Official Title: A Phase IIB, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Assess the Efficacy and Safety of MSTT1041A in Patients with Uncontrolled Severe Asthma

NCT Number: NCT02918019

Document Date: Protocol Version 4: 23 January 2019

PROTOCOL

TITLE:	**A PHASE IIB, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, DOSE-RANGING STUDY TO ASSESS THE EFFICACY AND SAFETY OF MSTT1041A IN PATIENTS WITH UNCONTROLLED SEVERE ASTHMA**
PROTOCOL NUMBER:	GB39242
VERSION NUMBER:	4
EUDRACT NUMBER:	2016-001549-13
IND NUMBER:	129714
TEST PRODUCT:	MSTT1041A (RO7187807)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 21 April 2016 Version 2: 31 May 2016 Version 3: 27 July 2017 Version 3 (VHP): 10 October 2017 Version 4: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	23-Jan-2019 22:46:39

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GB39242 has been amended primarily to reflect changes in the endpoint analyses. Changes to the protocol, along with a rationale for each change, are summarized below:

- The initial timepoint for measurement of efficacy endpoints has been changed to baseline. Definition of baseline for each endpoint will be specified in the Statistical Analysis Plan (Sections 2, 3.3.5, 6, 6.4.1, 6.4.2, 6.4.3, 6.9, and 6.10).
- The exploratory efficacy endpoint of change in nighttime symptoms has been removed, as this endpoint was included in error in the previous protocol version. Data from the nighttime symptom questions of the Asthma Daily Symptom Diary (ADSD) will be used in separate analyses to explore psychometric properties of the ADSD (Sections 2 and 6.9).
- Improvement in Standardized Asthma Quality-of-Life Questionnaire scores has been prioritized over improvement in St. George's Respiratory Questionnaire (SGRQ) scores for the secondary endpoint. Improvement in SGRQ scores is now included as an exploratory endpoint (Sections 2, 6.4.2, and 6.4.3).
- Language has been added to Section 4.5.2 to clarify that after a patient has entered the run-in period and received the single-blind placebo dose, the patient cannot be re-screened for any reason.
- Language has been added to clarify that data from the Patient Global Impression of Severity and the Patient Global Impression of Change will be used in separate analyses to explore psychometric properties of the ADSD (Section 6.9).
- Instructions for adverse event reporting after initiation of study drug have been amended to clarify that for patients who discontinue study drug prematurely, all adverse events (including serious adverse events and adverse events of special interest) will be reported until 20 weeks after the last dose of study drug or until the last study visit, whichever is later (Sections 5.3.1 and 5.4.2.2).
- The Statistical Considerations and Analysis Plan has been updated with a revision to the Type I error control strategy. Fixed sequence method will be implemented to control Type I error across dose levels for the primary endpoint and within a single dose level for selected secondary endpoints (Sections 6.4 and 6.4.1).
- Instructions for the evening diary questions in Appendix 4 have been corrected.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIB, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, DOSE-RANGING STUDY TO ASSESS THE EFFICACY AND SAFETY OF MSTT1041A IN PATIENTS WITH UNCONTROLLED SEVERE ASTHMA**
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MEDICAL MONITOR:	[redacted]
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 IIB, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, DOSE-RANGING STUDY TO ASSESS THE EFFICACY AND SAFETY OF MSTT1041A IN PATIENTS WITH UNCONTROLLED SEVERE ASTHMA**
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TEST PRODUCT:	MSTT1041A (RO7187807)
PHASE:	Phase IIb
INDICATION:	Uncontrolled severe asthma
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of MSTT1041A compared with placebo in patients with severe, uncontrolled asthma despite standard asthma therapy. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of MSTT1041A compared with placebo	• Incidence of asthma exacerbations *from baseline through Week 54*, with asthma exacerbation defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in one or both of the following: – Hospitalization or an emergency department visit with *administration of* systemic corticosteroid treatment – *Treatment with* systemic corticosteroids for ≥ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥ 3 days

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of MSTT1041A compared with placebo	• Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 54 • Time to first asthma exacerbation during the 52-week double-blind treatment period • *Achievement of improvement in AQLQ(S) score, defined as an increase of ≥0.5 points from baseline to Week 54* • Achievement of improvement in ACQ-5 score, defined as a decrease of ≥0.5 points *from baseline to Week 54* • Absolute change in patient-reported use of short-acting rescue therapy *from baseline to* Week 54 • Proportion of weeks without patient-reported asthma-related nighttime awakenings from *baseline* through Week 54 • Absolute change in patient-reported daytime asthma symptom severity as measured by the ADSD *from baseline to Week 54*
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of MSTT1041A compared with placebo	• Incidence of asthma exacerbations *from baseline through Week 54*, with asthma exacerbation defined as in Appendix 12 • Incidence of severe asthma exacerbations *from baseline through Week 54*, with severe asthma exacerbation defined as asthma symptoms requiring hospitalization or resulting in death attributed to asthma • Incidence of asthma exacerbations from *baseline* through Week 70 • Relative change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 54 • Absolute change in pre-bronchodilator FEV_1 (percentage predicted) *from baseline to* Week 54 • Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 70 • *Achievement of improvement in SGRQ score, defined as a decrease of ≥4 points from baseline to Week 54* • Achievement of improvement in ACQ-7 score, defined as a decrease of ≥0.5 points *from baseline to Week 54* • Clinician's global impression of change patient's asthma symptoms, as assessed through use of the CGIC, *from baseline to Week 26 and Week 54*
• To evaluate blood eosinophil levels as a predictive biomarker	• Incidence of asthma exacerbations *from baseline through Week 54* within each of the eosinophil-high (≥300 cells/μL) and eosinophil-low (<300 cells/μL) groups • Absolute change *from baseline to Week 54* in pre-bronchodilator FEV_1 (liters) within each of the eosinophil-high (≥ 300 cells/μL) and eosinophil-low (< 300 cells/μL) groups

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints
• To evaluate germline mutations in *IL1RL1* as a predictive biomarker	• Incidence of asthma exacerbations *from baseline through Week 54* by *IL1RL1* genotype • Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to Week 54* by *IL1RL1* genotype
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of MSTT1041A compared with placebo	• Incidence and severity of adverse events, with severity determined through use of the WHO-ART • Change from *baseline* in vital signs, ECGs, and clinical laboratory results • Incidence of ADAs
Pharmacokinetic Objective	**Corresponding Endpoint**
• To evaluate the pharmacokinetics of MSTT1041A	• Serum concentration of MSTT1041A at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to MSTT1041A	• Incidence of treatment-emergent ADAs and their potential impact on safety, efficacy, PK, and biomarker endpoints
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify biomarkers that can provide evidence of MSTT1041A activity, or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers (including germline mutations) in blood or urine (listed in Section 4.5.14) and safety, PK, immunogenicity, or other biomarker endpoints • Relative change in biomarker levels (e.g., FeNO) *from baseline to* Week 14, *Week* 26, and *Week* 54
Exploratory Health Status Objective	**Corresponding Endpoint**
• To collect data to support health status utility scores in economic modeling	• Change in health status utility as assessed by the EQ-5D-5L *from baseline to Week 54*

ACQ = Asthma Control Questionnaire ; ADA = anti-drug antibody; ADSD = Asthma Daily Symptom Diary; AQLQ(S) = Standardized Asthma Quality-of-Life Questionnaire; CGIC = Clinician Global Impression of Change; EQ-5D = EuroQol 5-Dimension Questionnaire; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; SGRQ = St. George's Respiratory Questionnaire.

Study Design

Description of Study

This is a Phase IIb, randomized, placebo-controlled, double-blind, multicenter, multi-arm study of MSTT1041A compared with placebo as add-on therapy in patients with severe, uncontrolled asthma who are receiving medium- or high-dose ICS therapy and at least one of the following additional controller medications: long-acting β-agonists (LABA), leukotriene modifier (LTM), long-acting muscarinic antagonist (LAMA), or long-acting theophylline preparation. Patients must have evidence of uncontrolled disease consisting of an Asthma Control Questionnaire–five items (ACQ-5) score of ≥ 1.5 and at least one symptom of asthma that is not controlled *during each of 2 consecutive weeks* (nighttime awakening ≥ 1 time/week and/or short-acting rescue therapy use > 2 days/week). Patients requiring use of systemic corticosteroids (oral, IV, or intramuscular [IM]) or biologic therapy (e.g., anti-IgE or anti-IL-5) at screening will be excluded from the study.

The study will consist of a 2- to 4-week screening period, a 2-week single-blind placebo run-in period, a 52-week double-blind treatment period, and a 16-week follow-up period concluding at the end-of-study (EOS) visit at Week 70.

At screening, patients must demonstrate acceptable inhaler, peak flow meter, and spirometry techniques. During the screening period, patients must demonstrate compliance with required daily use of an electronic device (eDiary) for documenting asthma controller medication use and answering questions related to asthma symptoms, nighttime awakenings due to asthma, and use of short-acting rescue therapy; compliance with daily measurement of peak expiratory flow rate (PEFR); and adherence to their usual asthma controller medication regimen (ICS plus at least one additional controller medication), as recorded daily in the eDiary (see protocol for details).

Patients who fail to meet eligibility criteria during the screening period will be permitted to re-screen twice for selected reasons, as described in the protocol. At the run-in visit (Week 0), scheduled for approximately 2 weeks prior to the randomization visit (Week 2), patients who meet enrollment criteria for the run-in period will receive one single-blind dose of placebo to allow for evaluation of unexpected variability in asthma control. At the randomization visit, patients will undergo further assessments to determine eligibility for randomization to the double-blind treatment period. Patients who experience unexpected variability in asthma control, as demonstrated by change in forced expiratory volume in 1 second (FEV_1) and/or fractional exhaled nitric oxide (FeNO) will not be eligible for double-blind treatment (see protocol).

A total of approximately 500 patients will be randomized in a 1:1:1:1 ratio to receive MSTT1041A at one of three doses (70 mg, 210 mg, or 490 mg) or placebo, stratified by blood eosinophil status at Visit 1 (< 150, ≥ 150 to < 300, ≥ 300 cells/μL), number of *documented* asthma exacerbations in the previous 12 months (1–2, ≥ 3), total daily ICS dose at Visit 1 (< 1000 μg, ≥ 1000 μg of fluticasone proportionate or equivalent), and country. Enrollment caps will be utilized to ensure adequate power for biomarker subgroup analysis based upon blood eosinophil status at Visit 1 (≥ 300, < 300 cells/μL). The randomization will be such that approximately 30 patients per arm will have eosinophil-high status and approximately 95 patients per arm will have eosinophil-low status. Study drug will be administered as four SC abdominal injections at the randomization visit (Week 2), Week 6, and every 4 weeks (Q4W) thereafter through Week 50.

Daily measurement of PEFR and daily assessment of asthma symptoms, nighttime awakenings due to asthma, and use of short-acting rescue therapy will be performed at home. More detailed assessments, including spirometry, FeNO measurements, and patient-reported outcome assessments, will be performed during scheduled site visits. All patients will undergo pharmacokinetic (PK), biomarker, and ADA sampling. Additional PK samples will be collected at prespecified timepoints for characterization of absorption and accumulation of MSTT1041A in approximately 80 patients who consent to this option.

Number of Patients

Approximately 500 patients will be randomized in the study (125 patients in each of the four treatment arms).

Target Population

Inclusion Criteria

Inclusion Criteria for Enrollment in the Run-In Period

Patients must meet the following criteria to be eligible for enrollment in the run-in period:

- Signed Informed Consent Form
- Age 18–75 years at time of signing Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Body mass index (BMI) of 18–38 kg/m^2 and weight ≥40 kg at screening
- Documented physician-diagnosed asthma for at least 12 months prior to screening
- On ICS therapy at a total daily dose ≥500 μg of fluticasone propionate or equivalent plus at least one additional allowed controller medication, for ≥3 months prior to screening, with no changes within 4 weeks prior to screening or during the screening period and no anticipated changes in controller dosing regimens throughout the study

  For patients receiving total daily dose of greater than (>) 500 μg of fluticasone propionate or equivalent, they may receive one or more of the following additional controller medications: LABA, LTM, LAMA, or long-acting theophylline preparation.

  For patients receiving total daily dose equal to 500 μg of fluticasone propionate or equivalent, at least one of their additional controller medication must be LABA.
- Morning pre-bronchodilator FEV_1 of 40%–80% of predicted at screening
- Post-bronchodilator reversibility of FEV_1 (liters) of ≥12% and ≥150 mL at screening

  Patients are allowed up to three attempts to meet reversibility criteria, within the screening period.

  Specific guidelines for performing and interpreting bronchodilator reversibility testing, including medication-withholding strategies and appropriate dosing of short-acting bronchodilators, will be provided to investigators.
- Uncontrolled asthma during the screening period, defined as an ACQ-5 score ≥1.5 and at least one of the following symptoms of asthma that is not controlled according to EPR3 (2007) and GINA (2015) guidelines *during each of 2 consecutive weeks*:
  - Nighttime awakening ≥ 1 time/week
  - Use of short-acting rescue therapy > 2 days/week
- Documented history of at least one asthma exacerbation within 12 months prior to screening while on daily ICS maintenance therapy (same or higher dose as at screening), defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in one or both of the following:
  - Hospitalization or emergency department, urgent care visit, or urgent unscheduled office visit requiring administration of asthma treatment, such as bronchodilators and/or systemic corticosteroids, in addition to baseline controller medications
  - Treatment with systemic corticosteroids for ≥ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥ 3 days
- Demonstrated compliance with required use of the eDiary, defined as documenting asthma controller medication use and answering questions related to asthma symptoms, nighttime awakenings due to asthma, and use of short-acting rescue therapy on 5 of 7 days during each of 2 consecutive weeks during the screening period
- Demonstrated compliance with required PEFR measurements, defined as measuring PEFR on 5 of 7 days during each of 2 consecutive weeks during the screening period

- Demonstrated adherence with usual asthma controller medication regimen, defined as patients responding affirmatively that they have taken their asthma controller medications on 5 of 7 days during each of 2 consecutive weeks during the screening period, as recorded in the eDiary
- Demonstration of acceptable inhaler, peak flow meter, and spirometry techniques at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for at least 20 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 20 weeks after the last 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 contraception.

Inclusion Criteria for Enrollment in the Double-Blind Treatment Period

To be eligible for enrollment in the double-blind treatment period, patients must meet all of the inclusion criteria for the run-in period (see protocol) and the following additional inclusion criteria:

- No changes in ICS therapy or allowed controller medications (see protocol) during the run-in period
- Morning pre-bronchodilator FEV_1 of 40%–80% of predicted at randomization (Week 2) visit

Exclusion Criteria

Exclusion Criteria for Enrollment in the Run-In Period

Patients who meet any of the following criteria will be excluded from enrollment in the run-in period:

- Diagnosis of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation associated with panic attacks, or other mimics of asthma
- Diagnosis of occupational asthma, aspirin-sensitive asthma, (if on chronic aspirin therapy within 2 weeks prior to screening or anticipated need of chronic aspirin therapy during the course of the study), asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome, or bronchiolitis, as determined by the investigator

- Pregnant or lactating, or intending to become pregnant during the study or within 20 weeks after the last dose of MSTT1041A

  Women of childbearing potential must have a negative serum pregnancy test result during the screening period and a negative urine pregnancy test result at the run-in visit.
- History of smoking (tobacco or marijuana) or "vaping" within 6 months prior to screening, significant smoking history (defined as ≥ 10 pack-years), or unwilling to abstain from smoking from the time of consent through the completion of the study

  A pack-year is defined as the average number of packs of cigarettes per day times the number of years of smoking.
- 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
- 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

  Patients with well-controlled comorbid disease on a stable treatment regimen for 4 weeks prior to screening are eligible for the study.
- 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
- Myocardial infarction, unstable angina pectoris, or stroke within 12 months prior to screening
- Any finding on the screening ECG that requires further cardiovascular evaluation (such as evidence of prior myocardial infarction, cardiomyopathy, or substantial left or right ventricular hypertrophy), in the opinion of the investigator
- QT interval corrected using Fridericia's formula (QTcF) >450 ms, if patient is male, or QTcF >470, if patient is female, demonstrated by the average of a triplicate of ECGs
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as 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
- Current treatment with medications that are well known to prolong the QT interval
- Evidence of active liver disease, including jaundice or AST, ALT, total bilirubin, or alkaline phosphatase $>2\times$ upper limit of normal (ULN)
- Acute infection requiring either surgical intervention (e.g., drainage) or medical therapy (e.g., antibiotics) within 4 weeks prior to screening
- Helminthic parasitic infection diagnosed within 6 months prior to screening that has not been treated or has not responded to standard-of-care therapy or exposure to water-born parasites within 6 weeks prior to the first dose of study drug

- Positive test for tuberculosis (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® test (QFT)

