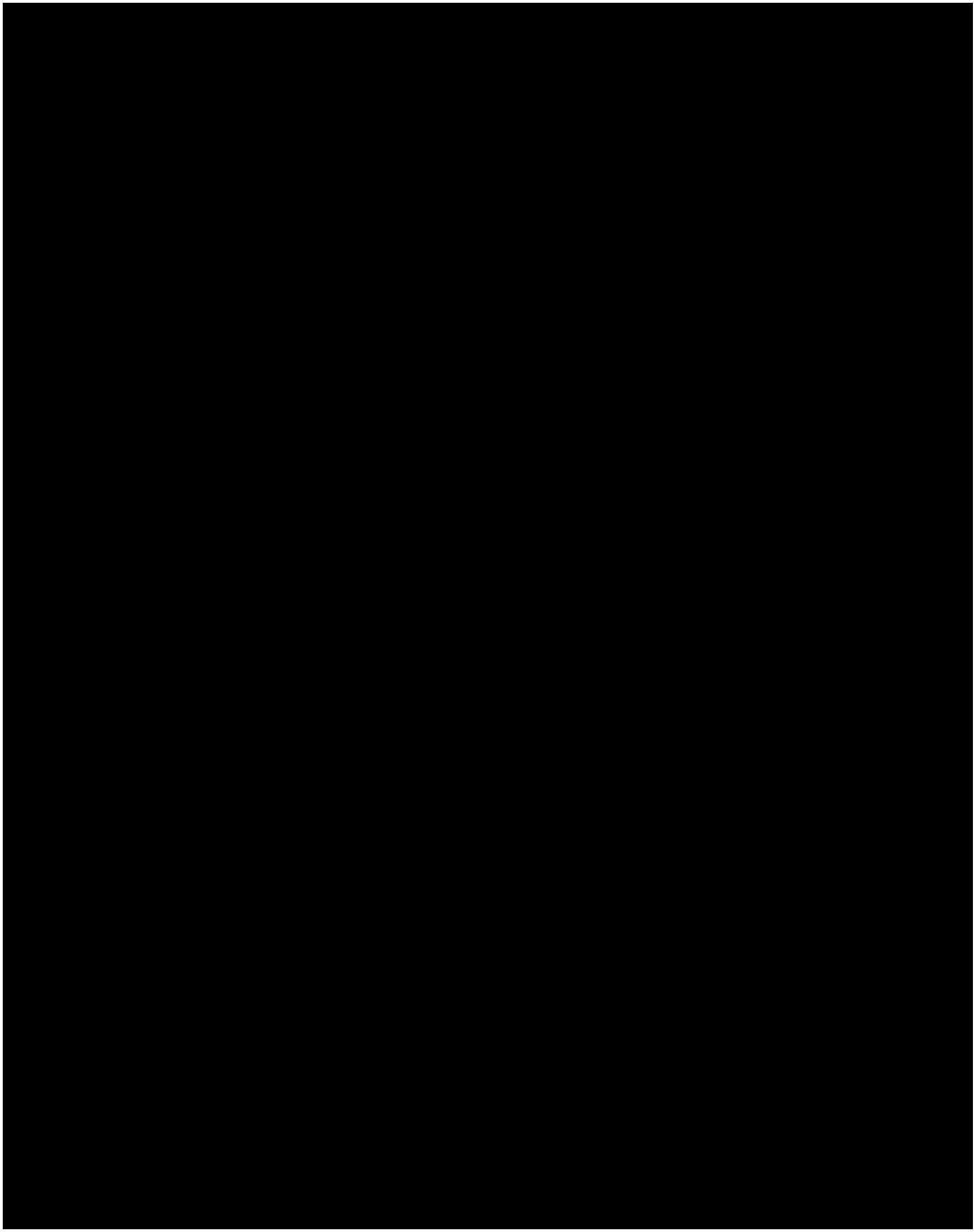
# Appendix 6
# Investigator Global Assessment

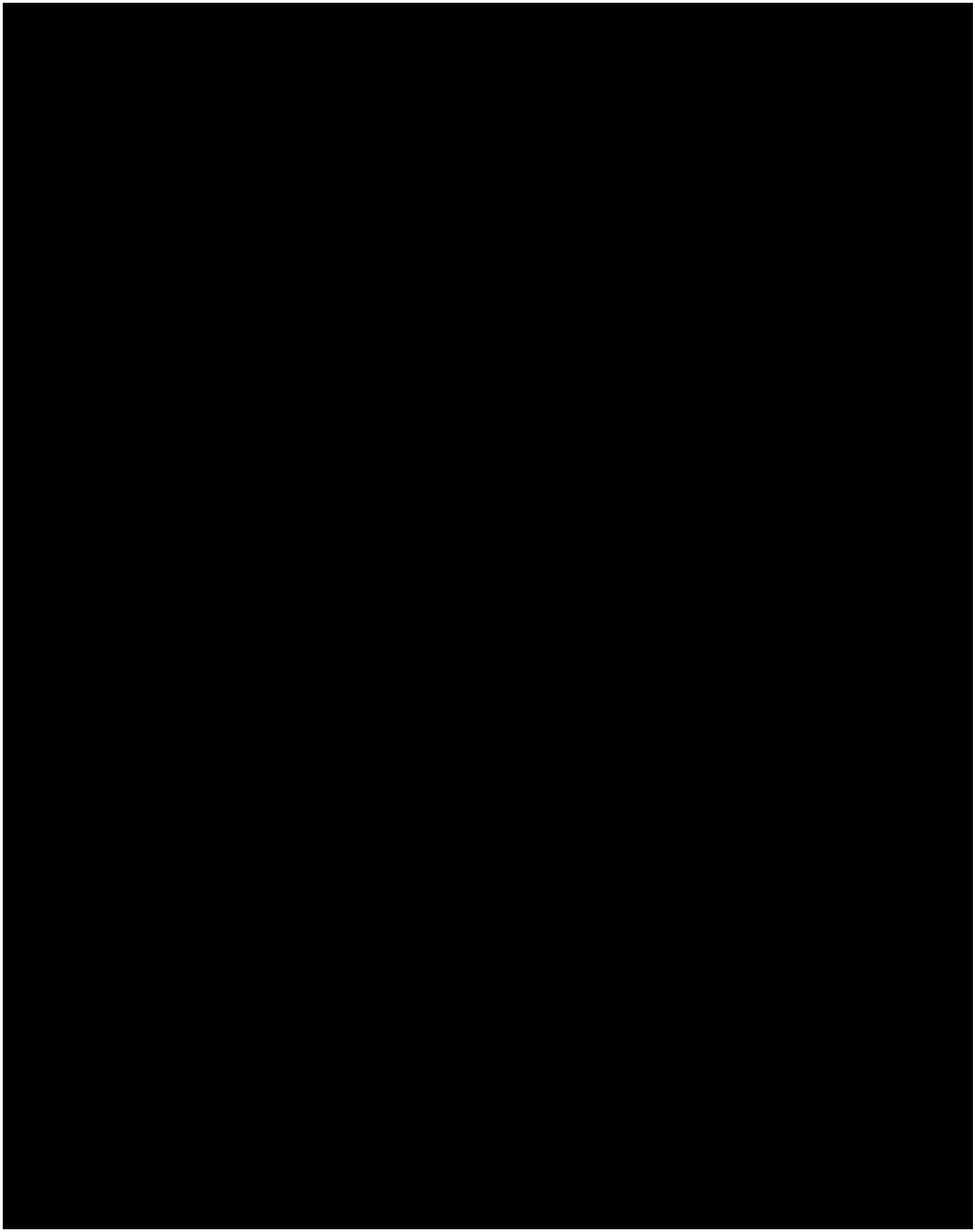
| Score | | Description |
|---|---|---|
| 0 | Clear | No erythema. No edema or induration/papulation. No oozing/crusting. Post inflammatory hyper- or hypopigmentation may be present. |
| 1 | Almost clear | Trace, faint pink erythema with barely perceptible edema and/or induration/papulation. No oozing/crusting. |
| 2 | Mild disease | Faint pink erythema with edema and/or induration and with papulation perceptible upon palpitation. No oozing/crusting. |
| 3 | Moderate disease | Pink-red with definite edema and/or induration of skin papules and plaques. There may be some oozing/crusting. |
| 4 | Severe disease | Deep/bright red erythema with significant edema and/or induration. Obvious raised borders with papules and plaques with oozing/crusting. |