  Patients with a history of Bacille Calmette-Guérin (BCG) 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) prior to screening
  - No known exposure to a case of active TB after most recent prophylaxis
  - No evidence of active TB on chest radiograph within 3 months prior to screening
- Positive hepatitis C virus (HCV) antibody test result at screening, unless the patient has undetectable HCV RNA test value of <15 IU/mL (or undetectable) for >6 months after completing a successful course of HCV anti-viral treatment and a HCV RNA test value <15 IU/mL at screening OR has a known history of HCV antibody positivity with history of undetectable HCV RNA for > 6 months and a HCV RNA test value <15 IU/mL at screening in the absence of history of HCV anti-viral treatment.
- Unacceptable test results for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody total (HBcAb) at screening.
- 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 ≥ 20 IU/mL or test cannot be performed
    - Patient is eligible, if HBV DNA test value is < 20 IU/mL
- History of anaphylaxis to any biologic therapy for any indication
- History of documented immune complex disease (Type III hypersensitivity reactions) to monoclonal antibody administration
- History of any known immunodeficiency disorder, including but not limited to HIV infection
- Active malignancy, including cutaneous basal or squamous cell carcinoma or melanoma
- History of malignancy within 5 years prior to screening, except for cases specifically involving cutaneous basal or squamous cell carcinoma (non-melanoma skin cancers), cervical carcinoma in situ, or breast ductal carcinoma in situ that have been treated and considered cured
- Planned surgical intervention during the course of the study

- Asthma exacerbation as defined in the protocol within 4 weeks prior to screening
- Intubation for respiratory failure due to asthma within 12 months prior to screening
- Maintenance oral corticosteroid therapy, defined as daily or alternate-day oral corticosteroid maintenance therapy, within 3 months prior to screening or during the screening period
- Treatment with systemic (oral, IV, or IM) corticosteroids within 4 weeks prior to screening or during the screening period for any reason, including an acute exacerbation event
- Treatment with intra-articular corticosteroids within 4 weeks prior to screening or during the screening period, or anticipated need for intra-articular corticosteroids during the course of the study
- Maintenance oral or SC β-agonist therapy (e.g., terbutaline) within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Initiation of or change in allergen immunotherapy within 3 months prior to screening or during the screening period
- Treatment with phosphodiesterase-4 inhibitors (e.g., roflumilast) within 4 weeks prior to screening or during the screening period, or anticipated need for phosphodiesterase-4 inhibitors during the course of the study
- Treatment with immunomodulatory, immunosuppressive (e.g., methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine), or experimental anti-inflammatory therapy within 3 months or 5 drug half-lives prior to screening (whichever is longer) or during the screening period, or anticipated need for these medications during the course of the study
- Treatment with immunoglobulin or blood products within 4 weeks prior to screening or during the screening period, or anticipated need for immunoglobulin or blood products during the course of the study
- Treatment with any live or live, attenuated vaccines within 4 weeks prior to screening or during the screening period, or anticipated need for live, attenuated vaccines during the course of the study
- Prior treatment with MSTT1041A
- Treatment with a licensed biologic agent (e.g., omalizumab, mepolizumab, suplatast) within 3 months or 5 drug half-lives prior to screening (whichever is longer) or during the screening period
- Treatment with any investigational therapy within 3 months or 5 drug half-lives prior to screening (whichever is longer) or during the screening period
- Maintenance oral or inhaled antibiotic therapy within 2 weeks prior to screening or during the screening period
- Treatment with β-blocking agents (topical, oral, or other systemic) within 2 weeks prior to screening or during the screening period, or anticipated need for β-blocking agents during the course of the study
- Treatment with homeopathic medications, herbal medications, acupuncture, or hypnosis within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Maintenance intermittent positive pressure ventilation physiotherapy within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Maintenance bilevel positive airway pressure therapy within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Bronchial thermoplasty treatment within 24 months prior to screening or during the screening period, or anticipated need during the course of the study
- Known sensitivity to any of the active substances or their excipients to be administered during dosing

Exclusion Criteria for Enrollment in the Double-Blind Treatment Period

Patients will be excluded from enrollment in the double-blind treatment period if they meet any of the exclusion criteria for the run-in period (see above) or any of the following additional exclusion criteria:

- Positive urine pregnancy test at the randomization visit
- Absolute percentage point change (increase or decrease) of 15 or more in morning pre-bronchodilator percentage of predicted FEV_1 from screening to the randomization visit
- Absolute change (increase or decrease) in FeNO of ≥ 20 ppb and ≥ 40% relative change between screening and randomization visits

If a patient is excluded from enrollment in the double-blind treatment period, the patient should be discontinued from the study. In addition, the patient should be informed that the first dose given at Visit 2 was a placebo and therefore there is no additional requirement for follow-up visits.

End of Study

The end of this study is defined as the date when all patients have completed the study completion visit or early termination visit or have otherwise been discontinued from the study. The total duration of this study for each subject is approximately 73 weeks, including screening, run-in, treatment, and follow-up.

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 40 months.

Investigational Medicinal Products

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

Non-Investigational Medicinal Products

- ICS therapy
- LABA therapy
- LTMs
- LAMA therapy
- Long-acting theophylline preparations
- Allergen immunotherapy
- Maintenance oral corticosteroids (daily or every other day)
- Other medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements)
- Systemic corticosteroids (oral, IV, or IM)
- Intra-articular corticosteroids
- Phosphodiesterase-4 inhibitors (e.g., roflumilast)
- Live or live, attenuated vaccines
- Immunoglobulin or blood products
- Maintenance oral and SC β-agonist therapy (e.g., terbutaline)
- Investigational therapy, including investigational use of a formulation of an approved drug
- Licensed biologic agents (e.g., omalizumab, mepolizumab, suplatast)
- Immunomodulatory, immunosuppressive, or experimental anti-inflammatory therapy other than biologic agents or corticosteroids (see separate exclusions in protocol)
- Maintenance oral or inhaled antibiotics
- β-blocking agents (topical, oral, or other systemic)

- Homeopathic medications, herbal medications, acupuncture, or hypnosis therapy
- Maintenance intermittent positive pressure ventilation physiotherapy
- Maintenance bilevel positive airway pressure therapy
- Bronchial thermoplasty
- Pulmonary rehabilitation

Statistical Methods

Primary Analysis

Determination of Sample Size

A total of approximately 500 patients will be randomly allocated in a 1:1:1:1 ratio to receive one of three doses of MSTT1041A or placebo. This sample size provides approximately 80% power to detect a 40% reduction in annualized asthma exacerbation rate (AER) between one MSTT1041A arm and the placebo arm, assuming 0.63 exacerbations per patient per year in the placebo arm, a 15% dropout rate, and a two-sided significance level (α) of 0.05.

Enrollment caps will be utilized to ensure adequate power for biomarker subgroup analysis based upon blood eosinophil status at Visit 1. Approximately 30 eosinophil-high patients ($\geq$ 300 cells/μL) per arm and approximately 95 eosinophil-low patients ($<$ 300 cells/μL) per arm will be randomly allocated. The sample size provides approximately 80% power to detect a 50% reduction in annualized AER in the subgroup of eosinophil-high patients assuming 1.0 exacerbation per patient per year in the placebo arm, a 15% dropout rate, a two-sided significance level of 0.15, and 30 patients in each treatment arm having eosinophil-high status. The sample size also provides approximately 67% power to detect a 35% reduction in annualized AER in the subgroup of eosinophil-low patients, assuming 0.5 exacerbations per patient per year in the placebo arm, a 15% dropout rate, a two-sided significance level of 0.15, and 95 patients in each treatment arm having eosinophil-low status.

Efficacy Analyses

Efficacy analyses will be conducted on a modified intend-to-treat (mITT) population, consisting of all randomly allocated patients who received at least one dose of study drug during the 52-week double-blind treatment period, with patients grouped according to the treatment assigned at randomization.

Comparisons of efficacy will be performed between each MSTT1041A dose level and the placebo group. Thus, there are three comparisons:

- MSTT1041A 70 mg with placebo
- MSTT1041A 210 mg with placebo
- MSTT1041A 490 mg with placebo

Hypothesis testing and estimation of treatment effects will be performed with regression models that use data from all four treatment arms at one time.

Type I error will be controlled using a *fixed sequence method across dose levels for the primary endpoint and within a single dose level for selected secondary endpoints. The testing order of the fixed sequence will be provided* in the SAP.

Unless otherwise noted, analyses of efficacy outcome measures will be adjusted by blood eosinophil level ($<$ 150, $\geq$ 150 to $<$ 300, $\geq$ 300 cells/μL), number of *documented* asthma exacerbations in the *previous* 12 months (1–2, $\geq$ 3), total daily ICS dose ($<$ 1000 μg, $\geq$ 1000 μg of fluticasone proportionate or equivalent), and *country*.

Optional Interim Analyses

No efficacy interim analyses are planned at this time. However, in order to adapt to information that may emerge during the course of this study, (e.g. based on compelling new competitor data or additional information on biomarker characteristics that emerges during the conduct of the trial), the Sponsor may choose to conduct one interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity, should such an optional interim analysis be executed.

The Sponsor will remain blinded to individual treatment assignment. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter to ensure integrity.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the SAP, and the SAP will be finalized prior to the conduct of the interim analysis. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis will be adjusted to maintain the protocol-specified overall type I error rate, as described in the standard Lan-DeMets theory.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance. If the predictive probability is below 20%, the iDMC should consider recommending that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC charter. An interim analysis that might lead to stopping the study for futility will not occur before at least 40% information has been accumulated.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADSD	Asthma Daily Symptom Diary
AER	asthma exacerbation rate
AQLQ(S)	Standardized Asthma Quality-of-Life Questionnaire
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	body mass index
CGIC	Clinician Global Impression of Change
ClinRO	clinician-reported outcome (ClinRO)
COPD	chronic obstructive pulmonary disease
CT	computed tomography (scan)
CRO	contract research organization
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension Questionnaire
EOS	end of study
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
iDMC	independent Data Monitoring Committee
IFN-γ	interferon-γ
IL	interleukin
IM	intramuscular
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive voice or web-based response system
LABA	long-acting β-agonist

Abbreviation	Definition
LAMA	long-acting muscarinic antagonist
LPLV	last patient, last visit
LTM	leukotriene modifier
MID	minimum important difference
mITT	modified intent-to-treat
MN	mobile nursing
NGS	next-generation sequencing
NOAEL	no-observed-adverse-effect level
PEFR	peak expiratory flow rate
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PPD	purified protein derivative
PRO	patient-reported outcome
Q4W	every 4 weeks
QFT	QuantiFERON® test
QTcF	QT interval corrected using Fridericia's formula
RBR	Research Biosample Repository
SABA	short-acting β-agonist
SAMA	short-acting muscarinic antagonist
SC	subcutaneous
SGRQ	St. George's Respiratory Questionnaire
TB	tuberculosis
Th1	Type 1 helper
Th2	Type 2 helper
TNF-α	tumor necrosis factor-α
ULN	upper limit of normal
VAS	Visual Analogue Scale
WGS	whole genome sequencing
WHO-ART	World Health Organization Adverse Drug Reaction Terminology

1. BACKGROUND

1.1 BACKGROUND ON ASTHMA

Asthma is a chronic inflammatory disorder of the airways that affects approximately 300 million people worldwide, 60 million of whom live in industrialized countries. The disease is characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing due to airflow obstruction and mucus hypersecretion (Global Initiative for Asthma [GINA] 2015). Despite the development of effective controller therapies for asthma, such as inhaled corticosteroids (ICSs), long-acting β-agonists (LABAs), and other controller medications, a substantial proportion of patients continue to have uncontrolled or poorly controlled asthma (Bateman et al. 2004; Peters et al. 2006; EPR3 2007; Taylor et al. 2008; Bousquet et al. 2010; GINA 2015). Episodic worsening can occur despite medical treatment in response to specific trigger events such as inhalation of irritants and allergens, exercise-related stress, specific medications, or development of upper airway infections associated with respiratory viruses. These episodes, known as asthma exacerbations, occur most frequently in patients with advanced disease and are indicators of poor asthma control.

Patients with severe asthma are at increased risk of exacerbations. These events adversely affect their quality of life and drive increased health care resource utilization. Whereas the population of patients with severe asthma represents a minority of patients, they account for the majority of health care expenditures and adverse effects that asthma has on workplace productivity. New, more effective treatments that reduce the frequency of exacerbations in the severe asthma population and improve quality of life would address an important unmet medical need.

1.2 BACKGROUND ON MSTT1041A

MSTT1041A is a human, Chinese hamster ovary cell–derived IgG2 anti-ST2 monoclonal antibody that selectively targets the receptor for human interleukin 33 (IL-33), blocking signaling via this important inflammatory pathway. 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 interrupts signaling of the IL-33 inflammatory pathway. IL-33 is an IL-1 class cytokine and member of a new family of epithelial-derived mediators known as “alarmins” that are released in response to tissue injury (Kato et al. 2007). This unique cytokine binds to a receptor on parenchymal and inflammatory cells known as the ST2 receptor. There is strong genetic and biologic evidence supporting a central role for the IL-33/ST2 pathway in determining asthma susceptibility and severity (Jackson et al. 2014). Inhaled allergens and respiratory viruses are potent inducers of IL-33 synthesis and release (Lambrecht et al. 2015). ST2 is the receptor for IL-33 and is

present on inflammatory cells throughout the airways, including Type 2 innate lymphoid cells, monocytes, natural killer cells, T lymphocytes, mast cells, basophils, and eosinophils. Binding of IL-33 to ST2 can activate both Type 1 and Type 2 helper T-cell (Th1 and Th2) inflammation depending on the underlying milieu. Signaling via ST2 leads to release of multiple mediators including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, IL-5, IL-6, IL-9, and IL-13. All of these may contribute to the pathobiology of asthma via discrete and non-redundant mechanisms.

Based on current perspectives of asthma immunology, new biologic therapies for those patients whose asthma is not well controlled with conventional therapy are being developed. These novel treatments target specific downstream inflammatory pathways, and several have been effective in patients with specific biomarker profiles (Castro et al. 2014; Castro et al. 2015; Corren et al. 2011; Pavord et al. 2012; Piper et al. 2013). However, to date, responses to these novel treatments have been incomplete and limited to small subgroups of the population with severe asthma, including the subgroup of patients with a Type 2 high inflammation profile, which is associated with an eosinophilic phenotype and increased activity of the Type 2 cytokines IL-4, IL-5, and IL-13. ST2 is expressed on multiple cells that have been shown to play a role in asthma, and the IL-33/ST2 pathway is hypothesized to be involved in both Type 2 high and Type 2 low asthma endotypes. Current estimates suggest that Type 2 low asthmatics account for approximately half of the severe asthma population (Lambrecht et al. 2015). Patients with asthma characterized by the Type 2 low endotype may not respond adequately to current novel biologic therapies (e.g., mepolizumab).

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 Type 2 high and Type 2 low asthma. The ability to blunt inflammation across the broad asthma population independent of trigger or underlying subtype is novel, 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 subcutaneous (SC) or intravenous (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 (NOAEL, 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, and 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. Thus, the favorable safety profile in healthy volunteers supports further development of MSTT1041A in patients with asthma.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of MSTT1041A compared with placebo in patients with severe, uncontrolled asthma despite standard asthma therapy. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of MSTT1041A compared with placebo	• Incidence of asthma exacerbations *from baseline through Week 54*, with asthma exacerbation defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in one or both of the following: – Hospitalization or an emergency department visit with *administration of* systemic corticosteroid treatment – *Treatment with* systemic corticosteroids for ≥ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥ 3 days
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of MSTT1041A compared with placebo	• Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 54 • Time to first asthma exacerbation during the 52-week double-blind treatment period • *Achievement of improvement in AQLQ(S) score, defined as an increase of ≥0.5 points from baseline to Week 54* • Achievement of improvement in ACQ-5 score, defined as a decrease of ≥0.5 points *from baseline to Week 54* • Absolute change in patient-reported use of short-acting rescue therapy *from baseline to* Week 54 • Proportion of weeks without patient-reported asthma-related nighttime awakenings from *baseline* through Week 54 • Absolute change in patient-reported daytime asthma symptom severity as measured by the ADSD *from baseline to Week 54*

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of MSTT1041A compared with placebo	• Incidence of asthma exacerbations *from baseline through Week 54*, with asthma exacerbation defined as in Appendix 12 • Incidence of severe asthma exacerbations *from baseline through Week 54*, with severe asthma exacerbation defined as asthma symptoms requiring hospitalization or resulting in death attributed to asthma • Incidence of asthma exacerbations from *baseline* through Week 70 • Relative change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 54 • Absolute change in pre-bronchodilator FEV_1 (percentage predicted) *from baseline to* Week 54 • Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 70 • *Achievement of improvement in SGRQ score, defined as a decrease of ≥4 points from baseline to Week 54* • Achievement of improvement in ACQ-7 score, defined as a decrease of ≥0.5 points *from baseline to Week 54* • Clinician's global impression of change patient's asthma symptoms, as assessed through use of the CGIC, *from baseline to Week 26 and Week 54*
• To evaluate blood eosinophil levels as a predictive biomarker	• Incidence of asthma exacerbations *from baseline through Week 54* within each of the eosinophil-high (≥300 cells/μL) and eosinophil-low (<300 cells/μL) groups • Absolute change *from baseline to Week 54* in pre-bronchodilator FEV_1 (liters) within each of the eosinophil-high (≥ 300 cells/μL) and eosinophil-low (< 300 cells/μL) groups
• To evaluate germline mutations in *IL1RL1* as a predictive biomarker	• Incidence of asthma exacerbations *from baseline through Week 54* by *IL1RL1* genotype • Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to Week 54* by *IL1RL1* genotype
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of MSTT1041A compared with placebo	• Incidence and severity of adverse events, with severity determined through use of the WHO-ART • Change from *baseline* in vital signs, ECGs, and clinical laboratory results • Incidence of ADAs

Table 1 Objectives and Corresponding Endpoints (cont.)

Pharmacokinetic Objective	Corresponding Endpoint
• To evaluate the pharmacokinetics of MSTT1041A	• Serum concentration of MSTT1041A at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to MSTT1041A	• Incidence of treatment-emergent ADAs and their potential impact on safety, efficacy, PK, and biomarker endpoints
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify biomarkers that can provide evidence of MSTT1041A activity, or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers (including germline mutations) in blood or urine (listed in Section 4.5.14) and safety, PK, immunogenicity, or other biomarker endpoints • Relative change in biomarker levels (e.g., FeNO) *from baseline to* Week 14, *Week* 26, and *Week* 54
Exploratory Health Status Objective	**Corresponding Endpoint**
• To collect data to support health status utility scores in economic modeling	• Change in health status utility as assessed by the EQ-5D-5L *from baseline to Week 54*

ACQ=Asthma Control Questionnaire ; ADA=anti-drug antibody; ADSD=Asthma Daily Symptom Diary; AQLQ(S)=Standardized Asthma Quality-of-Life Questionnaire; CGIC=Clinician Global Impression of Change; EQ-5D=EuroQol 5-Dimension Questionnaire; FeNO=fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; SGRQ=St. George's Respiratory Questionnaire.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase IIb, randomized, placebo-controlled, double-blind, multicenter, multi-arm study of MSTT1041A compared with placebo as add-on therapy in patients with severe, uncontrolled asthma who are receiving medium- or high-dose ICS therapy and at least one of the following additional controller medications: LABA, leukotriene modifier (LTM), long-acting muscarinic antagonist (LAMA), or long-acting theophylline preparation. Patients must have evidence of uncontrolled disease consisting of an Asthma Control Questionnaire–five items (ACQ-5) score of ≥1.5 and at least one symptom of asthma that is not controlled *during each of 2 consecutive weeks* (nighttime awakening ≥1 time/week and/or short-acting rescue therapy use >2 days/week). Patients requiring use of systemic corticosteroids (oral, IV, or intramuscular [IM]) or biologic therapy (e.g., anti-IgE or anti-IL-5) at screening will be excluded from the study.

The study will consist of a 2- to 4-week screening period, a 2-week single-blind placebo run-in period, a 52-week double-blind treatment period, and a 16-week follow-up period concluding at the end-of-study (EOS) visit at Week 70.

At screening, patients must demonstrate acceptable inhaler, peak flow meter, and spirometry techniques. During the screening period, patients must demonstrate compliance with required daily use of an electronic device (eDiary) for documenting asthma controller medication use and answering questions related to asthma symptoms, nighttime awakenings due to asthma, and use of short-acting rescue therapy; compliance with daily measurement of peak expiratory flow rate (PEFR); and adherence to their usual asthma controller medication regimen (ICS plus at least one additional controller medication), as recorded daily in the eDiary (see Section 4.1.1 for details).

Patients who fail to meet eligibility criteria during the screening period will be permitted to re-screen twice for selected reasons, as described in Section 4.5.2. At the run-in visit (Week 0), scheduled for approximately 2 weeks prior to the randomization visit (Week 2), patients who meet enrollment criteria for the run-in period will receive one single-blind dose of placebo to allow for evaluation of unexpected variability in asthma control. At the randomization visit, patients will undergo further assessments to determine eligibility for randomization to the double-blind treatment period. Patients who experience unexpected variability in asthma control, as demonstrated by change in forced expiratory volume in 1 second (FEV_1) and/or fractional exhaled nitric oxide (FeNO) will not be eligible for double-blind treatment (see Section 3.3.4).

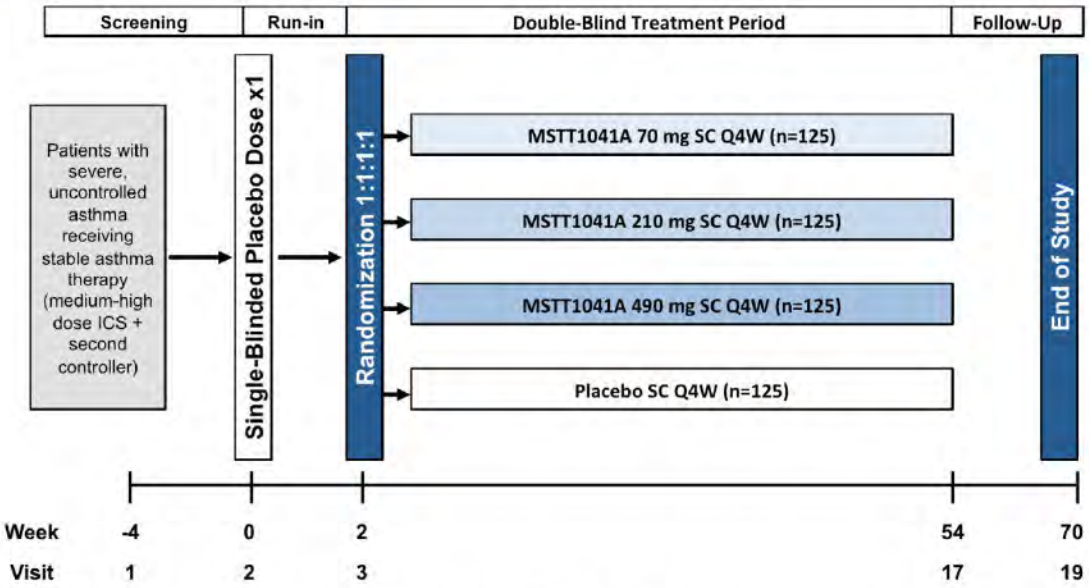
A total of approximately 500 patients will be randomized in a 1:1:1:1 ratio to receive MSTT1041A at one of three doses (70 mg, 210 mg, or 490 mg) or placebo, stratified by blood eosinophil status at Visit 1 (<150, ≥ 150 to <300, ≥ 300 cells/μL), number of *documented* asthma exacerbations *(as defined in Appendix 12)* in the previous 12 months (1–2, ≥3), total daily ICS dose at Visit 1 (<1000 μg, ≥ 1000 μg of fluticasone proportionate or equivalent), and country. Enrollment caps will be utilized to ensure adequate power for biomarker subgroup analysis based upon blood eosinophil status at Visit 1 (≥ 300, <300 cells/μL). The randomization will be such that approximately 30 patients per arm will have eosinophil-high status and approximately 95 patients per arm will have eosinophil-low status. Study drug will be administered as four SC abdominal injections at the randomization visit (Week 2), Week 6, and every 4 weeks (Q4W) thereafter through Week 50.

Daily measurement of PEFR and daily assessment of asthma symptoms, nighttime awakenings due to asthma, and use of short-acting rescue therapy will be performed at home. More detailed assessments, including spirometry, FeNO measurements, and patient-reported outcome assessments, will be performed during scheduled site visits. All patients will undergo pharmacokinetic (PK), biomarker, and ADA sampling. Additional PK samples will be collected at prespecified timepoints for characterization of

absorption and accumulation of MSTT1041A in approximately 80 patients who consent to this option (see Appendix 2).

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

Figure 1 Study Schema



ICS = inhaled corticosteroid; Q4W = every 4 weeks; SC = subcutaneous.

3.1.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor data on safety and study conduct on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet approximately every 3 months to review unblinded safety and study conduct data prepared by an external independent Data Coordinating Center (iDCC). In addition, ad hoc reviews may be requested by the iDMC or Sponsor at any time to address potential safety concerns.

Safety monitoring reviews conducted by the iDMC will include unblinded evaluation of all adverse events, serious adverse events, adverse events of special interest, major protocol deviations, ECG, and laboratory data. If the iDMC deems a benefit-risk assessment is necessary to make a recommendation about modifying or stopping the study early for a potential safety signal, the iDMC may also review unblinded efficacy data. The iDMC may recommend stopping the study early for safety reasons. However, the iDMC may not recommend stopping the trial early for positive efficacy or solely for futility. Formal stopping guidelines for assessing safety or the balance between the risks and benefits related to continuing the study will not be provided by the Sponsor. The

iDMC will use its collective judgment to recommend early termination of the study if the data indicate an unacceptable safety profile. Details will be provided in the iDMC Charter.

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 Boards/Ethics Committees (IRBs/ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when all patients have completed the study completion visit or early termination visit or have otherwise been discontinued from the study. The total duration of this study for each subject is approximately 73 weeks, including screening, run-in, treatment, and follow-up.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 40 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

The current high unmet medical need in asthma is uncontrolled disease despite adherence to guidelines-based standard-of-care therapy. In this study, the target population is patients with severe asthma whose disease remains uncontrolled despite daily use of ICS therapy (total daily dose of $\geq$500 μg of fluticasone propionate or equivalent) and at least one additional controller medication. Patients must have a diagnosis of asthma and an ACQ-5 score of $\geq$1.5 and have experienced at least one asthma exacerbation (as defined in Appendix 12) within the 12 months prior to screening as evidence of uncontrolled disease.

Patients with uncontrolled severe asthma despite treatment represent a high unmet medical need because they have exhausted conventional therapeutic options. Therapeutic options for these patients are limited because of the flat dose-response curve for ICS therapy beyond moderate doses (i.e., most of the improvement in asthma control is gained at low to moderate doses), the heterogeneity of clinical response to controller medications, and the substantial side effects of high-dose ICS and oral corticosteroid therapy (Wong et al. 2000; Holt et al. 2001; Suissa et al. 2002; Szefler et al. 2002; Masoli et al. 2004a, 2004b; Masoli et al. 2005; Adams and Jones 2006; Sears et al. 2009; Lemanske et al. 2010).

The EPR3 (2007) and GINA (2015) guidelines include several options for additional controller medications, including the addition of LAMAs (e.g., tiotropium), which reflect the heterogeneity of clinical response to each medication class (Lemanske et al. 2010). Consequently, the protocol-defined additional controller medications include LABAs, LTMs, LAMAs, and long-acting theophylline preparations.

3.3.2 Rationale for MSTT1041A Dose and Schedule

To assess the most appropriate dose of MSTT1041A in this population of patients with asthma, three MSTT1041A arms (70 mg, 210 mg, or 490 mg) and one placebo arm are proposed for this Phase IIb study. Treatment will be given Q4W for 1 year, for a total of 13 doses. Each dose will consist of four SC abdominal injections of MSTT1041A and/or matching placebo. The selection of doses and regimens was determined by three factors: achieving an efficacious clinical response, providing a broad range of exposures to assess the dose-response relationship, and ensuring patient safety.

[redacted]

The selected Phase IIb doses (70, 210, and 490 mg) are well within the dose range previously evaluated in Phase I studies. In Phase I studies, 700 mg of MSTT1041A was administered intravenously as a single dose and on a Q4W regimen (3 doses). In addition, 560 mg of MSTT1041A was administered subcutaneously as a single dose, which consisted of four SC abdominal injections (four 2-mL injections, for a total of 8 mL). Both doses were well tolerated, and no significant safety issues were identified.

3.3.3 Rationale for Control Group

A placebo-treated control group will be used in this study to assess differences in asthma exacerbations, pulmonary function, asthma control, symptoms, 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 symptoms and lung function. All patients will continue to receive standard-of-care asthma treatment in addition to study drug (MSTT1041A or placebo) throughout the study.

3.3.4 Rationale for Single-Blind Placebo Dose

The "placebo effect" is a readily observed phenomenon in clinical trials and specifically in clinical trials involving the testing of a pharmacologically active moiety in asthma (Kemeny et al. 2007; Enck et al. 2008; Dutile et al. 2014). Because of this phenomenon, significant variability has been observed in previous trials in severe asthma. In an effort to minimize the placebo effect, eligible patients will be given one single-blind placebo dose at the run-in visit (Week 0), 2 weeks prior to randomization. Patients will not be eligible for randomization to double-blind treatment if they meet at least one of the following criteria:

- Absolute percentage point change (increase or decrease) of 15 or more in morning pre-bronchodilator percentage of predicted FEV_1 from screening to the randomization visit
- Absolute change (increase or decrease) in FeNO of $\geq$20 ppb and $\geq$40% relative change between screening and randomization visits

Patients will remain on their background asthma medications throughout the screening, run-in, and treatment periods.

3.3.5 Rationale for Primary Endpoint

The rate of asthma exacerbations *from baseline through Week 54* was chosen as the most appropriate primary endpoint because it has direct clinical relevance for patients and is a reflection of the potential clinical impact of the mechanism of action. Exacerbations are associated with substantial morbidity, health status decrement, health care utilization, and health care costs. Although rare, acute asthma exacerbations may lead to asthma-associated mortality. Exacerbations also constitute a key aspect of the risk dimension of asthma control in the EPR3 (2007) and GINA (2015) guidelines. The 52-week assessment period also allows for evaluation of exacerbation events over a year, which takes into account seasonal variability.

3.3.6 Rationale for Biomarker Assessments

Biomarker assessments, before and at various timepoints after treatment, will be used to demonstrate evidence of the biologic activity of MSTT1041A in patients, identify biomarkers that may be predictive of response to MSTT1041A, define PK/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.

Blood samples will be collected at the randomization visit for DNA extraction to enable identification of germline mutations in *IL1RL1, IL33,* and *GLCCI1* that may be predictive of response to study drug, are associated with progression to a more severe disease state, or can increase the knowledge and understanding of disease biology.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 500 patients will be randomized in the study (125 patients in each of the four treatment arms).

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for Enrollment in the Run-In Period

Patients must meet the following criteria to be eligible for enrollment in the run-in period:

- Signed Informed Consent Form
- Age 18–75 years at time of signing Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Body mass index (BMI) of 18–38 kg/m^2 and weight ≥40 kg at screening
- Documented physician-diagnosed asthma for at least 12 months prior to screening
- On ICS therapy at a total daily dose ≥500 μg of fluticasone propionate or equivalent plus at least one additional allowed controller medication, for ≥3 months prior to screening, with no changes within 4 weeks prior to screening or during the screening period and no anticipated changes in controller dosing regimens throughout the study

  For patients receiving total daily dose of greater than (>) 500 μg of fluticasone propionate or equivalent, they may receive one or more of the following additional controller medications: LABA, LTM, LAMA, or long-acting theophylline preparation.

  For patients receiving total daily dose equal to 500 μg of fluticasone propionate or equivalent, at least one of their additional controller medication must be LABA.
- Morning pre-bronchodilator FEV_1 of 40%–80% of predicted at screening
- Post-bronchodilator reversibility of FEV_1 (liters) of ≥12% and ≥150 mL at screening

  Patients are allowed up to three attempts to meet reversibility criteria, within the screening period (see Section 4.5.2 for details).

  Specific guidelines for performing and interpreting bronchodilator reversibility testing, including medication-withholding strategies and appropriate dosing of short-acting bronchodilators, will be provided to investigators.
- Uncontrolled asthma during the screening period, defined as an ACQ-5 score ≥1.5 and at least one of the following symptoms of asthma that is not controlled according to EPR3 (2007) and GINA (2015) guidelines *during each of 2 consecutive weeks*:
  - Nighttime awakening ≥1 time/week
  - Use of short-acting rescue therapy >2 days/week

- Documented history of at least one asthma exacerbation within 12 months prior to screening while on daily ICS maintenance therapy (same or higher dose as at screening), defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in one or both of the following:
  - Hospitalization or emergency department, urgent care visit, or urgent unscheduled office visit requiring administration of asthma treatment, such as bronchodilators and/or systemic corticosteroids, in addition to baseline controller medications
  - Treatment with systemic corticosteroids for ≥3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥3 days
- Demonstrated compliance with required use of the eDiary, defined as documenting asthma controller medication use and answering questions related to asthma symptoms, nighttime awakenings due to asthma, and use of short-acting rescue therapy on 5 of 7 days during each of 2 consecutive weeks during the screening period (see Section 4.5.5.2 and Section 4.5.5.3 for details)
- Demonstrated compliance with required PEFR measurements, defined as measuring PEFR on 5 of 7 days during each of 2 consecutive weeks during the screening period (see Section 4.5.5.1 for details)
- Demonstrated adherence with usual asthma controller medication regimen, defined as patients responding affirmatively that they have taken their asthma controller medications on 5 of 7 days during each of 2 consecutive weeks during the screening period, as recorded in the eDiary
- Demonstration of acceptable inhaler, peak flow meter, and spirometry techniques at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of <1% per year during the treatment period and for at least 20 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 20 weeks after the last 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 contraception.

4.1.1.2 Inclusion Criteria for Enrollment in the Double-Blind Treatment Period

To be eligible for enrollment in the double-blind treatment period, patients must meet all of the inclusion criteria for the run-in period (see Section 4.1.1.1) and the following additional inclusion criteria:

- No changes in ICS therapy or allowed controller medications (see Section 4.1.1.1) during the run-in period
- Morning pre-bronchodilator FEV_1 of 40%–80% of predicted at randomization (Week 2) visit

4.1.2 Exclusion Criteria

4.1.2.1 Exclusion Criteria for Enrollment in the Run-In Period

Patients who meet any of the following criteria will be excluded from enrollment in the run-in period:

- Diagnosis of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation associated with panic attacks, or other mimics of asthma
- Diagnosis of occupational asthma, aspirin-sensitive asthma (if on chronic aspirin therapy within 2 weeks prior to screening or anticipated need of chronic aspirin therapy during the course of the study), asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome, or bronchiolitis, as determined by the investigator
- Pregnant or lactating, or intending to become pregnant during the study or within 20 weeks after the last dose of MSTT1041A

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

- History of smoking (tobacco or marijuana) or "vaping" within 6 months prior to screening, significant smoking history (defined as $\geq$10 pack-years), or unwilling to abstain from smoking from the time of consent through the completion of the study

  A pack-year is defined as the average number of packs of cigarettes per day times the number of years of smoking.

- 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
- 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

  Patients with well-controlled comorbid disease on a stable treatment regimen for 4 weeks prior to screening are eligible for the study.
- 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
- Myocardial infarction, unstable angina pectoris, or stroke within 12 months prior to screening
- Any finding on the screening ECG that requires further cardiovascular evaluation (such as evidence of prior myocardial infarction, cardiomyopathy, or substantial left or right ventricular hypertrophy), in the opinion of the investigator
- QT interval corrected using Fridericia's formula (QTcF) > 450 ms, if patient is male, or QTcF > 470, if patient is female, demonstrated by the average of a triplicate of ECGs
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as 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
- Current treatment with medications that are well known to prolong the QT interval
- Evidence of active liver disease, including jaundice or AST, ALT, total bilirubin, or alkaline phosphatase > 2 × upper limit of normal (ULN)
- Acute infection requiring either surgical intervention (e.g., drainage) or medical therapy (e.g., antibiotics) within 4 weeks prior to screening
- Helminthic parasitic infection diagnosed within 6 months prior to screening that has not been treated or has not responded to standard-of-care therapy or exposure to water-born parasites within 6 weeks prior to the first dose of study drug

- Positive test for tuberculosis (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® test (QFT)

  Patients with a history of Bacille Calmette-Guérin (BCG) 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) prior to screening
  - No known exposure to a case of active TB after most recent prophylaxis
  - No evidence of active TB on chest radiograph within 3 months prior to screening
- Positive hepatitis C virus (HCV) antibody test result at screening, unless the patient has undetectable HCV RNA test value of <15 IU/mL (or undetectable) for >6 months after completing a successful course of HCV anti-viral treatment and a HCV RNA test value <15 IU/mL at screening OR has a known history of HCV antibody positivity with history of undetectable HCV RNA for >6 months and a HCV RNA test value <15 IU/mL at screening in the absence of history of HCV anti-viral treatment.
- Unacceptable test results for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody total (HBcAb) at screening.
- 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 ≥20 IU/mL or test cannot be performed
    - Patient is eligible, if HBV DNA test value is <20 IU/mL

- History of anaphylaxis to any biologic therapy for any indication
- History of documented immune complex disease (Type III hypersensitivity reactions) to monoclonal antibody administration
- History of any known immunodeficiency disorder, including but not limited to HIV infection
- Active malignancy, including cutaneous basal or squamous cell carcinoma or melanoma
- History of malignancy within 5 years prior to screening, except for cases specifically involving cutaneous basal or squamous cell carcinoma (non-melanoma skin cancers), cervical carcinoma in situ, or breast ductal carcinoma in situ that have been treated and considered cured
- Planned surgical intervention during the course of the study
- Asthma exacerbation as defined in Appendix 12 within 4 weeks prior to screening
- Intubation for respiratory failure due to asthma within 12 months prior to screening
- Maintenance oral corticosteroid therapy, defined as daily or alternate-day oral corticosteroid maintenance therapy, within 3 months prior to screening or during the screening period
- Treatment with systemic (oral, IV, or IM) corticosteroids within 4 weeks prior to screening or during the screening period for any reason, including an acute exacerbation event
- Treatment with intra-articular corticosteroids within 4 weeks prior to screening or during the screening period, or anticipated need for intra-articular corticosteroids during the course of the study
- Maintenance oral or SC β-agonist therapy (e.g., terbutaline) within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Initiation of or change in allergen immunotherapy within 3 months prior to screening or during the screening period
- Treatment with phosphodiesterase-4 inhibitors (e.g., roflumilast) within 4 weeks prior to screening or during the screening period, or anticipated need for phosphodiesterase-4 inhibitors during the course of the study
- Treatment with immunomodulatory, immunosuppressive (e.g., methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine), or experimental anti-inflammatory therapy within 3 months or 5 drug half-lives prior to screening (whichever is longer) or during the screening period, or anticipated need for these medications during the course of the study
- Treatment with immunoglobulin or blood products within 4 weeks prior to screening or during the screening period, or anticipated need for immunoglobulin or blood products during the course of the study

- Treatment with any live or live, attenuated vaccines within 4 weeks prior to screening or during the screening period, or anticipated need for live, attenuated vaccines during the course of the study
- Prior treatment with MSTT1041A
- Treatment with a licensed biologic agent (e.g., omalizumab, mepolizumab, suplatast) within 3 months or 5 drug half-lives prior to screening (whichever is longer) or during the screening period
- Treatment with any investigational therapy within 3 months or 5 drug half-lives prior to screening (whichever is longer) or during the screening period
- Maintenance oral or inhaled antibiotic therapy within 2 weeks prior to screening or during the screening period
- Treatment with β-blocking agents (topical, oral, or other systemic) within 2 weeks prior to screening or during the screening period, or anticipated need for β-blocking agents during the course of the study
- Treatment with homeopathic medications, herbal medications, acupuncture, or hypnosis within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Maintenance intermittent positive pressure ventilation physiotherapy within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Maintenance bilevel positive airway pressure therapy within 2 weeks prior to screening or during the screening period, or anticipated need during the course of the study
- Bronchial thermoplasty treatment within 24 months prior to screening or during the screening period, or anticipated need during the course of the study
- Known sensitivity to any of the active substances or their excipients to be administered during dosing

4.1.2.2 Exclusion Criteria for Enrollment in the Double-Blind Treatment Period

Patients will be excluded from enrollment in the double-blind treatment period if they meet any of the exclusion criteria for the run-in period (see Section 4.1.2.1) or any of the following additional exclusion criteria:

- Positive urine pregnancy test at the randomization visit
- Absolute percentage point change (increase or decrease) of 15 or more in morning pre-bronchodilator percentage of predicted FEV_1 from screening to the randomization visit
- Absolute change (increase or decrease) in FeNO of ≥20 ppb and ≥40% relative change between screening and randomization visits

If a patient is excluded from enrollment in the double-blind treatment period, the patient should be discontinued from the study. In addition, the patient should be informed that the first dose given at Visit 2 was a placebo and therefore there is no additional requirement for follow-up visits.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Following successful completion of the run-in period, at the Week 2 visit, patients will be randomly allocated to one of four treatment arms (MSTT1041A 70 mg, MSTT1041A 210 mg, MSTT1041A 490 mg, or placebo) at a 1:1:1:1 ratio through an interactive voice or web-based response system (IxRS). Randomization will be stratified by blood eosinophil status at Visit 1 (<150, ≥ 150 to <300, ≥ 300 cells/μL), number of *documented* asthma exacerbations *(as defined in Appendix 12)* in the previous 12 months (1–2, ≥ 3), total daily ICS dose at Visit 1 (<1000 μg, ≥ 1000 μg of fluticasone proportionate or equivalent), and country. A dynamic randomization method will be employed.

Patients, study site personnel, contract research organization (CRO) personnel, and other Sponsor agents (with the exception of the IxRS provider and bioanalytical labs for excluding placebo PK samples from testing) will remain blinded to individual treatment assignment. The iDMC members will be unblinded throughout the study and will not have direct contact with study site personnel.

Treatment codes should not be broken except in emergency situations. If emergency unblinding is necessary for patient management (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. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event). Unblinding at the study site for any other reason will be considered a protocol deviation.

For regulatory reporting purposes or if required by local health authorities, the Sponsor will break the treatment code for all unexpected serious adverse events (see Section 5.7) that are considered by the investigator to be related to study drug.

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 MSTT1041A and Placebo

MSTT1041A and matching placebo will be supplied by the Sponsor in glass vials that contain sterile, clear, and colorless to slightly yellow liquid for SC administration. Each vial will contain approximately 1 mL of either 70 mg/mL MSTT1041A or diluent (placebo).

For information on the formulation and handling of MSTT1041A, see the study drug preparation instructions and the MSTT1041A Investigator's Brochure.

4.3.1.2 Other Protocol-Mandated Asthma Medications

All patients must be on a stable asthma treatment regimen consisting of ICS therapy plus at least one additional controller medication (see Section 4.4.1 for details). Refer to the prescribing information for the formulation, packaging, and handling of these medications.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 MSTT1041A and Placebo

Patients who meet eligibility criteria during the screening period will be enrolled and receive a single-blind dose of placebo at the run-in visit (Week 0). At Week 2, patients deemed eligible will be randomly allocated to receive treatment with MSTT1041A 70 mg, 210 mg, or 490 mg or placebo, administered as four SC abdominal injections every 28 (±5) days (Q4W) from the randomization visit (Week 2) through Week 50. With the exception of the single-blind placebo dose, no more than one dose should be administered within any 21-day period. If the dosing window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date. There will be no dose adjustments in this study.

Study drug administration must occur after all other procedures have been completed at each clinic visit. Study drug will be administered at the study site by trained medical personnel. Each dose of study drug (MSTT1041A or placebo) will be administered as four SC injections (one 1-mL injection and three 2-mL injections, for a total of 7 mL), one in each quadrant of the abdomen. All patients will be held for observation for at least 2 hours after each of the first six doses (i.e., Week 0 through Week 18, including the single-blind placebo dose). Dosing on subsequent dosing days should include a minimum length of observation time of 15 minutes, and longer in the event of an injection site reaction, approximately 60 minutes or other, as determined by 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. Section 5.1.2.2 provides specific guidelines for withholding or discontinuing study drug for patients who experience hepatotoxicity.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Other Protocol-Mandated Asthma Medications

All patients must be on a stable asthma treatment regimen consisting of ICS therapy plus at least one additional controller medication. Refer to Section 4.4.1 for details regarding asthma treatment regimens.

4.3.3 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, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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.

4.3.4 Post-Trial Access to MSTT1041A

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide 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 Web site:

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

4.4 ASTHMA THERAPY AND CONCOMITANT THERAPY

Asthma medications used by the patient from 12 months prior to initiation of study drug (Week 0) through the end-of-study visit should be recorded on the appropriate eCRF. Other medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to screening through the end-of-study visit should be recorded on the Concomitant Medications eCRF.

Patients should not be asked to alter their standard therapy in any way until the informed consent process is complete.

4.4.1 Required Asthma Controller Therapy

All patients will continue on a stable asthma treatment regimen that is consistent with GINA guidelines, as outlined below:

- ICS therapy at a total daily dose of ≥500 μg of fluticasone propionate or equivalent plus at least one additional controller medication, for ≥3 months prior to screening, with no changes within 4 weeks prior to screening or during the screening or run-in periods and no anticipated changes in dosing regimens throughout the study
    - For patients receiving total daily dose of >500μg of fluticasone propionate or equivalent, they may receive one or more of the following additional controller medications: LABA, LTM, LAMA, or long-acting theophylline preparation.
    - For patients receiving total daily dose equal to 500 μg of fluticasone propionate or equivalent, at least one of their additional controller medication must be LABA.

Any changes to the formulation or dose of ICS or any additional controller medications should be avoided, with the exception of the theophylline dose, which may be adjusted as appropriate on the basis of serum theophylline levels. If changes to the ICS brand or formulation are unavoidable, the patient may be switched to another ICS brand or formulation at a dose equivalent to the ICS dose that the patient was receiving at study entry (please see Appendix 3 for examples of ICS dose equivalence information). All changes to a patient's controller medications should be documented on the eCRF.

In order to maintain stable controller medication doses, patients may not use an ICS/LABA combination inhaler (i.e., single maintenance and reliever therapy) as rescue therapy.

Restrictions on the timing of administration of bronchodilators are described in Section 4.4.5.

4.4.2 Short-Acting Rescue Therapy

It is expected that the majority of patients will be using short-acting β-agonist (SABA) or short-acting muscarinic antagonist (SAMA) therapy for symptoms of uncontrolled asthma per existing treatment guidelines. Combination SABA or SAMA inhalers (e.g., albuterol/ipratropium) are also permitted. Short-acting rescue therapy must be administered via the patient's prescribed inhaler or nebulizer.

Any short-acting therapy that is prescribed as asthma rescue medication over the course of the study or administered during hospitalization or an emergency department, urgent care visit, or urgent unscheduled office visit should be documented on the appropriate eCRF.

Restrictions on the timing of administration of SABA or SAMA therapy relative to PEFR and spirometry measurements are described in Section 4.4.5.

4.4.3 Systemic Corticosteroid Use

Patients who require any systemic corticosteroids (oral, IV, or IM) within 4 weeks prior to screening or during the screening or run-in periods will not be eligible for the trial (see Section 4.1.2).

The use of systemic corticosteroids is permitted for acute patient management after randomization. Corticosteroids used for treatment of asthma (e.g., an acute exacerbation event as defined in Appendix 12) should be documented on the appropriate eCRF. Whereas systemic corticosteroids should not be used other than for asthma exacerbation, in the event that they are used to treat other medical conditions, this should be documented on the Concomitant Medications eCRF.

4.4.4 Asthma Therapy and Concomitant Therapy Restrictions

Asthma therapy and concomitant therapy restrictions are summarized in Table 2.

Table 2 Asthma Therapy and Concomitant Therapy Restrictions

Medication	Restrictions [a]
ICS therapy	On a stable regimen for ≥3 months prior to screening, with no changes within 4 weeks prior to screening, during the screening or run-in periods, or during the treatment period
LABA therapy LTMs LAMA therapy	No changes in dose or initiation of therapy within 4 weeks prior to screening, during the screening or run-in periods, or during the treatment period
Long-acting theophylline preparations	No changes in dose or initiation of therapy within 4 weeks prior to screening, during the screening or run-in periods, or during the treatment period, except for dose adjustments as appropriate on the basis of serum theophylline levels
Allergen immunotherapy	No changes in dose or initiation of therapy within 3 months prior to screening, during the screening or run-in periods, or during the treatment period Must not be administered on the same day as study drug
Maintenance oral corticosteroids (daily or every other day)	Prohibited within 3 months prior to screening
Systemic corticosteroids (oral, IV, or IM)	Prohibited within 4 weeks prior to screening and during the screening and run-in periods Prohibited for treatment of any condition other than asthma exacerbations during the 52-week double-blind treatment period
Intra-articular corticosteroids Phosphodiesterase-4 inhibitors (e.g., roflumilast) Live or live, attenuated vaccines Immunoglobulin or blood products	Prohibited within 4 weeks prior to screening, during the screening and run-in periods, and during the 52-week double-blind treatment period

Table 2 Asthma Therapy and Concomitant Therapy Restrictions (cont.)

Medication	Restrictions [a]
Maintenance oral and SC β-agonist therapy (e.g., terbutaline)	Prohibited within 2 weeks prior to screening, during the screening and run-in periods, and during the 52-week, double-blind, treatment period
Investigational therapy, including investigational use of a formulation of an approved drug [b]	Prohibited within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening and run-in periods, and during the 52-week, double-blind treatment period
Licensed biologic agents (e.g., omalizumab, mepolizumab, suplatast)	Prohibited within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening and run-in periods, and during the 52-week, double-blind treatment period
Immunomodulatory, immunosuppressive, or experimental anti-inflammatory therapy other than biologic agents or corticosteroids (see separate exclusions above)	Prohibited within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening and run-in periods, and during the 52-week, double-blind treatment period
Maintenance oral or inhaled antibiotics β-blocking agents (topical, oral, or other systemic) Homeopathic medications, herbal medications, acupuncture, or hypnosis therapy Maintenance intermittent positive pressure ventilation physiotherapy Maintenance bilevel positive airway pressure therapy	Prohibited within 2 weeks prior to screening, during the screening and run-in periods, and during the 52-week double-blind treatment period
Bronchial thermoplasty	Prohibited within 24 months prior to screening, during the screening and run-in periods, and during the 52-week, double-blind, treatment period
Pulmonary rehabilitation	Prohibited except on an outpatient basis for patients who have been participating for ≥6 months prior to screening and will continue to participate during the 52-week, double-blind, treatment period

ICS = inhaled corticosteroid; IM = intramuscular; IV = intravenous; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; LTM = leukotriene modifier; SC = subcutaneous.

[a] The Medical Monitor should be consulted in cases of uncertainty.

[b] Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.

Patients who take any prohibited concomitant medications should not necessarily be withdrawn from the study or discontinue study treatment, as described in Section 4.6. The Medical Monitor should be consulted to ensure that there are no safety risks associated with continuing study drug or if a study treatment interruption should be considered.

4.4.5 Medication Use prior to Peak Expiratory Flow Rate and Spirometry Measurements

Patients will measure PEFR once daily, prior to taking their morning controller medications (see Section 4.5.5.1 for details). At specified timepoints during the study, patients will undergo pre-bronchodilator spirometry measurements in the clinic (see Section 4.5.12.1 for details). Bronchodilator use is prohibited within a specified window prior to PEFR and pre-bronchodilator spirometry measurements, as follows:

- Twice-daily LABA and LAMA: prohibited within 12 hours prior to PEFR or spirometry
- Once-daily LABA and LAMA: prohibited within 24 hours prior to PEFR or spirometry
- SABA or SAMA: prohibited within 4 hours prior to spirometry

At screening, patients will undergo post-bronchodilator FEV_1 measurements. Up to 8 puffs of SABA or nebulized equivalent (e.g., 2 treatments with 2.5 mg albuterol/salbutamol) will be administered in a step-wise fashion, as described in Section 4.5.12.2.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

At applicable sites, certain PK blood samples may be collected by a mobile nursing (MN) professional at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. A schedule for PK blood sample collection is provided in Appendix 2.

4.5.1 Informed Consent Forms

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

4.5.2 Screening and Run-In Assessments

Patients who meet eligibility requirements during the 2- to 4-week screening period will be enrolled in the run-in period and will receive one single-blind dose of placebo at the run-in visit (Week 0).

Compliance with the required use of the eDiary and PEFR measurements as well as adherence with usual asthma controller medication regimen (see Section 4.1.1) must be demonstrated on 5 of 7 days during each of 2 consecutive weeks during the screening period. The earliest timepoint a patient can satisfy these eligibility criteria is 12 days after study consent. The 2- to 4-week screening period is intended to allow sufficient time for a patient to meet all eligibility requirements. However, if all eligibility requirements are met earlier (i.e., between 12 and 28 days after study consent), including confirmation of spirometry and ECG results, patients may be enrolled into the run-in period prior to the end of the 4 weeks of screening.

Patients who meet all eligibility requirements for enrollment in the run-in period with the exception of morning pre-bronchodilator FEV_1 of 40%-80% or post-bronchodilator reversibility of FEV_1 of $\geq$12% and $\geq$150 mL are allowed up to two additional attempts to meet these two eligibility criteria within the screening period, if their morning pre-bronchodilator FEV_1 was between 35%-85%.

Patients who have received the single-blind placebo dose and not meet any of the following inclusion criteria or meet any of the following exclusion criteria at the randomization visit (Week 2) will be considered run-in failures and are not eligible for randomization (see Section 4.1.1.2 and Section 4.1.2.2):

- Inclusion Criteria:
  - No changes in ICS therapy or allowed controller medications (see Section 4.1.1.1) during the run-in period
  - Morning pre-bronchodilator FEV_1 of 40%–80% of predicted at randomization (Week 2) visit
- Exclusion Criteria:
  - Absolute percentage point change (increase or decrease) of 15 or more in morning pre-bronchodilator percentage of predicted FEV_1 from screening to the randomization visit
  - Absolute change (increase or decrease) in FeNO of $\geq$20 ppb and $\geq$ 40% relative change between screening and randomization visits

These patients should be discontinued from the study and they are not eligible for re-screening. In addition, these patients should be informed that the first dose given at Visit 2 was a placebo and therefore there is no additional requirement for follow-up visits. However, patients who meet all eligibility requirements for enrollment in the double-blind treatment period with the exception of the morning pre-bronchodilator FEV1 of 40%-80 are allowed one additional attempt to meet the criteria within the run-in period, if their morning pre-bronchodilator FEV1 was between 35%-85%.

Note that after a patient has entered the run-in period and received the single-blind placebo dose, the patient cannot be re-screened for any reason.

Patients who are unable to complete or meet eligibility requirements during one screening period will be permitted to be re-screened twice for a total of up to three screenings.

Patients who fail to meet eligibility requirements ≤6 weeks after Informed Consent Form completion are required to repeat only the assessments that triggered screen failure.

Patients who fail to meet eligibility requirements >6 weeks after Informed Consent Form completion are required to repeat the consent process and all screening and run-in assessments except TB screening, and hepatitis serologies. However, TB screening and hepatitis serologies should be repeated if the re-screening takes place >6 months after initial screening.

If the second screening takes place within 6 weeks of the first screening, the patient must wait at least 4 weeks after the second screening for the third screening.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility (if applicable).

4.5.3 Medical History and Demographic Data

Medical history includes, but is not limited to, clinically significant diseases, surgeries, reproductive status, smoking history, and use of alcohol and drugs of abuse. Targeted medical history will include specific information pertaining to diseases commonly associated with asthma, including, but not limited to, allergic rhinitis, atopic dermatitis, Type 2 diabetes, arthritis, osteoporosis, and heart disease. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to screening will be recorded. Asthma or allergy medications used within 12 months prior to screening will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment.

4.5.4 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 ≥3 mm and documented negative control]), ImmunoCAP, or other specific IgE test. Regardless of atopy status, total and specific IgE testing will be performed at the randomization visit.

4.5.5 Assessments Completed by the Patient at Home

At the screening visit, patients will receive a peak flow meter that will be used for measuring PEFR and an eDiary that will be used for documenting asthma controller medication use and answering questions related to asthma symptoms, nighttime awakenings due to asthma, and use of short-acting rescue therapy. Patients will be given instructions on how to measure PEFR and record information in the eDiary at home on a daily basis. Site staff will review daily diary compliance at each subsequent visit and provide refresher training if needed.

4.5.5.1 Peak Expiratory Flow Rate

Patients will always measure PEFR in the morning (5:00–9:00 a.m.), at approximately the same time each day, prior to taking asthma controller medications. PEFR measurements should consist of three good efforts. Patients should complete their PEFR measure prior to taking their daily LABA and LAMA asthma controller medication as prescribed. PEFR windows are as follows:

- 12 hours after taking last dose of twice-daily LABA or twice-daily LAMA
- 24 hours after taking last dose of once-daily LABA or once-daily LAMA

On the days of study visits, if the patient had not performed the morning PEFR measurement before arrival at the clinic, the PEFR should be measured at the clinic.

4.5.5.2 Compliance with Asthma Controller Medication

Patients will be instructed to indicate whether or not they have taken their asthma controller medication each evening in the eDiary, during the screening period through Week 54, to monitor compliance with asthma controller medications. A copy of the Compliance with Asthma Controller Medication question is provided in Appendix 11.

4.5.5.3 Daily Diary Symptom-Related Asthma Assessments

Patients will complete daily diary questions on the eDiary twice a day. The daily diary comprises morning items (to be completed when patients wake up) and evening items (to be completed at bedtime). The eDiary will remind patients when it is time to complete their diary. Details about the specific content are described in Morning Diary Questions and Evening Diary Questions below.

Morning Diary Questions

The morning diary (see Appendix 4) is comprised of 4 measures:

1. Asthma Daily Symptom Diary: Nighttime Symptoms

The Asthma Daily Symptom Diary (ADSD) (nighttime symptoms) includes 7 items that allow patients to rate the severity of their nighttime asthma symptoms since they went to bed the previous night on an 11-point scale ranging from 0 (none) to 10 (as bad as you can imagine).

A single item is used to assess each of the following concepts:

- Breathing
- Wheezing
- Shortness of breath
- Chest tightness
- Chest pain
- Cough
- Feeling of mucus in the chest

The ADSD nighttime symptom questions will be administered on 3 non-consecutive days during screening, run-in visit, randomization visit, daily for 7 days prior to Week 26, and daily for 7 days prior to Week 54.

2. Nighttime awakening due to asthma

Patients will respond to a single item asking whether they woke up because of their asthma symptoms (yes/no). The nighttime awakening due to asthma question will be administered every morning beginning at screening through Week 54.

3. Short acting symptom relief medication (short-acting rescue therapy)

Patients will be asked whether they used short-acting rescue medication to relieve their asthma symptoms during the night (yes/no). If "yes," they will be asked whether they used an inhaler and whether they used a nebulizer ("breathing machine") with instruction to choose "all that apply." The short-acting symptom relief medication question will be administered every morning beginning at screening through Week 54.

4. Patient Global Impression of Severity

The Patient Global Impression of Severity (PGIS) completed in the morning diary asks patients to rate their nighttime asthma symptoms on an 11-point scale ranging from 0 (no symptoms) to 10 (as bad as you can imagine). The morning diary PGIS will be administered 4 times: at the run-in visit, the randomization visit, one day prior to Week 26 visit, and one day prior to Week 54 visit.

Evening Diary Questions

The evening diary (Appendix 4) is comprised of 3 measures.

1. Asthma Daily Symptom Diary: Daytime Symptoms

The ADSD (daytime symptoms) includes 7 items that allow patients to rate the severity of their daytime asthma symptoms since they got up in the morning on an 11-point scale ranging from 0 (none) to 10 (as bad as you can imagine).

A single item is used to assess each of the following concepts:

- Breathing
- Wheezing
- Shortness of breath
- Chest tightness
- Chest pain
- Cough
- Feeling of mucus in the chest
- The ADSD daytime symptom questions will be asked daily from screening (Visit 1) through Week 54.

- 2. Short-acting symptom relief medication (short-acting rescue therapy)

Patients will be asked whether they used short acting rescue medication to relieve their asthma symptoms during the day (yes/no). If "yes," they will be asked whether they used an inhaler and whether they used a nebulizer ("breathing machine") with instruction to choose "all that apply." The short-acting symptom relief medication question will be administered every evening beginning at screening through Week 54.

3. Patient Global Impression of Severity

The PGIS completed in the evening diary asks patients to rate their daytime asthma symptoms on an 11-point scale ranging from 0 (no symptoms) to 10 (as bad as you can imagine). The evening diary PGIS will be administered 5 times: at the run-in visit, the randomization visit, one day prior to Week 14 visit, one day prior to Week 26 visit, and one day prior to the Week 54 visit.

4.5.6 Patient-Reported and Clinician-Reported Outcomes Assessed during Site Visits

Patients will complete patient-reported outcome (PRO) assessments to capture their direct experience and potentially characterize the clinical impact of MSTT1041A. The questionnaires, translated into the local language as required, 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-administered before the patient receives any information on disease status, prior to the performance of other site-visit assessments and procedures and prior to the administration of study treatment.

Clinician-reported outcome (ClinRO) data will be collected via a self-administered questionnaire to allow clinicians to report their impression of each patient's change in asthma symptoms. Clinicians will complete the questionnaire after they have examined patients and performed other study-related health assessments.

Patients will use an electronic device to complete their PRO assessments. The PRO questionnaires will be pre-programmed on electronic devices so that the appropriate questionnaires will be administered in order at specific site visits as specified in the schedule of activities (see Appendix 1). The PRO assessments should take between approximately 5 and 25 minutes to complete (shorter at most visits, longer at the randomization visit, Week 26, and Week 54 visit). The electronic device and/or instructions for completing the questionnaires electronically will be provided by the investigator 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.

4.5.6.1 Asthma Control Questionnaire

Asthma control, as measured by the Asthma Control Questionnaire (ACQ) (Juniper et al. 1999b), will be assessed by asking patients to recall their experience with asthma during the previous week. The full ACQ consists of seven questions: five questions related to symptoms (i.e., nighttime awakening, asthma symptoms upon awakening in the morning, activity limitation, shortness of breath, and wheezing frequency), one question about use of short-acting rescue therapy, and one question about FEV_1 (to be completed by site staff). The items are scored on a scale ranging from 0 (totally controlled) to 6 (extremely poorly controlled). The items are equally weighted. The ACQ can be scored three ways: 1) the mean of the five symptom-related items (ACQ-5); 2) the mean of the five symptom-related items plus the short-acting rescue use item (ACQ-6); or 3) the mean of all 7 items (ACQ). The ACQ has strong measurement properties for use in both clinical practice and clinical trials. The ACQ-5 is part of the eligibility criteria and will be administered at the screening and run-in visits. The ACQ will be administered at the randomization visit, Week 26, and Week 54.

A copy of the ACQ is provided in Appendix 5.

4.5.6.2 Standardized Asthma Quality of Life Questionnaire

The Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) will be used to assess the patients' asthma-specific health-related quality of life (Juniper et al. 1999a). The 32-item questionnaire contains four domains: activity limitations, symptoms, emotional function, and environmental stimuli. The AQLQ(S) has a recall specification of 2 weeks. Items are scored on a 7-point scale ranging from 1 (severe impairment) to 7 (no impairment. A copy of the AQLQ(S) is provided in Appendix 6. The AQLQ(S) will be administered at the randomization visit, Week 26, and Week 54.

4.5.6.3 St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is a 50-item respiratory-specific quality-of-life questionnaire initially developed and validated for use in COPD (Jones et al. 1992). It includes questions that assess the impact of disease on symptoms, activity, and functionality. The symptom scale assesses the severity of respiratory symptoms, the activity scale examines impairment in patient activity as a result of respiratory

symptoms, and the impact scale evaluates effects of respiratory symptoms on overall function and well-being. Each scale is scored from 0 to 100, and a total score represents the weighted average of these three subscores. Items are assessed on various response scales, including a 5-point Likert scale and a true/false scale. The SGRQ has a recall period of the past 4 weeks. Recently, the SGRQ has been applied more broadly to assess patients with airflow limitation due to causes other than COPD, including asthma (Ortega et al. 2014). The SGRQ will be administered in the clinic at the randomization visit, Week 26, and Week 54. A copy of the SGRQ is provided in Appendix 7.

4.5.6.4 Clinician Global Impression of Change

The Clinician Global Impression of Change (CGIC) is a single-item assessment of the clinician's impression of a patient's change in asthma symptoms since beginning the 52-week double-blind treatment period (Visit 3). Change in asthma symptoms is rated on a 7-point scale ranging from "very much worse" to "very much improved." The CGIC is completed by the clinician and takes less than 1 minute to complete. The CGIC will be completed at Weeks 26 and 54. A copy of the CGIC is provided in Appendix 8.

4.5.6.5 Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is a single-item assessment of the patient's impression of his or her change in asthma symptoms since beginning the 52-week double-blind treatment period. Change in asthma symptoms is rated on a 7-point scale ranging from "very much worse" to "very much improved." The PGIC will be administered in the clinic at Weeks 26 and 54. A copy of the PGIC is provided in Appendix 9.

4.5.6.6 EuroQol 5-Dimension Questionnaire

The EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D-5L will be utilized in this study for economic modeling. The EQ-5D-5L will be administered in the clinic at the randomization visit and at the Week 54 visit. A copy of the EQ-5D-5L is provided in Appendix 10.

4.5.7 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from abnormalities recorded at screening should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.8 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure. Patients should *ideally* be in a seated position in a rested and calm state for at least 5 minutes before taking vital sign measurements.

4.5.9 Electrocardiograms

Triplicate ECG recordings will be obtained at specified visits, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled visits as indicated. Three interpretable ECG recordings (e.g., without artifacts) *should* be obtained at each visit, typically within 15 minutes. The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT).

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 a central ECG laboratory. The following should be recorded: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented. 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 value at the randomization visit, 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 (i.e., triplicate ECGs) 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).

4.5.10 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 prior to screening and the report is available for review. A chest computed tomography (CT) 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.

4.5.11 Asthma Exacerbations

At each study visit, the investigator will ask directed questions to assess whether the patient experienced any asthma exacerbations as defined in Appendix 12 since the last study visit.

Given that asthma exacerbations are the primary endpoint in this study, a dedicated eCRF will be used to record information regarding asthma exacerbation events. An asthma exacerbation must also be reported as an adverse event (or serious adverse event as applicable) (refer to Section 5 for more details). Sites should record all medications used for treatment of the asthma exacerbation in the appropriate eCRF.

Patients who experience symptoms consistent with an asthma exacerbation should be asked to come to the clinic for an unscheduled visit if possible. Patients will be asked to bring from home a urine sample collected at symptom onset. Additional evaluations will be performed as outlined in the schedule of activities (Appendix 1).

4.5.12 Spirometry

Spirometry, including the procedure for bronchodilator testing, will be conducted as per the study pulmonary function testing manual, which is based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement "Standardisation of Spirometry" (Miller et al. 2005). The manual will include information on equipment, procedures, patient instructions, and precautions. Standardized ATS- and ERS-compliant spirometric equipment, including software, will be dispensed to all sites. Training on equipment use, system calibration, and data storage and transfer will be provided.

4.5.12.1 Pre-Bronchodilator Spirometry

Pre-bronchodilator spirometry evaluations should be performed in the morning, before use of bronchodilators. Asthma therapies that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed. Patients must be made aware that bronchodilator use is prohibited within a specified window prior to each clinic visit, with the exception of the screening visit or an unscheduled visit, as follows:

- Twice-daily LABA and twice-daily LAMA: prohibited within 12 hours prior to spirometry
- Once-daily LABA and once-daily LAMA: prohibited within 24 hours prior to spirometry
- SABA or SAMA: prohibited within 4 hours prior to spirometry

With the exception of an unscheduled visit, a patient's visit must be rescheduled if the patient arrives for a study visit having used a bronchodilator within the time window defined above for each medication. To accommodate the rescheduled visit, the usual visit window specified in the schedule of activities (see Appendix 1) may be extended to ±4 days for Week 4 or ±6 days for Week 6–54.

For safety reasons, consideration should be given to omitting spirometry if a patient is having an acute asthma exacerbation event at the time of the scheduled study visit.

Spirometric assessments will include FEV_1, forced vital capacity (FVC), percentage of predicted values for FEV_1 and FVC, FEV_1 to FVC ratio, and average expiratory flow during the middle portion of the expiration ($FEF_{25–75}$). The percentage of predicted values for FEV_1 and FVC will be derived from the third National and Nutrition Examinations Survey (Hankinson et al. 1999). Each test procedure requires that three valid spirometry maneuvers be performed within 1 hour. The highest FEV_1 and FVC values from the set of three accepted maneuvers will be recorded. Other parameters will be taken from the accepted maneuver with the highest sum of FEV_1 and FVC. A hard-copy report of the spirometry results will be maintained in the patient's medical record.

4.5.12.2 Post-Bronchodilator Spirometry

At screening, post-bronchodilator FEV_1 measurements will be recorded 15 to 45 minutes after bronchodilator use. Up to 8 puffs of SABA or nebulized equivalent (e.g., 2 treatments with 2.5 mg albuterol/salbutamol) should be administered in a step-wise fashion, as follows:

- Administer 4 puffs, followed by spirometry.
- If bronchodilator reversibility improvement criteria are not met, administer 2 to 4 additional puffs, followed by spirometry.

4.5.13 Fractional Exhaled Nitric Oxide

FeNO is a volatile marker of airway inflammation and has been demonstrated to decrease with ICS treatment. Standard nitric oxide machines will be provided to the site and should be used for all study-related FeNO measurements. Patients will be asked to refrain from nitrate-rich foods (such as processed meats [bacon, lunchmeat, hot dogs, sausage], spinach, green beans, broccoli, and cauliflower) for at least 8 hours prior to the study visit and to avoid food or drink for at least 1 hour prior to completing at least three (and up to six) separate measurements according to ATS guidelines (training and guidance to be provided separately) (American Thoracic Society 2005).

4.5.14 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 shows a positive result, study drug will not be administered that day. The 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 confirmed pregnancy.
- TB tests: PPD or QFT (QFT may be conducted by the central laboratory, per Sponsor agreement with site)
- Serum theophylline levels (only for patients taking theophylline, per standard of care)

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

- Serum pregnancy test for all women of childbearing potential

  Serum pregnancy tests will be performed at screening and at subsequent visits if a local urine pregnancy test is positive. Study drug will not be administered if a patient has a positive pregnancy test. Refer to Section 5.4.3.1 for management of a patient with a confirmed pregnancy.
- Hematology: WBC count, RBC count, RBC morphology, hemoglobin, hematocrit, platelet count, ANC, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, magnesium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH
- Fasting lipids: cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
- Fasting glucose and HbA_{1c}

- Viral serology: hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody
  - HCV RNA
  - HBV DNA

  Note: For patients with eligible HBV DNA test result at screening, the HBV DNA test will be repeated at Week 14 and Week 38. If the HBV DNA test value is ≥20 IU/mL at Week 14 and Week 38, the medical monitor should be notified.
- Urinalysis: pH, specific gravity, glucose, protein, ketones, blood, RBCs, WBCs, epithelial cells, bacteria, bilirubin, and leukocyte esterase

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 total and specific IgE test
- Blood RNA, blood DNA, serum, plasma, and urine samples for exploratory research on biomarkers (see Table 3)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 3.

Table 3 Proposed Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Biomarkers
Plasma	Prior to active treatment and subsequent timepoints during treatment	• Inflammatory chemokines
Serum	Prior to active treatment and subsequent timepoints during treatment	• IgE, periostin, CCL13, CCL17, sST2, IL-13, IL-33, IL-5, amphiregulin, LIGHT
Breath	Prior to active treatment and subsequent timepoints during treatment	• FeNO
Urine	Prior to active treatment and subsequent timepoints during treatment	• Inflammatory lipids
Blood	Prior to active treatment and subsequent timepoints during treatment	• Eosinophils, neutrophils
RNA extracted from blood	Prior to active treatment and subsequent timepoints during treatment	• Inflammatory gene signature
DNA extracted from blood	Prior to active treatment	• *IL1RL1, IL-33, GLCCI1*

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 optional exploratory research (see Section 4.5.15), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK analysis or immunogenicity analysis will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood RNA, blood DNA, serum, plasma, and urine samples collected for biomarker analysis 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.

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

4.5.15 Optional Samples for Research Biosample Repository

4.5.15.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.15.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.15) will not be applicable at that site.

4.5.15.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to asthma or MSTT1041A:

- Blood samples collected at the randomization visit
- Leftover blood, serum, plasma, RNA, DNA, and urine samples

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.15.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens 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.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens 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.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.15.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.15.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. *global_rcr-withdrawal@roche.com*

A patient's withdrawal from Study GB39242 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GB39242.

4.5.15.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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. For patients randomized to the double-blind treatment period, reasons for withdrawal from the study should only include the following:

- Patient withdrawal of consent at any time
- 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. 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.

Patients who discontinue the study prematurely should return to the clinic for an early termination visit 4 weeks after the last dose of study drug and should be asked to return for safety follow-up visits (see Appendix 1).

Patients who receive placebo during the run-in period but fail to meet the additional eligibility criteria for the double-blind treatment period (see Section 4.1.1.2 and Section 4.1.2.2) should be discontinued from the study and prohibited from re-screening. In addition, these patients should be informed that the first dose given at Visit 2 was a placebo and, therefore, they are not required to return for follow-up visits.

4.6.2 Study Treatment Discontinuation

Reasons for discontinuation of study drug may include, but are not limited to, 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 drug (see Section 5.1.2 for further guidance)
- Investigator or Sponsor determines it is in the best interest of the patient

- 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 5.3.5.7)
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Every attempt should be made to prevent non-compliance with the study protocol. Before permanently discontinuing study treatment, either initiated by the patient or the investigator, an interruption should be considered. Patients who have temporarily discontinued study drug medication for any reason should restart as soon as medically justified in the opinion of the investigator (see Section 5.1.2).

Patients who discontinue study treatment prematurely should be asked to continue with all scheduled study assessments through the end of the study. Patients who are unable or unwilling to complete the study assessments in the double-blind treatment period should complete an early termination visit and both safety follow-up visits (see Appendix 1).

4.6.3 Study and Site Discontinuation

The Sponsor may stop the study for medical or ethical reasons. Possible 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.

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 Conference on 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 anywhere in the world, and clinical development is ongoing. The safety plan for patients in this Phase IIb study is based on clinical experience with MSTT1041A in completed Phase I studies. 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 mg to 560 mg and IV doses ranging from 210 to 700 mg, or atopic asthma patients (n=2) who received a single 700 mg IV dose of MSTT1041A. Potential risks for MSTT1041A are described below. Please refer to the MSTT1041A Investigator's Brochure for a complete summary of safety information.

Measures will be taken to ensure the safety of patients participating in this study, including stringent eligibility criteria that are designed to exclude patients at higher risk for toxicities (see Section 4.1) and close monitoring of patients, including assessment of the nature, frequency, and severity of adverse events. In addition, an iDMC will monitor safety data on an ongoing basis (see Section 3.1.2 for details). Guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Potential Risks for MSTT1041A

5.1.1.1 Immunogenicity

As with administration of any exogenous protein, there is potential risk for development of anti-drug antibodies (ADAs). Such antibodies can be neutralizing with potential for reduced therapeutic effect of the drug or the endogenous protein 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 test positive for antibodies and have clinical sequelae that are considered potentially related to an ADA response may also be asked to return for additional follow-up testing.

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.

No allergic reactions associated with MSTT1041A were observed following a single IV dose or repeat SC doses in cynomolgus monkeys and healthy volunteers. 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, or drug allergies will be excluded from the study according to the exclusion criteria listed in Section 4.1.2.1.

Investigators and health care professionals administering MSTT1041A 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 Adverse Event 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 SAEs 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.

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.

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. MSTT1041A may have additional, unanticipated immune-mediated side effects.

5.1.1.5 Metabolic or Cardiovascular Effects

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). However, 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, no biologically significant changes were exhibited by MSTT1041A.

There is evidence supporting use of the soluble form of the ST2 receptor (sST2) as a prognostic biomarker of cardiovascular disease outcome (Sabatine et al. 2008; Shah and Januzzi 2010; 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 certain forms of cardiovascular disease will be excluded from the study. To observe for any immediate cardiovascular toxicity, ECGs will be monitored (in triplicate). In addition, fasting glucose, HbA_{1c}, and lipid panels will be monitored to observe and/or identify any effects of MSTT1041A on cardiovascular risk factors.

During the study, investigators and healthcare professionals administering MSTT1041A should accurately report all Major Adverse Cardiac Events (MACE) on the Adverse Event eCRF, as instructed in Section 5.2 and Section 5.3, and should report these events immediately to the Sponsor as SAEs if appropriate. Major Adverse Cardiac Events include death due to cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack (TIA), unstable angina or chest pain requiring hospitalization, coronary revascularization, and congestive heart failure (CHF) requiring hospitalization.

5.1.2 Management of Patients Who Experience Specific Adverse Events

5.1.2.1 Treatment Interruption

Study treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If study treatment has been withheld for two or more consecutive dosing visits because of toxicity, the patient should be discontinued from study treatment. However, if the adverse event(s) that led to withholding dosing shows clear evidence of improvement, treatment may be resumed following discussion with and approval by the Medical Monitor. Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures), but must be approved by the Medical Monitor. The investigator and the Medical Monitor will determine an acceptable length of time for the treatment interruption.

5.1.2.2 Guidelines for Treatment Interruption or Discontinuation for Patients Who Experience Hepatotoxicity

Table 4 provides specific guidelines for withholding or discontinuing study drug for patients who experience hepatotoxicity.

Table 4 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×ULN in combination with TBILI >2×ULN or clinical jaundice	Discontinue MSTT1041A.
If criteria for Hy's law are not met: ALT or AST increase that meets at least one of the following criteria: • >8×ULN • >5×ULN for ≥2 weeks • >3×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 criteria for Hy's law are not met: TBILI >3×ULN	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.
Alkaline phosphatase >3×ULN	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.

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, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.1.2.4 Anaphylaxis

For the current guidelines, refer to:

http://www.aaaai.org/practice-resources/statements-and-practice-parameters/practice-parameter-guidelines.aspx

In accordance with the current guidelines, the measurement of serum tryptase and plasma histamine levels should be considered to support a diagnosis of anaphylaxis.

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 patient 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), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at the screening visit
- 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 5.3.5.11)
- 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, or severe, or according to World Health Organization Adverse Drug Reaction Terminology (WHO-ART); 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 include the following:

- 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 5.3.5.7)
- 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.

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 5.3.5.4).

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, *including for patients who discontinue study drug prematurely,* all adverse events will be reported until 20 weeks after the last dose of study drug *or until the last study visit, whichever is later.*

For patients who receive a placebo dose during the run-in period but are not randomly allocated, adverse events will be reported until 6 weeks after the placebo dose.

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 clinic 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 World Health Organization (WHO) toxicity grading scale will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 5 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 6):

- 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 6 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. 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 for injection reactions. 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 for injection reactions.

5.3.5.2 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.

5.3.5.3 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.

5.3.5.4 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. 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.

5.3.5.5 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., alkaline phosphatase and bilirubin 5 $\times$ 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 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 5.3.5.2) 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).

5.3.5.8 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). This includes death attributed to progression of asthma.

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. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

If the death is attributed to progression of asthma, "asthma progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.9 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").

5.3.5.10 Lack of Efficacy or Worsening of Asthma

Medical occurrences or symptoms of deterioration that are anticipated as part of asthma 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 (e.g., an asthma exacerbation). When recording an unanticipated worsening of asthma 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 asthma").

5.3.5.11 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.

The following hospitalization scenarios are not considered to be adverse events:

- 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 because of the expected normal progression of the disease.
  - The patient has not experienced an adverse event.
- The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:
  - Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded 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).

No safety data related to overdosing of MSTT1041A are available.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

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 (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

CRO Medical Monitor contact information:

Medical Monitor: [redacted]

Telephone Nos.: [redacted]

Alternate Genentech Medical Monitor contact information for all sites:

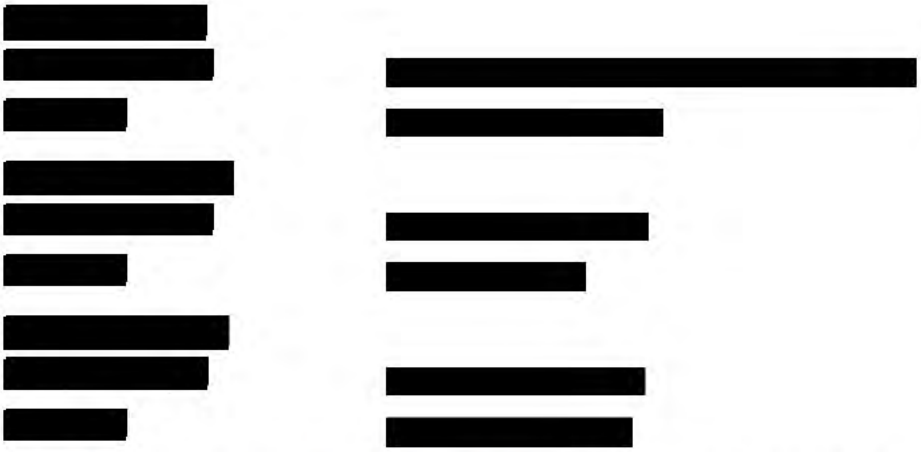
Medical Monitor: [redacted]

Telephone Nos.: [redacted]

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 below:



5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, *including for patients who discontinue study drug prematurely, all* serious adverse events and adverse events of special interest will be reported until 20 weeks after the last dose of study drug *or until the last study visit, whichever is later.*

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 Roche 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 in Section 5.4.2.1. 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 *after the adverse event reporting period* 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 20 weeks after the last 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 in Section 5.4.2.1. 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 paper 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 20 weeks after the last 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 in Section 5.4.2.1. 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. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a paper 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 Abortions

Any 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).

5.4.3.4 Congenital Anomalies/Birth Defects

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).

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, electronic mail, 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 (*see Section 5.3.1*), 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 documents:

- 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.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Asthma exacerbations
- Symptoms assessed as relate to asthma (e.g., cough, wheezing, dyspnea, bronchospasm)

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Analysis of data from the 52–week double-blind treatment period of the study, *defined as the time of randomization (Week 2) through the Week 54 visit,* will be performed when all patients have *either*: (i) completed the Week 54 visit *(including patients who prematurely* discontinued *study* treatment *during* the 52–week double-blind treatment period but completed *study* visits *through* Week 54), or (ii) withdrawn from the study prior to Week 54. In addition, all data from *screening through Week 54* of the study are in the database and have been cleaned and verified. At this point, appropriate Sponsor personnel will be unblinded to patient-level treatment assignment.

Analysis of complete study data, including data from the safety follow-up period, will be performed when all patients have either completed the safety follow-up period or have discontinued early from the study, all data from the study are in the database, and the database is locked.

Aggregate results of the 54-week analysis, summarized by treatment arm, may be reported to the public before completion of the study. However, patients and study site personnel will remain blinded to individual treatment assignments until after the study is

completed (i.e., after all patients have either completed the safety follow-up period or discontinued early from the study), the database is locked, and the study analyses are final.

Detailed specifications of all statistical methods (including scoring of PRO instruments, missing data handling, and *definition of baseline*) will be provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 500 patients will be randomly allocated in a 1:1:1:1 ratio to receive one of three doses of MSTT1041A or placebo. This sample size provides approximately 80% power to detect a 40% reduction in annualized asthma exacerbation rate (AER) between one MSTT1041A arm and the placebo arm, assuming 0.63 exacerbations per patient per year in the placebo arm, a 15% dropout rate, and a two-sided significance level (α) of 0.05.

Enrollment caps will be utilized to ensure adequate power for biomarker subgroup analysis based upon blood eosinophil status at Visit 1. Approximately 30 eosinophil-high patients ($\geq$300 cells/μL) per arm and approximately 95 eosinophil-low patients (<300 cells/μL) per arm will be randomly allocated. The sample size provides approximately 80% power to detect a 50% reduction in annualized AER in the subgroup of eosinophil-high patients assuming 1.0 exacerbation per patient per year in the placebo arm, a 15% dropout rate, a two-sided significance level of 0.15, and 30 patients in each treatment arm having eosinophil-high status. The sample size also provides approximately 67% power to detect a 35% reduction in annualized AER in the subgroup of eosinophil-low patients, assuming 0.5 exacerbations per patient per year in the placebo arm, a 15% dropout rate, a two-sided significance level of 0.15, and 95 patients in each treatment arm having eosinophil-low status.

6.2 SUMMARIES OF CONDUCT OF STUDY

The final analysis will be based on patient data collected through patient discontinuation or study discontinuation, whichever occurs first. The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal 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. All summaries will be presented according to randomized treatment assignment.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Baseline demographics, disease characteristics, and exposure to study drug will be summarized by treatment group using descriptive statistics. For categorical endpoints, the descriptive statistics will include counts and proportions. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, and maximum.

6.4 EFFICACY ANALYSES

Efficacy analyses will be conducted on a modified intend-to-treat (mITT) population, consisting of all randomly allocated patients who received at least one dose of study drug during the 52-week double-blind treatment period, with patients grouped according to the treatment assigned at randomization.

Comparisons of efficacy will be performed between each MSTT1041A dose level and the placebo group. Thus, there are three comparisons:

- MSTT1041A 70 mg with placebo
- MSTT1041A 210 mg with placebo
- MSTT1041A 490 mg with placebo

Hypothesis testing and estimation of treatment effects will be performed with regression models that use data from all four treatment arms at one time.

Type I error will be controlled using a *fixed sequence method across dose levels for the primary endpoint and within a single dose level for selected secondary endpoints*, as described in Section 6.4.1. *The testing order of the fixed sequence will be provided* in the SAP.

Unless otherwise noted, analyses of efficacy outcome measures will be adjusted by blood eosinophil level (<150, ≥150 to <300, ≥300 cells/μL), number of *documented* asthma exacerbations *(as defined in Appendix 12)* in the *previous* 12 months (1–2, ≥3), total daily ICS dose (<1000 μg, ≥1000 μg of fluticasone proportionate or equivalent), and *country*.

6.4.1 Primary Efficacy Endpoint

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

Incidence of asthma exacerbations *from baseline through Week 54*, with asthma exacerbation defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in one or both of the following:

- Hospitalization or emergency department visit with *administration of* systemic corticosteroid treatment
- *Treatment with* systemic corticosteroids for ≥3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥3 days

The annualized AER will be estimated for each arm as the total number of protocol-defined asthma exacerbations observed over the treatment period divided by total patient–weeks at risk. For each individual patient, weeks at risk will be computed as the number of days from the date of randomization to the date of treatment

completion or discontinuation, divided by 7 days. Poisson regression with over-dispersion will be used in the analysis to assess the treatment effect on the rate of asthma exacerbations. Analyses will be based on observed exacerbations, with no imputation for premature discontinuation. The Poisson regression model will be adjusted for baseline covariates, as described in Section 6.4. In addition, a patient's time at risk, as defined above, will be computed and used as an offset term in the model.

Statistical testing in the overall mITT population will be performed as a two-sided test. Type I error across dose levels will be controlled using a *fixed sequence method.*

Further details will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 54
- Time to first asthma exacerbation during the 52-week double-blind treatment period
- *Achievement of improvement in AQLQ(S) score, defined as an increase of ≥0.5 points from baseline to Week 54*
- Achievement of improvement in ACQ-5 score, defined as a decrease of ≥0.5 points *from baseline to Week 54*
- Absolute change in patient-reported use of short-acting rescue therapy *from baseline to* Week 54
- Proportion of weeks without patient-reported, asthma-related, nighttime awakenings from *baseline* through Week 54
- Absolute change in patient-reported daytime asthma symptom severity as measured by the ADSD *from baseline to Week 54*

The secondary endpoints will be tested in the mITT population. Statistical models will be adjusted for baseline covariates, as described in Section 6.4. Continuous endpoints will be analyzed using mixed-model repeated measures (MMRM). Time-to-event endpoints will be analyzed using a Cox proportional hazards regression model. Improvement in ACQ and *AQLQ(S)* will be presented as proportion of responders, defined as achieving a minimally important difference (MID) in change score from the randomization visit, and will be analyzed using a logistic regression model. Descriptive summaries for continuous endpoints will include mean, standard deviation, median, and range. Descriptive summaries for categorical endpoints will include counts and proportions. *To control for Type I error across multiple secondary endpoints within a dose level, a hierarchical analysis of selected secondary endpoints will be performed according to a pre-specified order.* Further details will be described in the SAP.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Incidence of asthma exacerbations *from baseline through Week 54*, with asthma exacerbation defined as in Appendix 12
- Incidence of severe asthma exacerbations *from baseline through Week 54, with severe asthma exacerbation* defined as asthma symptoms requiring hospitalization or resulting in death attributed to asthma
- *Incidence of asthma exacerbations from baseline through Week 70*
- Relative change in pre-bronchodilator FEV_1 (liters) *from baseline to* Week 54
- Absolute change in pre-bronchodilator FEV_1 (percentage predicted) *from baseline to* Week 54
- Absolute change from the randomization visit in pre-bronchodilator FEV_1 (liters) at Week 70
- *Achievement of improvement in SGRQ score, defined as a decrease of ≥4 points from baseline to Week 54*
- Achievement of improvement in ACQ-7 score, defined as a decrease of ≥0.5 points *from baseline to Week 54*
- Clinician's global impression of change patient's asthma symptoms, as assessed through use of the CGIC, *from baseline to Week 26 and Week 54*
- Incidence of asthma exacerbations *from baseline through Week 54* within each of the eosinophil-high (≥300 cells/μL) and eosinophil-low (< 300 cells/μL) groups
- Absolute change *from baseline to Week 54* in pre-bronchodilator FEV_1 (liters) within each of the eosinophil-high (≥ 300 cells/μL) and eosinophil-low (< 300 cells/μL) groups
- Incidence of asthma exacerbations *from baseline through Week 54* by *IL1RL1* genotype
- Absolute change in pre-bronchodilator FEV_1 (liters) *from baseline to Week 54* by *IL1RL1* genotype

Analysis of exploratory efficacy endpoints will be described in the SAP.

6.5 SAFETY ANALYSES

Safety analyses will be based on all patients who receive at least one dose of study drug during the 52-week double-blind treatment period with patients grouped according to the actual treatment received (MSTT1041A or placebo).

Safety will be assessed through summaries of adverse events, laboratory test results, ECGs, and vital signs. Verbatim descriptions of treatment-emergent adverse events will be coded, and their incidence will be summarized by treatment arm. A treatment-emergent adverse event is defined as any new adverse event reported or worsening of an existing condition on or after the first dose of study drug during the

52-week double-blind treatment period. In addition, separate summaries will be generated for serious adverse events, adverse events of special interest (AESI), deaths, pregnancies, malignancies, anaphylaxis events, major cardiac adverse events, adverse events leading to discontinuation from the study, and adverse events leading to discontinuation of study drug.

Safety assessments will also be conducted on all patients who receive a placebo dose during the run-in period, regardless of whether or not the patient is randomly allocated into the double-blind treatment period. These safety analyses will consider adverse events that occur during the 2-week run-in period and will be followed until the event is resolved.

6.6 PHARMACOKINETIC ANALYSES

The concentration of MSTT1041A in serum samples will be determined using an immunoassay. Listings of individual serum MSTT1041A concentration-versus-time data will be reported. Summary statistics (mean and standard deviation) will be tabulated for each arm. Additional PK analyses will be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

Baseline prevalence and post-baseline incidence of ADA to MSTT1041A will be summarized. ADA response and potential correlation of response to relevant clinical safety and activity endpoints will be assessed for all subjects treated during the study.

The immunogenicity analyses will include patients with at least one postdose ADA assessment, with patients grouped according to treatment received.

Patients are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post–baseline samples is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative at baseline and all post–baseline samples are negative or if they are ADA positive at baseline but do not have any post–baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The incidence and percentage of patients who develop anti-MSTT1041A antibodies (binding) at any time will be tabulated by treatment group.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

6.8 BIOMARKER ANALYSES

Potential predictive biomarkers of MSTT1041A response will be assessed in primary and key secondary endpoints (e.g., asthma exacerbation rate, FEV_1) to assess if a subset of patients derives enhanced clinical benefit from MSTT1041A. Predictive biomarker candidates include, but are not limited to, blood eosinophils, and germline mutations in *IL1RL1*.

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

Further details related to biomarker analyses will be described in the SAP.

6.9 EXPLORATORY PSYCHOMETRIC VALIDATION

Data from the ADSD nighttime symptoms, the PGIS nighttime symptoms, PGIS daytime symptoms, and PGIC symptoms questions will be used in separate analyses to explore psychometric properties of the ADSD. The exploratory psychometric validation endpoints are as follows:

- *Change in patient-reported nighttime asthma symptom severity, as measured by the ADSD, from baseline to Week 26 and Week 54*
- Patient's global impression of change from the randomization visit in asthma symptoms as assessed through use of the PGIC *from baseline to* Week 26 and Week 54
- Patient's global impression of severity of asthma symptoms as assessed through use of the PGIS at *Week 14,* Week 26, and Week 54

6.10 EXPLORATORY HEALTH STATUS ANALYSES

Health status utility scores will be calculated as the change from *baseline* in EQ-5D-5L index-based and Visual Analogue Scale (VAS) scores at Week 54.

The EQ-5D-5L health status data will be used for generating health utility scores for use in economic models for reimbursement. Patients without post–randomization visit assessments will be excluded from this analysis. Further analysis details will be described in the SAP.

6.11 OPTIONAL INTERIM ANALYSES

No efficacy interim analyses are planned at this time. However, in order to adapt to information that may emerge during the course of this study, (e.g. based on compelling new competitor data or additional information on biomarker characteristics that emerges during the conduct of the trial), the Sponsor may choose to conduct one interim efficacy

analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity, should such an optional interim analysis be executed.

The Sponsor will remain blinded to individual treatment assignment. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter to ensure integrity.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the SAP, and the SAP will be finalized prior to the conduct of the interim analysis. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis will be adjusted to maintain the protocol-specified overall type I error rate, as described in the standard Lan-DeMets theory.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance. If the predictive probability is below 20%, the iDMC should consider recommending that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC charter. An interim analysis that might lead to stopping the study for futility will not occur before at least 40% information has been accumulated.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A CRO will be responsible for the 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC study specification document that describes the quality checking to be performed on the data. Central laboratory 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 data will be collected through the use of an electronic device provided by a vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The electronic data are available for viewing only via secure access on a web server. Only identified and trained users may view the data, and their actions 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.

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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use electronic devices to capture PRO data. The data will be automatically transmitted wirelessly after entry to a centralized database maintained by the electronic device vendor.

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 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, patient-reported outcomes, 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, the investigators and institutions must provide the Sponsor or a delegate 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 PRO and ClinRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 the analyses, data derived from exploratory biomarker specimens 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 Roche 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.

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 (i.e., last patient last visit [LPLV]).

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.

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 iDMC 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. Data reported by patients regarding their asthma symptoms and medication use will be captured electronically via handheld mobile devices. Patients will be randomized through use of an IxRS.

9.5 PUBLICATION 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, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.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).

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Appendix 1 Schedule of Activities

	Screen Visit [a]	Run-In Visit [b]	Pre-Rand.	Post-Rand.	Double-Blind Treatment Period: Treatment Every 28 (±N) Days [c]														Safety Follow-Up Period: Follow-Up Visit	Safety Follow-Up Period: EoS Visit	ET Visit [c]	UV [d]
Week	-4 to -2	0	2		4	6	10	14	18	22	26	30	34	38	42	46	50	54	62	70	–	–
(Visit Window in Days) [e]					(±3)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±14)	(±14)	–	–
Visit	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	–	–
Informed consent	x																					
Demographic data	x																					
Medical history and baseline conditions	x																					
Atopy status [f]	x																					
ACQ [g]	x	x	x								x							x				
PGIC [g]											x							x				
AQLQ(S) [g]			x								x							x				
SGRQ [g]			x								x							x				
EQ-5D-5L [g]			x															x				
CGIC [h]											x							x				
Complete physical examination [i]	x																					
Limited physical examination [j]			x								x							x		x	x	x
Weight (BMI) and height (height at screening only)	x																	x		x	x	
Vital signs [k]	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1 Schedule of Activities (cont.)

	Screen Visit [a]	Run-In Visit [b]	Pre-Rand.	Post-Rand.	Double-Blind Treatment Period: Treatment Every 28 (±N) Days [c]														Safety Follow-Up Period: Follow-Up Visit	Safety Follow-Up Period: EoS Visit	ET Visit [c]	UV [d]
Week	-4 to -2	0	2		4	6	10	14	18	22	26	30	34	38	42	46	50	54	62	70	–	–
(Visit Window in Days) [e]					(±3)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±14)	(±14)	–	–
Visit	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	–	–
ECG (12-lead; triplicate) [l]	x	x	x		x						x							x		x	x	
Asthma exacerbation		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Distribute eDiary	x																					
Retrieve eDiary																		x				
Review eDiary data		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Evaluation of patient inhaler, peak flow meter, and spirometry techniques	x																					
eDiary [m]	Daily [m]																					
Peak expiratory flow rate [n]	Daily [n]																					
Pre-bronchodilator spirometry [o]	x	x	x [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x
Post-bronchodilator spirometry (reversibility)	x [q]																					
FeNO [r]	x	x	x [p]		x	x		x			x			x				x				x
TB test	x																					
Chest X-ray, TB worksheet [s]	x																					
Pregnancy test [t]	x	x	x [p]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1 Schedule of Activities (cont.)

	Screen Visit [a]	Run-In Visit [b]	Pre-Rand.	Post-Rand.	Double-Blind Treatment Period: Treatment Every 28 (±N) Days [c]														Safety Follow-Up Period: Follow-Up Visit	Safety Follow-Up Period: EoS Visit	ET Visit [c]	UV [d]
Week	-4 to -2	0	2		4	6	10	14	18	22	26	30	34	38	42	46	50	54	62	70	–	–
(Visit Window in Days) [e]					(±3)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±14)	(±14)	–	–
Visit	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	–	–
Hematology [u]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	
Chemistry [v]	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	
Fasting lipids & glucose [w,x]		x				x												x		x	x	
HbA_{1c}	x					x												x		x	x	
Hepatitis B & C serologies [y]	x																					
Quantitative hepatitis C RNA PCR [z]	x																					
Hepatitis B DNA [aa]	x							x						x								
Urinalysis [bb]	x			x							x							x		x	x	
Serum specific IgE				x																		
PK sample (all patients) [l, cc]				x		x	x	x			x			x			x	x		x	x	
Additional PK samples (selected sites/patients)		See Appendix 2																				
Anti-drug antibodies				x				x			x			x				x		x	x	
Plasma and serum samples for biomarker analysis		x		x	x		x	x			x			x				x		x	x	x

Appendix 1 Schedule of Activities (cont.)

	Screen Visit [a]	Run-In Visit [b]	Pre-Rand.	Post-Rand.	Double-Blind Treatment Period: Treatment Every 28 (±N) Days [c]														Safety Follow-Up Period: Follow-Up Visit	Safety Follow-Up Period: EoS Visit	ET Visit [c]	UV [d]
Week	-4 to -2	0	2		4	6	10	14	18	22	26	30	34	38	42	46	50	54	62	70	–	–
(Visit Window in Days)[e]					(±3)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±5)	(±14)	(±14)	–	–
Visit	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	–	–
Urine sample for biomarker analysis		x		x	x			x			x							x				x [dd]
Blood sample for RNA analysis (PAXgene tube)				x														x				x
Blood sample for specified DNA SNP analysis [ee]				x																		
Blood sample for RBR (DNA WGS) (optional, if applicable to site) [ff]				x																		
Single-blind study drug (placebo) administration [gg]		x																				
Study drug administration (MSTT1041A or placebo) [hh]				x [gg]		x [gg]	x [gg]	x [gg]	x [gg]	x	x	x	x	x	x	x	x					
Concomitant medications [ii]	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [jj]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1 Schedule of Activities (cont.)

ACQ = Asthma Control Questionnaire; ACQ-7 = Asthma Control Questionnaire (7 items); ACQ-5 = Asthma Control Questionnaire (5 items); AQLQ = Asthma Quality-of-Life Questionnaire; BMI = body mass index; CGIC = Clinician Global Impression of Change; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic Diary; EoS = End-of-Study; ET = early termination; EQ-5D = EuroQol 5-Dimension Questionnaire; FeNO = fractional exhaled nitric oxide; HbA1c = hemoglobin A1c; HbsAg = hepatitis B surface antigen; HbsAb = hepatitis B surface antibody; HbcAb = hepatitis B core antibody; HCV = hepatitis C virus; IgE = Immunoglobulin E; PCR = polymerase chain reaction; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; PPD = purified protein derivative; PRO = patient-reported outcome; Q4W = every 4 weeks; QFT = QuantiFERON® test; Rand. = randomization; RBR = Roche Biosample Repository; SC = subcutaneous; Screen = screening; SGRQ = St. George's Respiratory Questionnaire; TB = tuberculosis; UV = unscheduled visit; WGS = whole genome sequencing.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Patients who are unable to tolerate study drug will discontinue study drug but should continue follow-up for all other study procedures and measurements through the end of the study.

[a] The screening period may be between 12 and 28 days after study consent, as described in Section 4.5.2.

[b] The run-in visit should be scheduled 2 weeks (±5 days) prior to the randomization visit.

[c] Patients who are randomly allocated into the 52-week double-blind treatment period but discontinue study drug should continue follow-up for all other study procedures and measurements through the end of the study. Patients who discontinue from the study prior to Week 50 should return to the site for an early termination visit 4 weeks (±5 days) after the last dose of study drug and then enter the safety follow-up period.

[d] Patients who experience symptoms consistent with an asthma exacerbation as defined in Appendix 12 will be asked to come to the clinic for an unscheduled visit. Patients will be asked to bring a urine sample and will undergo additional evaluations.

[e] Visit windows are relative to randomization visit.

[f] Atopy status (atopic or non-atopic) will be assessed on the basis of historical documentation (e.g., patient's medical records), as described in Section 4.5.4.

[g] PRO questionnaires will be completed before the patient receives any information on disease status, prior to the performance of other site-visit assessments and procedures, and prior to the administration of study treatment. Both the full (7 items) and 5 item (ACQ-5) version of the ACQ will be administered in this study. The ACQ-5 is part of the eligibility criteria and will be administered at screening and run-in visits. The full ACQ-7 will be administered at the remaining timepoints as indicated in the Schedule of Activities (randomization visit, Week 26, and Week 54).

[h] Clinicians will complete the CGIC after they have examined the patient and evaluated data that support an overall health assessment, which may include, but are not limited to, FEV_1, FeNO, and medical records.

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed prior to dosing at Visit 2 on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 1 Schedule of Activities (cont.)

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

[k] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is *ideally* in a seated position, and temperature. Record abnormalities observed prior to dosing at Visit 2 on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] If mean QTcF is >500 ms and/or >60 ms longer than the baseline value, a PK sample will be obtained (if the visit does not already include a scheduled PK sample), see Section 4.5.9. 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.

[m] Patients will use an electronic diary ("eDiary") to record assessments twice a day: in the morning, diary items are asthma symptoms experienced during the night (Asthma Daily Symptom Diary - nighttime), nighttime awakenings, and short-acting rescue medication use, and a single item assessment of overnight symptom severity (PGIS). In the evening, daytime symptom severity (Asthma Daily Symptom Diary - ADSD daytime symptoms), short-acting rescue medication use, and a single-item assessment of daytime symptom severity. Most daily diary items will be completed everyday through Week 54. A single-item compliance with daily controller medication will also be included in the evening diary.

[n] On the days of study visits, if the patient had not performed the morning PEFR measurement before arrival at the clinic, the PEFR should be measured at the clinic.

[o] A patient's visit must be rescheduled if the patient has used a bronchodilator within the time window defined in Section 4.5.12.1. To accommodate the rescheduled visit, the usual visit window during the treatment period may be extended to ±4 days for Week 4 or ±6 days for Weeks 6–54.

[p] Patients who are not eligible for randomization into the double-blind treatment should be discontinued from the study, and they are not eligible for re-screening. In addition, these patients should be informed that the first dose given at Visit 2 was a placebo and, therefore, there is no additional requirement for follow-up visits.

[q] Patients who meet all eligibility requirements at screening with the exception of morning pre-bronchodilator FEV1 of 40%-80% or post-bronchodilator reversibility of FEV_1 of ≥12% and ≥150 mL are allowed additional attempt(s) to meet the reversibility criteria within the screening or run-in period as described in Section 4.5.2.

[r] Please refer to Section 4.5.13 for FeNO procedure restrictions.

[s] 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 prior to screening and the report is available for review. A chest CT scan may substitute for a chest X-ray. Chest X-rays should only be performed if patients first meet all other study inclusion criteria.

[t] 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 is positive, it must be confirmed by a serum pregnancy test.

Appendix 1 Schedule of Activities (cont.)

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

[v] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, magnesium, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH.

[w] Lipid panel includes cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.

[x] If patient has not fasted for 8 hours, patient must return to site for fasting blood draw. Patients will be given 2 weeks to return for a fasting blood draw.

[y] Includes hepatitis B surface antibody, hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody.

[z] Measurement of HCV RNA with use of a quantitative PCR assay is only required when the patient was tested positive for HCV antibody at screening and has a known history of HCV antibody positivity with past documentation of undetectable HCV RNA, either with or without history of anti-viral treatment. Patients with newly diagnosed HCV antibody positivity are not eligible for this study and, therefore, do not require measurement of HCV RNA.

[aa] For patients with a HbsAg negative, HbsAb positive, and HbcAb positive test result at screening only, as described in Section 4.1.2.1. Patients with a HBV DNA test value ≥20 IU/mL at screening are not eligible. Patients with a HBV DNA test value <20 IU/mL at screening must undergo re-testing of HBV DNA at Week 14 and Week 38. If the HBV DNA test value at Week 14 and Week 38 is ≥20 IU/mL, the medical monitor should be notified.

[bb] Urinalysis includes pH, specific gravity, glucose, protein, ketones, blood, RBCs, WBCs, epithelial cells, bacteria, bilirubin, and leukocyte esterase.

[cc] PK samples to be collected prior to study drug administration.

[dd] Patients will be supplied with urine collection cups to allow for urine sample collection at home prior to coming to the clinic for an unscheduled visit. If the patient did not bring in a urine sample collected at home, the patient will be asked to provide the urine sample at the visit.

[ee] If the DNA is not collected at the randomization visit for any reason, it may be collected at any later timepoint.

[ff] Patients must provide consent to participate. Not applicable for a site that has not been granted approval for RBR sampling. If the DNA is not collected at the randomization visit for any reason, it may be collected at any later timepoint.

[gg] All patients will be held for observation for at least 2 hours after the single-blind placebo dose and after the first five double-blind doses. Dosing on subsequent dosing days should include a minimum length of observation time of 15 minutes, and longer in the event of an injection site reaction, approximately 60 minutes or other, as determined by the investigator.

[hh] Patients will receive MSTT1041A 70 mg, 210 mg, or 490 mg or placebo, administered as four SC injections (one in each quadrant of the abdomen) every 28 (±N) days (Q4W). More than *one dose* should not be administered within any 21-day period. If the dosing window is missed, that dose will not be administered and the next dose will be administered at the next scheduled dosing date.

[ii] Asthma medications used by the patient from 12 months prior to screening through the end-of-study visit should be recorded on the appropriate eCRF. Other medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 3 month prior to screening through the end-of-study visit should be recorded on the Concomitant Medications eCRF.

Appendix 1 Schedule of Activities (cont.)

[jj] 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, *including for patients who discontinue study drug prematurely,* all adverse events will be reported until 20 weeks after the last dose of study drug *or until the last study visit, whichever is later. For patients who receive a placebo dose during the run-in period but are not randomly allocated, adverse events will be reported until 6 weeks after the placebo dose.* 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). 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.

Appendix 2
Schedule of Additional Pharmacokinetic Samples for Selected Patients

Visit [a]	Timepoint	Sample Type
3a	3 days after Visit 3 (±1 day)	MSTT1041A PK (serum)
3b	7 days after Visit 3 (±1 day)	MSTT1041A PK (serum)
4	Visit 4 (see schedule of activities [Appendix 1])	MSTT1041A PK (serum)
10a	3 days after Visit 10(±1 day)	MSTT1041A PK (serum)
10b	7 days after Visit 10 (±1 day)	MSTT1041A PK (serum)
10c	10 days after Visit 10 (±1 day)	MSTT1041A PK (serum)

PK = pharmacokinetic.

Note: Additional PK samples will be collected from approximately 80 patients at selected sites. PK samples are to be collected at approximately the same time each day.

[a] PK sampling visits that are between regular study visits are given a letter suffix. These timepoint designations will not be shown in the schedule of activities in Appendix 1.

Appendix 3
Examples of Estimated Equipotent Daily Doses of Inhaled Corticosteroids in the United States

The following table lists inhaled corticosteroids commonly used in the United States at the time of protocol publication, to serve as examples of eligible corticosteroid doses. **Country-specific tables will be distributed to participating sites and should be used when determining eligibility for individual patients.**

Generic ICS/combination Name	Formulation	Brand Name	ICS Dose (μg)	Dose (μg) equivalent to 500 μg/d FP[a]	Dose (μg) equivalent to 1000 μg/d FP
Beclomethasone dipropionate	HFA-MDI	Qvar®	40,80	480[b]	960
Budesonide	DPI	Pulmicort Flexhaler®	90, 180	720	1440
Budesonide	DPI	Pulmicort Turbuhaler®	200	800	1600
Budesonide/formoterol	HFA-MDI	Symbicort®	80, 160	640	1280
Ciclesonide	HFA-MDI	Alvesco®	80, 160	320	640
Fluticasone propionate/ salmeterol	HFA-MDI	Advair® HFA	45, 115, 230	460	920
Fluticasone propionate	HFA-MDI	Flovent® HFA	44, 110, 220	440	880
Fluticasone propionate/ salmeterol	DPI	Advair Diskus®	100, 250, 500	500	1000
Fluticasone propionate	DPI	Flovent Diskus®	50, 100, 250	500	1000
Fluticasone furoate	DPI	Breo Ellipta®	100, 200	100	200[c]
Fluticasone furoate	DPI	Arnuity Ellipta®	100, 200	100	200[c]
Mometasone furoate/ formoterol	HFA-MDI	Dulera®	100, 200	400	800
Mometasone furoate	DPI	Asmanex Twisthaler®	110, 220	440	880

DPI = dry powder inhaler; FP = fluticasone propionate; HFA = hydrofluoroalkane; MDI = metered dose inhaler.
Note: Dose information is intended as a guide when determining eligibility for the studies and is not intended as a prescribing guide.
[a] GINA 2015.
[b] EPR3 2007.
[c] Busse et al. 2012.

Appendix 4 Daily Diary

MORNING DIARY QUESTIONS

Asthma Daily Symptom Diary (ADSD): Night Time Symptoms

[Administered on 3 non-consecutive days during screening; Run-in Visit; Randomization Visit; Daily for 7 days prior to Week 26; Daily for 7 days prior to Week 54]

[INSTRUCTION 1M] We would like you to complete this diary every morning when you get up.

[INSTRUCTION 2M] For each question, please choose the number that best describes your experience.

[INSTRUCTION 3M] Please answer each question by thinking about your asthma symptoms last night from when you went to bed until now.

[ITEM 1] Please rate your difficulty breathing at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 2] Please rate your wheezing at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

Appendix 4 Daily Diary (cont.)

MORNING DIARY QUESTIONS

[ITEM 3] Please rate your shortness of breath at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 4] Please rate your chest tightness at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 5] Please rate your chest pain at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

Appendix 4 Daily Diary (cont.)

MORNING DIARY QUESTIONS

[ITEM 6] Please rate your cough at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 7] Please rate the feeling of mucus (phlegm) in your chest at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

Appendix 4 Daily Diary (cont.)

MORNING DIARY QUESTIONS

Nighttime Awakening Due To Asthma

[Administered every morning from screening through Week 54]

Did any of your asthma symptoms wake you up since you went to bed last night?

- ☐ Yes
- ☐ No

Short-Acting Symptom Relief Medication

[Administered every morning from screening through Week 54]

After going to sleep last night, did you take any rescue medication for your asthma symptoms (shortness of breath, cough, wheeze, or chest tightness)?

- ☐ No, I did not take any rescue medication
- ☐ Yes, I used a rescue inhaler
- ☐ Yes, I used a nebulizer (breathing machine)
- ☐

Patient Global Impression of Severity (PGIS)

[Administered at 4 time points: Run-in Visit; Randomization Visit; one day prior to Week 26; one day prior to Week 54]

Overall, please rate your asthma symptoms since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
No Symptoms										**As bad as you can imagine**

Appendix 4 Daily Diary (cont.)

EVENING DIARY QUESTIONS

Asthma Daily Symptom Diary (ADSD): Day Time Symptoms

[Administered every evening from Screening through Week 54]

[INSTRUCTION 1E] We would like you to complete this diary every night before you go to bed.

[INSTRUCTION 2E] For each question, please choose the number that best describes your experience.

[INSTRUCTION 3E] Please answer each question by thinking about your asthma symptoms today, from when you got up this morning until now.

[ITEM 1] Please rate your difficulty breathing at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 2] Please rate your Wheezing at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 3] Please rate your shortness of breath at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

Appendix 4 Daily Diary (cont.)

EVENING DIARY QUESTIONS

[ITEM 4] Please rate your chest tightness at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 5] Please rate your chest pain at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 6] Please rate your cough at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 7] Please rate the feeling of mucus (phlegm) in your chest at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

Appendix 4 Daily Diary (cont.)

EVENING DIARY QUESTIONS

Short-Acting Symptom Relief Medication

[Administered every evening from Screening through Week 54]

Did you take any rescue medication for your asthma symptoms today (shortness of breath, cough, wheeze, or chest tightness)?

- ☐ No, I did not take any rescue medication
- ☐ Yes, I used a rescue inhaler
- ☐ Yes, I used a nebulizer (breathing machine)

Patient Global Impression of Severity (PGIS)

[Administered at 5 time points: Run-in Visit; Randomization Visit; one day prior to Week 14; one day prior to Week 26; one day prior to Week 54]

Overall, please rate your asthma symptoms since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
No Symptoms										**As bad as you can imagine**

Appendix 5 Asthma Control Questionnaire (ACQ)

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

™

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DECEMBER 2002

Revised September 2010
ACQ-SA North American English Version

Appendix 5 Asthma Control Questionnaire (cont.)

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID: _____

DATE: _____

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal

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ACQ-SA North American English Version

Appendix 5 Asthma Control Questionnaire (cont.)

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID: _____

DATE: _____

5.	In general, during the past week, how much of the time did you **wheeze?**	0	Not at all
		1	Hardly any of the time
		2	A little of the time
		3	A moderate amount of the time
		4	A lot of the time
		5	Most of the time
		6	All the time
6.	On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg., Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0	None
		1	1 - 2 puffs/inhalations most days
		2	3 - 4 puffs/inhalations most days
		3	5 - 8 puffs/inhalations most days
		4	9 - 12 puffs/inhalations most days
		5	13 - 16 puffs/inhalations most days
		6	More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7.	FEV_1 pre-bronchodilator:	0	> 95% predicted
		1	95 - 90%
	FEV_1 predicted:	2	89 - 80%
		3	79 - 70%
	FEV_1 %predicted:	4	69 - 60%
	(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	5	59 - 50%
		6	< 50% predicted

Revised September 2010
ACQ-SA North American English Version

Appendix 6 Asthma Quality of Life Questionnaire with Standardised Activities (AQLQ(S))

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED

™

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Modified September 2010
AQLQ(S)-SA North American English Version

Appendix 6 Asthma Quality of Life Questionnaire (cont.)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES (tasks you have to do at work*) *If you are not employed or self-employed, these should be tasks you have to do most days.	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

Appendix 6 Asthma Quality of Life Questionnaire (cont.)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

Appendix 6 Asthma Quality of Life Questionnaire (cont.)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of he Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

Appendix 6 Asthma Quality of Life Questionnaire (cont.)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

Appendix 6 Asthma Quality of Life Questionnaire (cont.)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

Appendix 7 St. George's Respiratory Questionnaire (SGRQ)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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Appendix 7 St. George's Respiratory Questionnaire (cont.)

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (☐ *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (☐ *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (☐ *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐ less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (☐ *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (☐ *one*:
- No ☐
- Yes ☐

Appendix 7 St. George's Respiratory Questionnaire (cont.)

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (☐ *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problems ☐

If you have ever held a job:

Please check (☐ *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (☐ ***the box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

USA / US English version

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath these days.

	For each statement please check (☐ ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you these days.

	For each statement, please check (☐ ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (☐ ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

USA / US English version

continued...

Appendix 7 St. George's Respiratory Questionnaire (cont.)

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	True	False
For each statement, please check (☐) ***the box*** that applies to you ***because of your respiratory problems***:		
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	True	False
For each statement, please check (☐) ***the box*** that applies to you ***because of your respiratory problems***:		
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

USA / US English version

continued...

Appendix 7 St. George's Respiratory Questionnaire (cont.)

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

USA / US English version

Appendix 8 Clinician Global Impression of Change

Clinician Global Impression of Change (CGIC)

How would you rate the change in the subject's asthma symptoms since they started taking the study drug?

- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ No change
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

Appendix 9 Patient Global Impression of Change

Patient Global Impression of Change (PGIC)

How would you rate the change in your asthma symptoms since starting the study drug?

- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ No change
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

Appendix 10 EuroQol 5-Dimension Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the USA

Appendix 10 EuroQol 5-Dimension Questionnaire (cont.)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

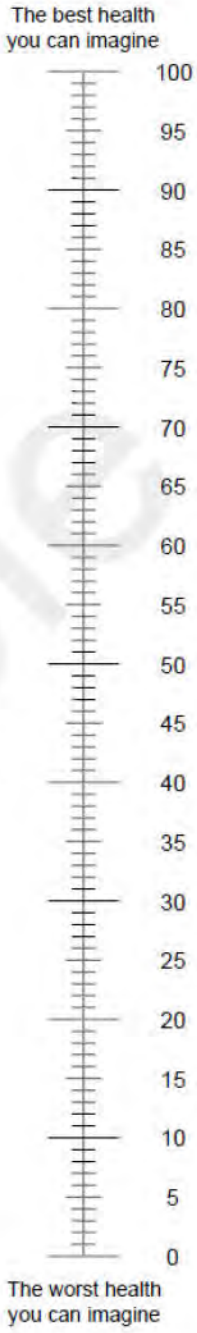
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix 10 EuroQol 5-Dimension Questionnaire (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 11 Compliance With Asthma Controller Medication

[Included in evening daily from screening through Week 54]

Did you take your preventive inhaler (medications) today?

☐ Yes

☐ No

Appendix 12
Definition of Asthma Exacerbation for Inclusion Criteria and Reporting of Adverse Events

Asthma exacerbation is defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in one or both of the following:

- Hospitalization or emergency department, urgent care visit or urgent unscheduled office visit requiring administration of asthma treatment, such as bronchodilators and/or systemic corticosteroids, in addition to baseline controller medications
- Treatment with systemic corticosteroids for ≥3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥3 days

Severe asthma exacerbation is defined as asthma symptoms requiring hospitalization or resulting in death attributed to asthma.