# Appendix 8
# WHO Toxicity Grading Scale

| ITEM | Grade 1 Toxicity | Grade 2 Toxicity | Grade 3 Toxicity | Grade 4 Toxicity |
|---|---|---|---|---|
| **HEMATOLOGY** | | | | |
| Hemoglobin | 9.5–10.5 gm/Dl | 8.0–9.4 gm/Dl | 6.5–7.9 gm/Dl | < 6.5 gm/Dl |
| Absolute neutrophil count | 1000–1500/$mm^3$ | 750–999/$mm^3$ | 500–749/$mm^3$ | <500/$mm^3$ |
| Platelets | 75000–99000/$mm^3$ | 50000–74999/$mm^3$ | 20000–49000/$mm^3$ | <20000/$mm^3$ |
| PT | 1.01–1.25 × ULN | 1.26-1.5 × ULN | 1.51 -3.0 × ULN | >3 × ULN |
| aPPT | 1.01 -1.66 × ULN | 1.67–2.33 × ULN | 2.34–3 × ULN | > 3 × ULN |
| Fibrinogen | 0.75–0.99 × LLN | 0.50–0.74 × LLN | 0.25–0.49 × LLN | < 0.25 × LLN |
| Fibrin split product | 20–40 mcg/ml | 41–50 mcg/ml | 51–60 mcg/ml | > 60 mcg/ml |
| Methemoglobin | 5–9.9 % | 10.0–14.9 % | 15.0–19.9% | > 20 % |
| **LIVER ENZYMES** | | | | |
| AST (SGOT) | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | > 10 × ULN |
| ALT (SGPT) | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | > 10 × ULN |
| GGT | 1.25–2.5 × ULN | 1.6–5 × ULN | 5.1–10 × ULN | > 10 × ULN |
| ALP | 1.25–2. 5 × ULN | 1.6–5 × ULN | 5.1–10 × ULN | > 10 × ULN |
| Amylase | 1.1–1.5 × ULN | 1.6–2.0 × ULN | 2.1–5.0 × ULN | > 5.1 × ULN |
| **CHEMISTRIES** | | | | |
| Hyponatremia | 130–135 mEq/L | 123–129 mEq/L | 116–122 mEq/L | < 116 or mental status changes or seizures |
| Hypernatremia | 146–150 mEq/L | 151–157 mEq/L | 158–165 mEq/L | > 165 mEq/L or mental status changes or seizures |
| Hypokalemia | 3.0–3.4 mEq/L | 2.5–2.9 mEq/L | 2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required. | < 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia |
| Hyperkalemia | 5.6–6.0 mEq/L | 6.1–6.5 mEq/L | 6.6–7.0 mEq/l | > 7.0 mEq/L or life-threatening arrhythmia |
| Hypoglycemia | 55–64 mg/dL | 40–54 mg/dL | 30–39 mg/dL | <30 mg/dL or mental status changes or coma |
| Hyperglycemia (note if fasting) | 116–160 mg/dL | 161– 250 mg/dL | 251–500 mg/dL | > 500 mg/dL or ketoacidosis or seizures |

**Appendix 8: WHO Toxicity Grading Scale**

| ITEM | Grade 1 Toxicity | Grade 2 Toxicity | Grade 3 Toxicity | Grade 4 Toxicity |
|---|---|---|---|---|
| Hypocalcemia (corrected for albumin) | 8.4–7.8 mg/dL | 7.7–7.0 mg/dL | 6.9–6.1 mg/dL | < 6.1 mg/dL or life-threatening arrhythmia or tetany |
| Hypercalcemia (correct for albumin) | 10.6–11.5 mg/dL | 11.6–12.5 mg/dL | 12.6–13.5 mg/dL | > 13.5 mg/dL life-threatening arrhythmia |
| Hypomagnesemia | 1.4–1.2 mEq/L | 1.1–0.9 mEq/L | 0.8–0.6 mEq/L | < 0.6 mEq/L or life-threatening arrhythmia |
| Hypophosphatemia | 2.0–2.4 mg/dL | 1.5 –1.9 mg/dL or replacement Rx required | 1.0 –1.4 mg/dL intensive Rx or hospitalization required | < 1.0 mg/dL or life-threatening arrhythmia |
| Hyperbilirubinemia | 1.1–1.5 × ULN | 1.6–2.5 × ULN | 2.6–5 × ULN | > 5 × ULN |
| BUN | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | > 10 × ULN |
| Creatinine | 1.1 × 1.5 × ULN | 1.6–3.0 × ULN | 3.1–6 × ULN | > 6 × ULN or required dialysis |
| **URINALYSIS** | | | | |
| Proteinuria | 1+ or<br>< 0.3% or<br><3 g/L or<br>200 mg-1 gm loss/day | 2 –3 + or<br>0.3%–1.0% or<br>3–10 g/L or<br>1– 2 gm loss/day | 4+ or<br>> 1.0% or<br>> 10 g/L or<br>2–3.5 gm loss/day | nephrotic syndrome or<br>> 3.5 gm loss/day |
| Hematuria | Microscopic only | Gross, no clots | Gross+ clots | Obstructive or required transfusion |
| **CARDIAC DYSFUNCTION** | | | | |
| Cardiac rhythm | | Asymptomatic, transient signs, no Rx required | Recurrent/persistent; No Rx required | Requires treatment |
| Hypertension | Transient inc. > 20 mm; no Rx | Recurrent, chronic, > 20 mm, Rx required | Requires acute Rx; no hospitalization | Requires hospitalization |
| Hypotension | Transient orthostatic hypotension, no Rx | Symptoms correctable with oral fluids Rx | Requires IV fluids; no hospitalization required | Requires hospitalization |
| Pericarditis | Minimal effusion | Mild/moderate asymptomatic effusion, no Rx | Symptomatic effusion; pain; EKG changes | Tamponade; pericardiocentesis or surgery required |

**Appendix 8: WHO Toxicity Grading Scale**

| ITEM | Grade 1 Toxicity | Grade 2 Toxicity | Grade 3 Toxicity | Grade 4 Toxicity |
|---|---|---|---|---|
| Hemorrhage, blood loss | Microscopic/occult | Mild, no transfusion | Gross blood loss;<br>1–2 units transfused | Massive blood loss;<br>> 3 units transfused |
| **RESPIRATORY** | | | | |
| Cough | Transient-no Rx | Treatment associated cough; local Rx | Uncontrolled | |
| Bronchospasm, acute | Transient; no Rx<br>< 80%–70% $FEV_1$<br>(or peak flow) | Requires Rx normalizes with bronchodilator; $FEV_1$ 50%–70% (or peak Flow) | No normalization with bronchodilator; $FEV_1$ 25%–50% (or peak flow retractions) | Cyanosis: $FEV_1$ < 25% (or peak flow) or Intubated |
| **GASTROINTESTINAL** | | | | |
| Stomatitis | Mild discomfort;<br>no limits on activity | Some limits on eating/drinking | Eating/talking very limited | Requires IV fluids |
| Nausea | Mild discomfort;<br>maintains reasonable intake | Moderate discomfort; intake decreased significantly; some activity limited | Severe discomfort;<br>no significant intake;<br>activities limited | Minimal fluid intake |
| Vomiting | Transient emesis | Occasional/moderate vomiting | Orthostatic hypotension or IV fluids required | Hypotensive shock or hospitalization required for IV fluid therapy |
| Constipation | Mild | Moderate | Severe | Distensions w/ vomiting |
| Diarrhea | Transient 3–4 loose stools/day | 5–7 loose stools/day | Orthostatic hypotension or > 7 loose stools/day or required IV fluids | Hypotensive shock or hospitalization for IV fluid therapy required |
| **NEURO & NEUROMUSCULAR** | | | | |
| Neuro–cerebellar | Slight incoordination dysdiadochokinesis | Intention tremor, dysmetria, slurred speech; nystagmus | Locomotor ataxia | Incapacitated |
| Mood | Mild anxiety or depression | Moderate anxiety or depression and therapy required | Severe anxiety or depression or mania; needs assistance | Acute psychosis; incapacitated, requires hospitalization |

**Appendix 8: WHO Toxicity Grading Scale**

| ITEM | Grade 1 Toxicity | Grade 2 Toxicity | Grade 3 Toxicity | Grade 4 Toxicity |
|---|---|---|---|---|
| Neuro control | Mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected | Moderate confusion/agitation some limitation of ADL; minimal Rx | Severe confusion/agitation needs assistance for ADL; therapy required | Toxic psychosis; hospitalization |
| Muscle strength | Subjective weakness; no objective symptoms/signs | Mild objective signs/symptoms; no decrease in function | Objective weakness function limited | Paralysis |
| **OTHER PARAMETERS** | | | | |
| Fever: oral, > 12 hours | 37.7–38.5°C or 100.0–101.5°F | 38.6–39.5°C or 101.6–102.9°F | 39.6–40.5°C or 103–105°F | > 40 C or > 105°F |
| Headache | Mild, no Rx therapy | Transient, moderate; Rx required | Severe; responds to initial narcotic therapy | Intractable; required repeated narcotic therapy |
| Fatigue | No decrease in ADL | Normal activity decreased 25%-50% | Normal activity decreased > 50% can't work | Unable to care for self |
| Allergic reaction | Pruritus without rash | Localized urticaria | Generalized urticaria; angioedema | Anaphylaxis |
| Local reaction | Tenderness or erythema | Induration < 10 cm or phlebitis or inflammation | Induration > 10 cm or ulceration | Necrosis |
| Mucocutaneous | Erythema; pruritus | Diffuse, maculo-papular rash, dry desquamation | Vesiculation, moist desquamation, or ulceration | Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery |