PROTOCOL

TITLE:	**A PHASE IIa, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF MTPS9579A IN PATIENTS WITH ASTHMA REQUIRING INHALED CORTICOSTEROIDS AND A SECOND CONTROLLER**
PROTOCOL NUMBER:	GB41149
VERSION NUMBER:	4
EUDRACT NUMBER:	2019-000795-41
IND NUMBER:	[redacted]
NCT NUMBER:	NCT04092582
TEST PRODUCT:	MTPS9579A (RO7198434)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Sep-2021 03:41:26	Company Signatory	[redacted]

CONFIDENTIAL

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on title page	Germany	4	See electronic date stamp on title page
3	22 November 2019	Germany	3	1 April 2020
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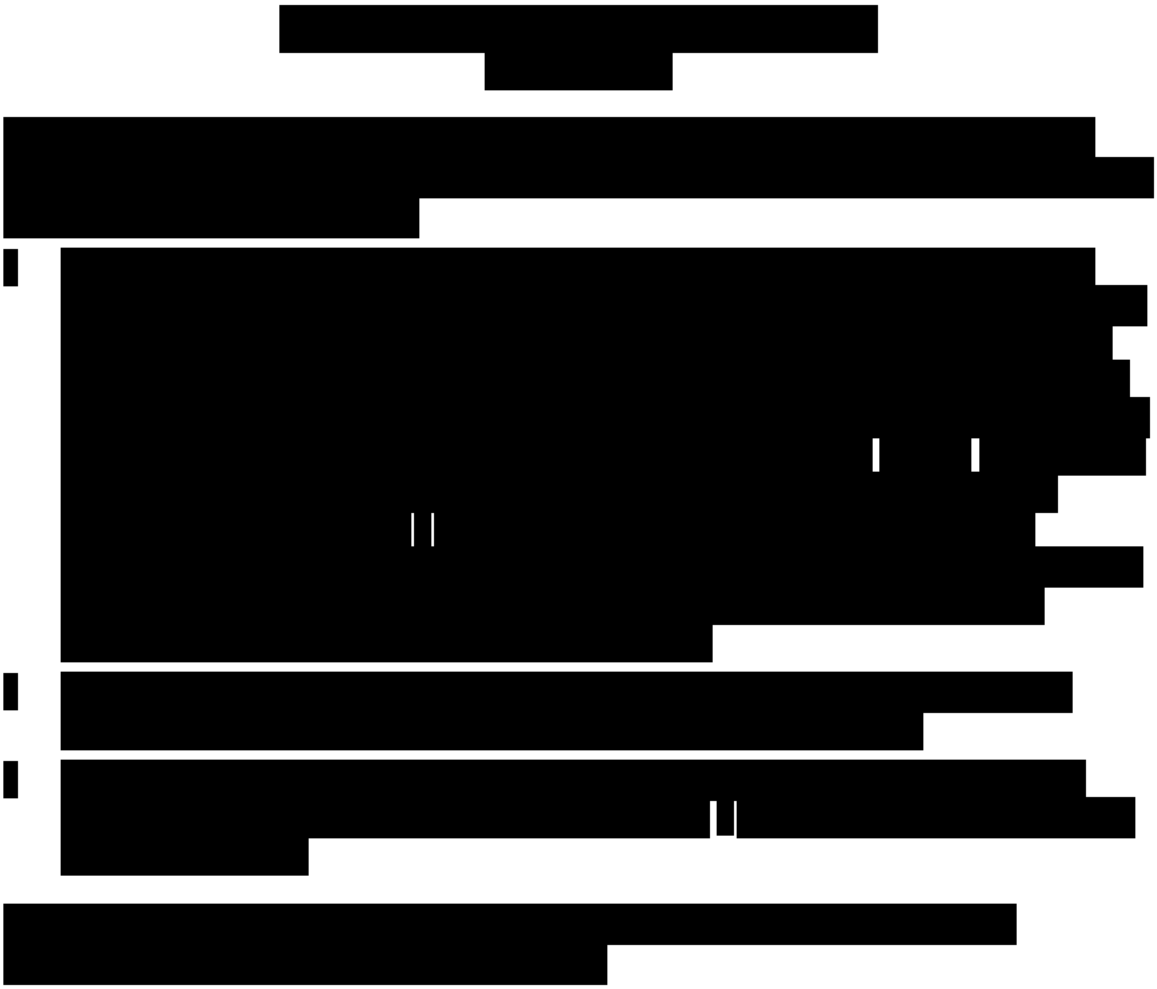

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIa, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF MTPS9579A IN PATIENTS WITH ASTHMA REQUIRING INHALED CORTICOSTEROIDS AND A SECOND CONTROLLER**
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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 to the Sponsor Representative.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIa, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF MTPS9579A IN PATIENTS WITH ASTHMA REQUIRING INHALED CORTICOSTEROIDS AND A SECOND CONTROLLER**
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EUDRACT NUMBER:	2019-000795-41
IND NUMBER:	[redacted]
TEST PRODUCT:	MTPS9579A (RO7198434)
PHASE:	IIa
INDICATION:	Asthma
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of MTPS9579A compared with placebo in patients with uncontrolled asthma despite the use of inhaled corticosteroids (ICS) and a second controller. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of MTPS9579A compared with placebo on the basis of the following endpoint:

- Time to first CompEx event, a composite endpoint defined as time from randomization to first asthma exacerbation or diary worsening during the 48-week double-blind treatment period (from the randomization visit [Week 2] to end of treatment [Week 50]). Asthma exacerbations and diary worsening are defined as follows:

  Asthma exacerbations are assessed by the investigator and 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 or urgent care visit requiring administration of systemic corticosteroid treatment

  Treatment with systemic (IV, intramuscular [IM], or oral) corticosteroids for $\geq$ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of $\geq$ 3 days

  Diary worsening is based on the occurrence of prespecified changes (deteriorations) in a subset of the following six parameters: morning peak expiratory flow rate (PEFR), evening PEFR, morning symptom score, evening symptom score, morning short-acting rescue therapy use, and evening short-acting rescue therapy use. A detailed definition of diary worsening is provided in the protocol.

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of MTPS9579A compared with placebo on the basis of the following endpoints:

- Rate of asthma exacerbations (as defined in primary efficacy objective and assessed by the investigator) during the 48-week double-blind treatment period
- Time to first asthma exacerbation during the 48-week double-blind treatment period
- Absolute and relative change from randomization in pre-bronchodilator forced expiratory volume in 1 second (FEV_1; liters) at Week 50
- Absolute and relative change from randomization in fractional exhaled nitric oxide (FeNO) at Week 50

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of MTPS9579A compared with placebo on the basis of the following endpoints:

- Rate of severe asthma exacerbations during the 48-week double-blind treatment period, defined as asthma symptoms requiring hospitalization or resulting in death attributed to asthma
- Absolute change from randomization in pre-bronchodilator FEV_1 (percentage predicted) at Week 50
- Absolute change from randomization in patient-reported daytime asthma symptom severity, as measured by a daily symptom diary (as defined in primary efficacy objective), at Week 50
- Absolute change from randomization in patient-reported nighttime asthma symptom severity, as measured by a daily symptom diary (as defined in primary efficacy objective), at Week 50
- Absolute change from randomization in patient-reported number of puffs of short-acting rescue inhaler or number of times nebulizer was used at Week 50
- Absolute and relative change from randomization visit in provocative dose of methacholine causing a 20% drop in FEV_1 (PD_{20}) as a measure of airway hyper-responsiveness at Week 30, in patients who consent to this optional assessment at select sites

Safety Objective

The safety objective for this study is to evaluate the safety of MTPS9579A compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the WHO Toxicity Grading Scale
- Change from randomization visit in physical examination findings
- Change from randomization visit in vital signs
- Change from randomization visit in ECG parameters
- Change from randomization visit in clinical laboratory results

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to characterize the MTPS9579A PK profile on the basis of the following endpoint:

- Serum concentration of MTPS9579A at specified timepoints

The exploratory PK objective for this study is to characterize concentrations of MTPS9579A in nasal mucosal lining fluid and to evaluate potential relationships between drug exposure and the efficacy and safety of MTPS9579A on the basis of the following endpoints:

- Relationship between serum concentration, nasal mucosal lining fluid concentration, or PK parameters for MTPS9579A and efficacy or pharmacodynamic (PD) endpoints
- Relationship between serum concentration, nasal mucosal lining fluid concentration, or PK parameters for MTPS9579A and safety endpoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to MTPS9579A on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at the randomization visit

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK/PD endpoints

Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to MTPS9579A (i.e., predictive biomarkers), can provide evidence of MTPS9579A activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Change from the randomization visit in biomarker levels in nasal mucosal lining fluid, urine, and serum samples
- Relationship among biomarker levels in nasal mucosal lining fluid, urine, and serum samples
- Relationship between biomarkers in nasal mucosal lining fluid, urine, and serum and efficacy, safety, PK, and immunogenicity endpoints
- Rate of asthma exacerbations within subgroups defined by blood eosinophils during the 48-week double-blind treatment period
- Time to first CompEx event (as defined in primary efficacy objective) within subgroups defined by blood eosinophils during the 48-week double-blind treatment period
- Rate of asthma exacerbations in subgroups defined by mutations in the genes encoding tryptase (*TPSAB1* and *TPSB2)* during the 48-week double-blind treatment period
- Time to first CompEx event (as defined in primary efficacy objective) in subgroups defined by mutations in the genes encoding tryptase (*TPSAB1* and *TPSB2*) during the 48-week double-blind treatment period

Study Design

Description of Study

This is a Phase IIa, randomized, placebo-controlled, double-blind, multicenter, two-arm study of MTPS9579A compared with placebo as an add-on therapy in patients with uncontrolled moderate to severe asthma who are receiving daily ICS therapy and at least one of the following additional controller medications: long-acting β-agonist (LABA), leukotriene modulator (leukotriene modifier [LTM] or leukotriene receptor antagonist [LTRA]), long-acting muscarinic antagonist (LAMA), or long-acting theophylline preparation. The study *initially was to* randomize approximately 160 patients at approximately 55 sites globally. *However, as of March 2021, study enrollment was halted with 134 patients enrolled, and in August 2021, a decision was made to permanently halt further enrollment.*

This study will consist of a 12–28 day screening period, a 2-week single-blind placebo run-in period, a 48-week double-blind treatment period, a safety follow-up visit at Week 54, and a safety follow-up phone call at Week 58. During the screening period, patients must demonstrate acceptable inhaler, peak flow meter, and spirometry techniques, in addition to compliance with required, twice-daily use of an electronic diary (eDiary) for answering questions related to asthma symptoms, PEFR, and short-acting rescue therapy use. Patients who fail to meet eligibility criteria during the screening period will be permitted to re-screen once as described in the protocol.

Patients who meet enrollment criteria for the run-in period will receive one single-blind dose of placebo (Week 0) to allow for the evaluation of variability in asthma control. At the randomization visit (Week 2), patients must meet additional eligibility criteria for the double-blind treatment period that includes continued compliance with required, twice-daily use of the eDiary.

Patients will be randomized in a 1:1 ratio to receive MTPS9579A (1800 mg IV every 4 weeks) or placebo. Study drug will be administered by IV infusion at the randomization visit (Week 2), Week 6, and every 4 weeks thereafter through Week 46.

During the treatment period, twice-daily assessment of asthma-related symptoms, PEFR, and use of short-acting rescue therapy will continue to be performed at home and recorded in the eDiary. More detailed assessments, including spirometry and FeNO measurements, will be performed during scheduled site visits. All patients will undergo PK, biomarker, and ADA sampling. An additional exploratory efficacy assessment, the methacholine challenge test to assess airway reactivity, will be conducted at select sites in a subset of patients (approximately 20 patients/study arm) who consent to this option and meet additional eligibility criteria.

A planned interim analysis will take place once approximately 51 patients have experienced a CompEx event in the 48-week, double-blind treatment period. The expected timing of this planned interim analysis is approximately 60 weeks after the first patient is randomized. *An optional interim analysis may also be conducted. These* interim *analyses* will be conducted *for potential enrollment decisions (e.g., temporary or permanent enrollment halt, change to number of total randomized patients), for early study termination, or* for administrative purposes (*e.g.*, planning of future studies).

Screening Period

The screening period of up to 4 weeks is intended to allow sufficient time for a patient to meet all eligibility requirements. Patients must complete at least 12 days of the screening period to demonstrate eDiary compliance. Patients who are unable to complete assessments or meet eligibility requirements during the screening period will be permitted to be re-screened once for a total of up to two times. Within a screening period, patients who do not meet the requirement of pre-bronchodilator FEV_1 of 40%–80% or post-bronchodilator reversibility of FEV_1 (liters) of $\geq$ 12% and $\geq$ 200 mL are allowed up to two additional attempts to meet these two eligibility criteria, but only if their pre-bronchodilator FEV_1 was between 35% and 85%.

Patients who rescreen $\leq$ 6 weeks after Informed Consent Form completion must only repeat the assessments that triggered screen failure. Patients who rescreen $>$ 6 weeks after Informed Consent Form completion are required to repeat the consent process and all screening assessments except tuberculosis (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 or if there is risk of exposure.

Run-In Period

Patients enrolled in the run-in period will receive one single-blind dose of placebo at the run-in visit (Week 0). eDiary compliance must continue to be demonstrated on at least 5 of 7 days during each of the 2 consecutive weeks of the run-in period. Patients who do not meet eligibility criteria for the double-blind treatment period will be discontinued from the study and are not eligible for rescreening.

Internal Monitoring Committee

Periodic safety reviews will be performed by the Sponsor's Internal Monitoring Committee (IMC) as outlined in the IMC Charter. This committee will be unblinded to treatment assignments and will include a clinical scientist, drug safety scientist, biostatistician, and statistical programmer from the Sponsor. The IMC members will not have direct contact with investigational staff or site monitors. The IMC may decide to unblind the study team to enable decision-making. The IMC may invite representatives from other functional areas on an ad-hoc basis when additional expertise is required (e.g., clinical pharmacology, research) or invite additional Sponsor scientists to participate in data analyses and review.

The IMC will meet at a frequency dictated by the IMC charter but no less frequently than once every 3 months. Additionally, ad-hoc IMC meetings may be convened immediately or expeditiously at any time to address potential safety concerns if periodic review of blinded safety data indicates 3 or more patients with serious or Grade 3 or higher adverse events (excluding asthma exacerbations) that the investigator or Sponsor determines to be related to study treatment, within the same MedDRA high level term. The IMC will assess the severity, relatedness, and reversibility of adverse events, the degree of imbalance between treatment arms, the similarity and frequency of events under a single higher level term, the plausibility of a

common mechanism, possible risk mitigation measures, and may recommend changes to study conduct (including termination of study) as appropriate.

At any time during the study, the Sponsor may choose to inactivate and suspend enrollment and further dosing or reduce the dose due to safety concerns as recommended by the IMC. Should an ad-hoc IMC meeting be convened, enrollment of patients may be temporarily halted if warranted by the frequency and severity of the blinded adverse events, until the IMC evaluates the unblinded data and decides whether resumption of dosing is safe to proceed, or until IMC-recommended changes to the conduct of the study are implemented.

Number of Patients

Approximately 160 patients with moderate to severe asthma *were originally planned to* be randomized in this study (80 patients in each of 2 treatment arms); *however, as of August 2021, study enrollment has been halted with 134 patients enrolled.*

Target Population

Inclusion Criteria

Inclusion Criteria for Enrollment in the Run-In Period

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

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Age 18–75 years, inclusive, at the time of signing the Informed Consent Form
- Body mass index of 18–38 kg/m^2 and weight ≥40 kg at screening
- Documented physician-diagnosed asthma for at least 12 months prior to screening
- Pre-bronchodilator FEV_1 40%–80% predicted at screening
- Post-bronchodilator reversibility of FEV_1 (liters) ≥12% and ≥200 mL at screening

  Post-bronchodilator reversibility testing, including medication-withholding strategies and appropriate dosing of short-acting bronchodilators, should be performed per American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al. 2005).

  Alternative evidence demonstrating variable expiratory airway limitation may be considered after discussion with the Medical Monitor.
- Treatment with asthma controller therapy (daily ICS [≥100 μg of fluticasone propionate or equivalent] and at least one additional controller therapy [LABA, LAMA, LTM/LTRA]) 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 a total daily ICS dose of <500 μg fluticasone propionate or equivalent, one of their additional controller therapies must be LABA.

  For patients receiving a total daily ICS dose of ≥ 500 μg fluticasone propionate or equivalent, they must receive one or more of the following additional controller therapies: LABA, LTM/LTRA, LAMA, or long-acting theophylline preparations.
- Asthma Control Questionnaire, 5-item version score ≥1.5 at screening
- Documented history (e.g., medical report, pharmacy prescription assessed by investigator) of ≥2 asthma exacerbations within the 12 months prior to screening while on daily ICS maintenance therapy, defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in at least one of the following:
  - Hospitalization or an emergency department or urgent care visit with systemic corticosteroid treatment
  - Use of systemic (IV, IM, or oral) corticosteroids for ≥ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥ 3 days
- Demonstration of acceptable inhaler, peak flow meter, and spirometry techniques at screening

- Demonstrated compliance with required use of the eDiary, defined as completing all required assessments (answering questions related to asthma symptoms, PEFR measurements, and use of short-acting rescue therapy) on at least 5 of 7 days during each of 2 consecutive weeks within the screening period (12–28 days)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 60 days after the final dose of MTPS9579A.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of MTPS9579A to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Inclusion Criteria for Enrollment in the Double-Blind Treatment Period

After completing the run-in period, patients must meet the following additional criteria for enrollment in the double-blind treatment period:

- Ongoing compliance with required use of the eDiary, defined as completing all required assessments (answering questions related to asthma symptoms, PEFR measurements, and use of short-acting rescue therapy) on at least 5 of 7 days during each of the 2 consecutive weeks of the run-in period
- No changes in ICS therapy or allowed controller medications during the run-in period
- No new asthma exacerbation or infection during the run-in period

Inclusion Criteria for the Optional Methacholine Challenge Test

Patients enrolled in the double-blind treatment period must meet the following additional criteria for enrollment into the optional methacholine challenge test:

- Signed Informed Consent Form for the Optional Methacholine Challenge Test
- Methacholine challenge at randomization ($PD_{20} \leq 200$ μg)
- FEV_1 60%–80% predicted

Exclusion Criteria

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

- History or evidence of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation associated with panic attacks, or other mimics of asthma
- History or evidence of significant respiratory disease other than asthma, including occupational asthma, aspirin-sensitive asthma, asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome, bronchiolitis, interstitial lung disease, or COPD
- Current smoker, electronic cigarette (e-cigarette) user, former smoker with smoking history of >10 pack-years, former e-cigarette user with an e-cigarette history of at least daily use for ≥ 10 years, or unwillingness to abstain from smoking and/or e-cigarette use from the time of consent through the completion of the study

  A current smoker is defined as someone who has smoked tobacco or marijuana products (by way of a cigarette, pipe, cigar, or e-cigarette) on at least 30 days within the 24 months prior to screening.

  A patient who smokes or uses e-cigarettes occasionally (smoked or "vaped" a tobacco or marijuana product on fewer than 30 days within the 24 months prior to screening) and has a total smoking history of ≤ 10 pack-years may be permitted but must agree to abstain from all smoking or e-cigarette use during the study.

  For e-cigarette users, no use of electronic cigarettes for at least 28 days prior to screening.
- History or evidence of substance abuse that, in the investigator's judgment, would affect the patient's ability to participate in the study, pose a risk to patient safety, interfere with the conduct of the study, or have an impact on the study results
- History or evidence of any clinically significant medical condition/disease (e.g., psychiatric, neurologic, cardiovascular, renal, hepatic, gastrointestinal, endocrine, autoimmune) or abnormalities in laboratory tests that, in the investigator's judgment, precludes the patient's safe participation and completion of the study, or interferes with the conduct and interpretation of 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 A_{1c} (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 chronic heart failure exacerbation within 12 months prior to screening or at risk for heart failure exacerbation in the investigator's opinion
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- QT interval corrected through use of Fridericia's formula (QTcF) >450 ms, if patient is male, or QTcF >470, if patient is female, demonstrated by at least two ECGs >30 minutes apart
- Active malignancy or history of malignancy within 5 years of screening, except for appropriately treated non-melanoma skin carcinoma, cervical carcinoma in situ, breast ductal carcinoma in situ, or Stage I uterine cancer
- Positive for hepatitis C virus (HCV) antibody at screening, unless HCV RNA <15 IU/mL (or undetectable) at screening and for 6 months if successfully completed HCV anti-viral treatment
- Positive hepatitis B surface antigen (HBsAg) at screening, or:

  Negative HBsAg and positive hepatitis B core antibody (HBcAb); with a positive hepatitis B virus DNA test
- Positive HIV antibody at screening

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

  For patients with a history of bacille Calmette-Guérin (BCG) vaccination, the following criteria for the QFT-G apply:

  – An indeterminate QFT-G should be repeated.
  – A positive QFT-G or two successive indeterminate QFT-G results should be considered a positive diagnostic TB test.
  – An indeterminate QFT-G followed by a negative QFT-G test should be considered a negative diagnostic TB test.

  Patients with a positive PPD test or QFT-G are eligible if they meet all of the following criteria:

  – No symptoms consistent with TB (see TB worksheet)
  – Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB per the treatment options as stated in the WHO guidelines) 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
- Acute infection requiring either surgical intervention (e.g., drainage) or medical therapy (e.g., antibiotics) within 4 weeks prior to screening
- Active parasitic infection within 6 months prior to screening
- Planned surgical intervention during the course of the study
- History of any known immunodeficiency disorder
- History of documented immune complex disease (Type III hypersensitivity reactions) to monoclonal antibody administration
- History of anaphylaxis to any biologic therapy for any indication
- Known sensitivity to any of the active substances or their excipients to be administered during dosing
- Initiation of or change in allergen immunotherapy within 3 months prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with immunoglobulin or blood products within 4 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with any live or live, attenuated vaccines within 4 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with any licensed biologic agent (e.g., omalizumab, mepolizumab, reslizumab, dupilumab) within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening period, or anticipated need during the course of the study
- Treatment with any investigational therapy within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening period, or anticipated need during the course of the study
- 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 corticosteroids within 4 weeks (oral or IV) or 12 weeks (IM) prior to screening or during the screening period for any reason, including treatment for an acute exacerbation event
- Treatment with intra-articular corticosteroids within 4 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Maintenance oral or SC β-agonist therapy (e.g., terbutaline) within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study

- Treatment with phosphodiesterase-4 inhibitors (e.g., roflumilast) within 4 weeks prior to screening, during the screening period, or anticipated need 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), during the screening period, or anticipated need for these medications during the course of the study
- Maintenance oral or inhaled antibiotic therapy within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with mast cell stabilizers (e.g., chromolyn) within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with homeopathic medications, herbal medications, acupuncture, or hypnosis for treatment of allergic disease within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Intubation for respiratory failure due to asthma within 12 months prior to screening
- Maintenance intermittent positive pressure ventilation within 2 weeks prior to screening, 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, during the screening period, or anticipated need during the course of the study
- Bronchial thermoplasty treatment within 24 months prior to screening, during the screening period, or anticipated need during the course of the study
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of MTPS9579A

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

End of Study

The end of this study is defined as the date when all patients have completed the study completion or early termination visit, or have otherwise been discontinued from the study. The total duration of this study for each patient is approximately 62 weeks, including screening, run-in, treatment, and follow-up.

In addition, the Sponsor may decide to terminate *enrollment or* the *entire* study at any time.

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 25 months.

Investigational Medicinal Products

MTPS9579A and Placebo

During the run-in period, patients will receive one single-blind dose of placebo (Week 0) to allow for evaluation of variability in asthma control. During the double-blind treatment period, MTPS9579A or placebo will be administered by IV infusion at the randomization visit (Week 2), Week 6, and every 4 weeks thereafter through Week 46.

Non-Investigational Medicinal Products

Methacholine is considered a non-investigational medicinal product (NIMP) for this study as it is a bronchial challenge agent. All patients must be on a stable asthma treatment regimen consisting of ICS therapy plus at least one additional controller medication. Refer to the local prescribing information for the formulation, packaging, and handling of these medications. Patients may not be on systemic (oral, IV, or IM) corticosteroids, biologic agents, or experimental therapeutics for the treatment of asthma (see the protocol for details).

Statistical Methods

Primary Analysis

The primary efficacy endpoint is time to first CompEx event, defined as time from randomization to first asthma exacerbation or diary worsening during the 48-week double-blind treatment period. Asthma exacerbations and diary worsening are defined as follows:

- Asthma exacerbations are assessed by the investigator and 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 or urgent care visit requiring administration of systemic corticosteroid treatment
  - Treatment with systemic (IV, IM, or oral) corticosteroids for ≥ 3 days or a long acting depot corticosteroid preparation with a therapeutic effectiveness of ≥ 3 days
- Diary worsening is based on the occurrence of prespecified changes (deteriorations) in the following six parameters: morning PEFR, evening PEFR, morning symptom score, evening symptom score, morning short-acting rescue therapy use, and evening short-acting rescue therapy use. Deterioration criteria, defined as either a change from baseline (threshold) or worsening of a certain magnitude (slope) over 5 consecutive days, are presented for each parameter in the protocol. Diary worsening is defined as occurrence of one or both of the following scenarios:
  - Patient meets threshold deterioration criterion (i.e., prespecified change from baseline) for PEFR (morning and/or evening) and at least one other parameter (i.e., morning symptom score, evening symptom score, morning rescue therapy use, and/or evening rescue therapy use) on 2 consecutive days.
  - Patient meets threshold deterioration criterion (i.e., prespecified change from baseline) for one parameter on 2 consecutive days and slope deterioration criterion (i.e., prespecified change over 5 consecutive days calculated via univariate linear regression) for all six parameters.

For the purposes of determining whether the threshold deterioration criteria are met, baseline levels are calculated for each individual as the mean over the 10 planned sessions conducted prior to time of randomization for each of the diary variables.

In the event that the first diary worsening scenario is met (i.e., threshold met in two parameters), the diary worsening event will start on the first of the 2 consecutive days (defined as Event Days 0 and 1).

In the event that the second diary worsening scenario is met (i.e., threshold in one parameter and slope in all six parameters), the diary worsening event will start on the first of the 2 consecutive days that the threshold was met (Event Days 0 and 1), and the slope criteria for the six parameters must be met on Day 0 and the 4 consecutive days prior to that day (i.e., Event Day –4 through Event Day 0).

To qualify for the second diary worsening scenario, data from at least 3 of the 5 consecutive days must be available for calculation of the slope for each parameter. Analyses will be based on observed asthma exacerbations and diary worsenings, with no imputation for premature discontinuation or missing diary entries.

The primary endpoint will be analyzed through use of a Cox proportional hazards regression model comparing MTPS9579A with placebo with respect to time to first CompEx event, with adjustment for baseline covariates. Estimated hazard ratios and their associated 95% confidence intervals will be provided. Further details regarding the primary endpoint and the analysis will be described in the Data Analysis Plan.

Determination of Sample Size

The primary goal of this trial is estimation rather than hypothesis testing. This is largely due to the uncharacterized distribution of CompEx in the placebo arm. The interim analysis based upon 51 events will yield reasonable precision for estimating the true underlying hazard ratio.

[redacted]

[redacted]

Interim Analyses

An interim analysis will take place after approximately 51 patients have experienced a CompEx event in this study. The expected timing of the interim analysis will be approximately 60 weeks after the first patient is randomized. No formal stopping rules or decision criteria have been defined for the result of the interim analysis.

The interim analysis will be performed and interpreted *for potential enrollment decisions (e.g., temporary or permanent enrollment halt, change to number of total randomized patients), for early study termination, or* for administrative purposes *(e.g., planning of future studies)* by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level.

Access to treatment assignment information will follow the Sponsor's standard procedures.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted *for potential enrollment decisions (e.g., temporary or permanent enrollment halt, change to number of total randomized patients), for early study termination, or for administrative purposes (e.g., planning of future studies)* by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ-5	Asthma Control Questionnaire, 5-item version
ADA	anti-drug antibody
ATS	American Thoracic Society
BCG	bacille Calmette-Guérin
CompEx	composite of diary events and asthma exacerbations (endpoint)
COPD	chronic obstructive pulmonary disease
DAP	Data Analysis Plan
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	electronic diary
ERS	European Respiratory Society
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids
IL	interleukin
IM	intramuscular
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LABA	long-acting β-agonist
LAMA	long-acting muscarinic antagonist
LTM	leukotriene modifier
LTRA	leukotriene receptor antagonist

Abbreviation	Definition
MAD	multiple ascending dose
mITT	modified intent-to-treat
NGS	next-generation sequencing
PD_{20}	provocative dose of methacholine producing a 20% drop in FEV_1
PD	pharmacodynamic
PEFR	peak expiratory flow rate
PFT	pulmonary function testing
PK	pharmacokinetic
PPD	purified protein derivative
PRO	patient-reported outcome
Q4W	every 4 weeks
QFT-G	QuantiFERON® TB Gold (test)
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
SABA	short-acting β-agonist
SAD	single ascending dose
SAMA	short-acting muscarinic antagonist
TB	tuberculosis
ULN	upper limit of normal
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON ASTHMA

Asthma is a chronic inflammatory disease of the airways with an increasing worldwide incidence (To et al. 2012). Approximately 420,000 people die each year as a result of asthma (Global Asthma Network 2018). The pathophysiology of the disease is characterized by variable airflow obstruction, airway inflammation, mucus hypersecretion, and subepithelial fibrosis (NHLBI 2007). Clinically, patients may present with cough, wheezing, and shortness of breath. Despite the development of effective controller therapies for asthma—such as inhaled corticosteroids (ICS), long-acting β-agonists (LABA), and other controller medications—a substantial proportion of patients continue to have uncontrolled symptoms, airflow obstruction, and exacerbations (Bateman et al. 2004; Peters et al. 2006; CDC 2014). Development of new therapies is needed for patients with asthma that remains uncontrolled despite standard-of-care therapies.

Substantial evidence indicates that asthma is not a uniform condition, and there is considerable heterogeneity in clinical characteristics, severity of disease, and underlying biology. The best characterized subtypes consist of those patients in whom the disease is driven by IgE and cytokines expressed by mast cells, type 2 T-helper cells, and type 2 innate lymphoid cells, namely interleukin (IL)-4, IL-5, and IL-13; allergic disease and peripheral eosinophilia are common features. Tryptase is the most abundant secretory granule protein in human lung mast cells and is secreted from mast cells upon activation during inflammatory or allergic responses (Zhang and Timmerman 1997; Payne and Kam 2004). Tryptase is a serine protease and is enzymatically active only in the tetrameric form. Tetrameric tryptase is assembled in the mast cell granule in the presence of heparin and an acidic environment and is released upon mast cell activation/degranulation. Catalytically active extracellular secreted tryptase promotes airway hyper-responsiveness, bronchoconstriction, and amplification of mast cell degranulation (Sommerhoff 2001; He et al. 2004; Bradding and Arthur 2016).

Tryptase levels are elevated in bronchial alveolar lavage fluid and serum of patients with asthma, and correlate with disease severity. Loss-of-function mutations in genes encoding tryptases (*TPSAB1* and *TPSB2*) are common in ethnically diverse populations. These mutations correlate with tryptase activity in vitro, total peripheral tryptase levels in patients with moderate to severe asthma, and clinical response to treatment with the anti-IgE antibody omalizumab (Choy et al. 2018). As these mutations determine expression of functional tryptase, they may predict clinical outcomes for inhibitors of tryptase activity. Multiple small molecule inhibitors blocking tryptase function have shown efficacy in rodent and sheep models of allergic asthma (Clark et al. 2001). In addition, a small molecule inhibitor of tryptase, APC 366, has been shown to exhibit clinical activity by attenuating inhaled allergen-induced late asthmatic response in patients with mild atopic asthma (Krishna et al. 2001).

1.2 BACKGROUND ON MTPS9579A

MTPS9579A is a full-length humanized IgG4 antibody that binds with high affinity to human and cynomolgus monkey tryptase. MTPS9579A inhibits tryptase activity by irreversibly dissociating the active tetramer into inactive monomers. MTPS9579A is currently under clinical investigation in a Phase Ia/b dose-escalation trial (GA40396) in approximately 106 healthy volunteers. The dose has been escalated in both single ascending dose (SAD) and multiple ascending dose (MAD) cohorts up to a maximum of 3600 mg IV for SAD or MAD (every 4 weeks [Q4W] for 3 doses). In addition, a Phase Ic study is planned to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) relationships of MTPS9579A in the lung using bronchoscopy in patients with asthma after a single dose. MTPS9579A has been well tolerated at all dose levels, with no serious adverse events and only one adverse event leading to discontinuation—a volunteer who developed Grade 2 increased blood creatine phosphokinase. All reported adverse events in 106 healthy volunteers have been Grade 1 or 2, and most events resolved without requiring treatment. After administration of MTPS9579A in these healthy volunteers, active tryptase measurements from the nasal mucosal lining fluid decreased below detection levels. Greater than 95% target inhibition is anticipated in patients with asthma at the proposed dose of 1800 mg IV Q4W.

Refer to the MTPS9579A Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The rationale for conducting this Phase IIa proof-of-activity study of MTPS9579A in patients with asthma requiring ICS and a second controller is to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics in a relevant patient population. Inhibiting tryptase with MTPS9579A is anticipated to block airway inflammation downstream of mast cell activation across all asthma types. The goals of this study are to determine the impact of monthly treatment with MTPS9579A on patients' signs and symptoms of asthma using a combination of patient-reported measures and functional measures of exacerbation and to continue to understand safety and the PK/PD relationships of MTPS9579A and tryptase.

The safety profile of MTPS9579A in healthy volunteers from the Phase Ia/b study (GA40396) is described in Section 1.2 and in the MTPS9579A Investigator's Brochure. Risks in patients with asthma are unknown, but the favorable safety profile in healthy volunteers supports further development in patients with asthma. The safety plan for patients in this study is described in Section 5.1.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of MTPS9579A compared with placebo in patients with uncontrolled asthma despite the use of ICS and

a second controller. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of MTPS9579A compared with placebo on the basis of the following endpoint:

- Time to first CompEx event (Fuhlbrigge et al. 2017), a composite endpoint defined as time from randomization to first asthma exacerbation or diary worsening during the 48-week double-blind treatment period (from the randomization visit [Week 2] to end of treatment [Week 50]). Asthma exacerbations and diary worsening are defined as follows:

  Asthma exacerbations are assessed by the investigator and 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 or urgent care visit requiring administration of systemic corticosteroid treatment
  - Treatment with systemic (IV, intramuscular [IM], or oral) corticosteroids for ≥ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of ≥ 3 days

- Diary worsening is based on the occurrence of prespecified changes (deteriorations) in a subset of the following six parameters: morning peak expiratory flow rate (PEFR), evening PEFR, morning symptom score, evening symptom score, morning short-acting rescue therapy use, and evening short-acting rescue therapy use. A detailed definition of diary worsening is provided in Section 6.4.1.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of MTPS9579A compared with placebo on the basis of the following endpoints:

- Rate of asthma exacerbations (as defined in primary efficacy objective and assessed by the investigator) during the 48-week double-blind treatment period
- Time to first asthma exacerbation during the 48-week double-blind treatment period
- Absolute and relative change from randomization in pre-bronchodilator forced expiratory volume in 1 second (FEV_1; liters) at Week 50
- Absolute and relative change from randomization in fractional exhaled nitric oxide (FeNO) at Week 50

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of MTPS9579A compared with placebo on the basis of the following endpoints:

- Rate of severe asthma exacerbations during the 48-week double-blind treatment period, defined as asthma symptoms requiring hospitalization or resulting in death attributed to asthma
- Absolute change from randomization in pre-bronchodilator FEV_1 (percentage predicted) at Week 50
- Absolute change from randomization in patient-reported daytime asthma symptom severity, as measured by a daily symptom diary (as defined in primary efficacy objective), at Week 50
- Absolute change from randomization in patient-reported nighttime asthma symptom severity, as measured by a daily symptom diary (as defined in primary efficacy objective), at Week 50
- Absolute change from randomization in patient-reported number of puffs of short-acting rescue inhaler or number of times nebulizer was used at Week 50
- Absolute and relative change from randomization visit in provocative dose of methacholine causing a 20% drop in FEV_1 (PD_{20}) as a measure of airway hyper-responsiveness at Week 30, in patients who consent to this optional assessment at select sites

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of MTPS9579A compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the WHO Toxicity Grading Scale
- Change from randomization visit in physical examination findings
- Change from randomization visit in vital signs
- Change from randomization visit in ECG parameters
- Change from randomization visit in clinical laboratory results

2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the MTPS9579A PK profile on the basis of the following endpoint:

- Serum concentration of MTPS9579A at specified timepoints

The exploratory PK objective for this study is to characterize concentrations of MTPS9579A in nasal mucosal lining fluid and to evaluate potential relationships between

drug exposure and the efficacy and safety of MTPS9579A on the basis of the following endpoints:

- Relationship between serum concentration, nasal mucosal lining fluid concentration, or PK parameters for MTPS9579A and efficacy or PD endpoints
- Relationship between serum concentration, nasal mucosal lining fluid concentration, or PK parameters for MTPS9579A and safety endpoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to MTPS9579A on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at the randomization visit

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK/PD endpoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to MTPS9579A (i.e., predictive biomarkers), can provide evidence of MTPS9579A activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Change from the randomization visit in biomarker levels in nasal mucosal lining fluid, urine, and serum samples
- Relationship among biomarker levels in nasal mucosal lining fluid, urine, and serum samples
- Relationship between biomarkers in nasal mucosal lining fluid, urine, and serum (listed in Section 4.5.9) and efficacy, safety, PK, and immunogenicity endpoints
- Rate of asthma exacerbations within subgroups defined by blood eosinophils during the 48-week double-blind treatment period
- Time to first CompEx event (as defined in primary efficacy objective) within subgroups defined by blood eosinophils during the 48-week double-blind treatment period
- Rate of asthma exacerbations in subgroups defined by mutations in the genes encoding tryptase (*TPSAB1* and *TPSB2)* during the 48-week double-blind treatment period
- Time to first CompEx event (as defined in primary efficacy objective) in subgroups defined by mutations in the genes encoding tryptase (*TPSAB1* and *TPSB2*) during the 48-week double-blind treatment period

3. STUDY DESIGN

3.1 OVERVIEW OF THE STUDY DESIGN

This is a Phase IIa, randomized, placebo-controlled, double-blind, multicenter, two-arm study of MTPS9579A compared with placebo as an add-on therapy in patients with uncontrolled moderate to severe asthma who are receiving daily ICS therapy and at least one of the following additional controller medications: LABA, leukotriene modulator (leukotriene modifier [LTM] or leukotriene receptor antagonist [LTRA]), long-acting muscarinic antagonist (LAMA), or long-acting theophylline preparation. The study *initially was to* randomize approximately 160 patients at approximately 55 sites globally. *However, as of March 2021, study enrollment was halted with 134 patients enrolled, and in August 2021, a decision was made to permanently halt further enrollment.*

This study will consist of a 12–28 day screening period, a 2-week single-blind placebo run-in period, a 48-week double-blind treatment period, a safety follow-up visit at Week 54, and a safety follow-up phone call at Week 58. During the screening period, patients must demonstrate acceptable inhaler, peak flow meter, and spirometry techniques, in addition to compliance with required, twice-daily use of an electronic diary (eDiary) for answering questions related to asthma symptoms, PEFR, and short-acting rescue therapy use (see Section 4.5.8). Patients who fail to meet eligibility criteria during the screening period will be permitted to re-screen once as described in Section 3.1.1.

Patients who meet enrollment criteria for the run-in period will receive one single-blind dose of placebo (Week 0) to allow for the evaluation of variability in asthma control. At the randomization visit (Week 2), patients must meet additional eligibility criteria for the double-blind treatment period that includes continued compliance with required, twice-daily use of the eDiary (see Section 4.1.1.2).

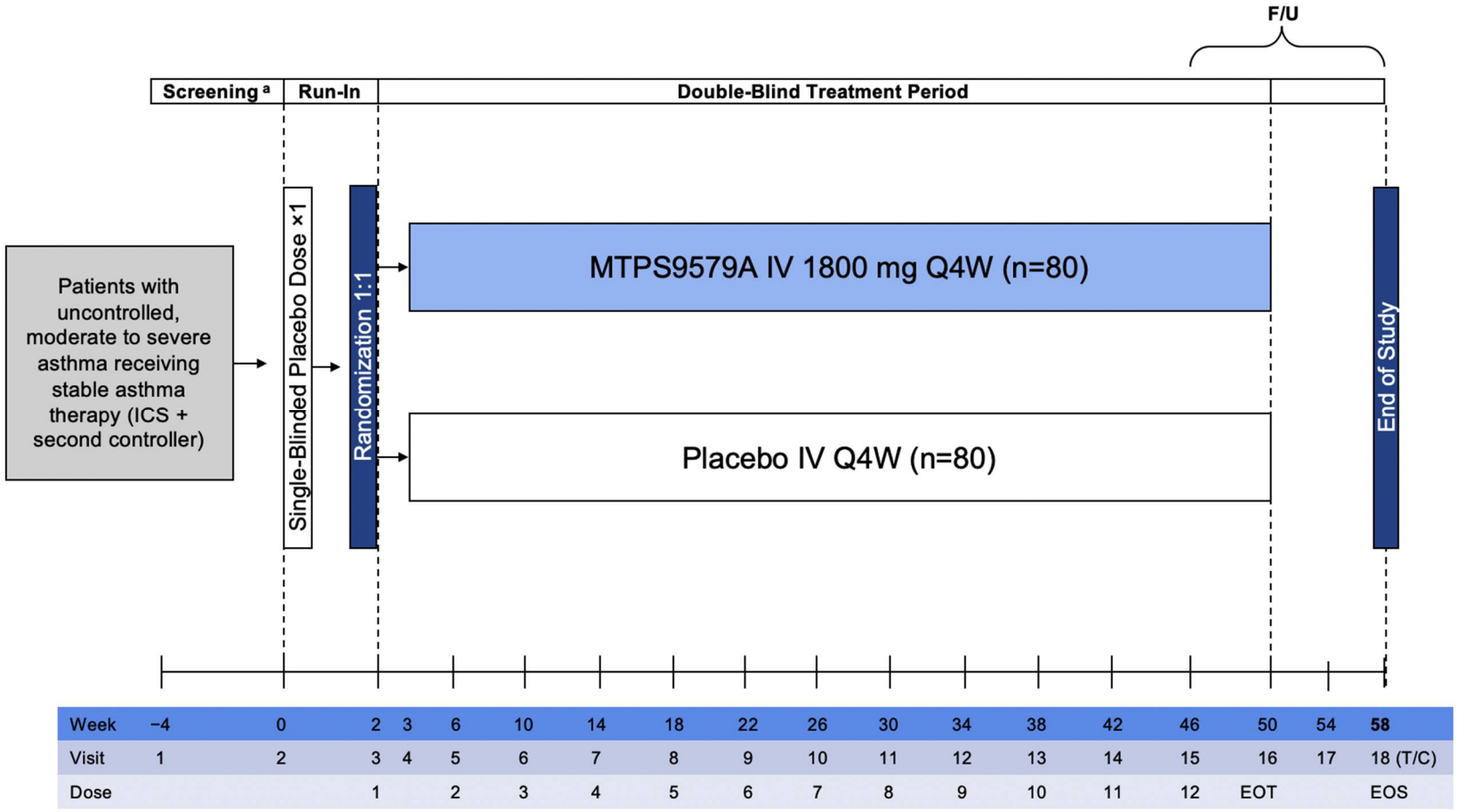
Patients will be randomized in a 1:1 ratio to receive MTPS9579A (1800 mg IV Q4W) or placebo as described in Section 4.2. Study drug will be administered by IV infusion at the randomization visit (Week 2), Week 6, and every 4 weeks thereafter through Week 46.

During the treatment period, twice-daily assessment of asthma-related symptoms, PEFR, and use of short-acting rescue therapy (see Section 4.5.8) will continue to be performed at home and recorded in the eDiary. More detailed assessments, including spirometry and FeNO measurements, will be performed during scheduled site visits. All patients will undergo PK, biomarker, and ADA sampling. An additional exploratory efficacy assessment, the methacholine challenge test to assess airway reactivity, will be conducted at select sites in a subset of patients (approximately 20 patients/study arm) who consent to this option and meet additional eligibility criteria (see Sections 4.1.1.3 and 4.5.14).

A planned interim analysis will take place once approximately 51 patients have experienced a CompEx event in the 48-week, double-blind treatment period. The expected timing of this planned interim analysis is approximately 60 weeks after the first patient is randomized. *An optional interim analysis may also be conducted. These* interim *analyses* will be conducted *for potential enrollment decisions (e.g., temporary or permanent enrollment halt, change to number of total randomized patients), for early study termination, or* for administrative purposes (*e.g.,* planning of future studies) *(see Section 6.9).*

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

Figure 1 Study Schema



EOS = end of study; EOT = end of treatment; F/U = safety follow-up; ICS = inhaled corticosteroids; T/C = telephone call; Q4W = every 4 weeks.

[a] Screening period is 12–28 days.

3.1.1 Screening Period

The screening period of up to 4 weeks is intended to allow sufficient time for a patient to meet all eligibility requirements. Patients must complete at least 12 days of the screening period to demonstrate eDiary compliance (see Section 4.1.1.1). Patients who are unable to complete assessments or meet eligibility requirements during the screening period will be permitted to be re-screened once for a total of up to two times. Within a screening period, patients who do not meet the requirement of pre-bronchodilator FEV_1 of 40%–80% or post-bronchodilator reversibility of FEV_1 (liters) of $\geq$ 12% and $\geq$ 200 mL are allowed up to two additional attempts to meet these two eligibility criteria, but only if their pre-bronchodilator FEV_1 was between 35% and 85%.

Patients who rescreen $\leq$6 weeks after Informed Consent Form completion must only repeat the assessments that triggered screen failure. Patients who rescreen $>$6 weeks after Informed Consent Form completion are required to repeat the consent process and all screening assessments except tuberculosis (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 or if there is risk of exposure.

3.1.2 Run-In Period

Patients enrolled in the run-in period will receive one single-blind dose of placebo at the run-in visit (Week 0). eDiary compliance must continue to be demonstrated on at least 5 of 7 days during each of the 2 consecutive weeks of the run-in period (see Section 4.1.1.2). Patients who do not meet eligibility criteria for the double-blind treatment period will be discontinued from the study and are not eligible for rescreening (see Section 4.6.2).

3.1.3 Internal Monitoring Committee

Periodic safety reviews will be performed by the Sponsor's Internal Monitoring Committee (IMC) as outlined in the IMC Charter. This committee will be unblinded to treatment assignments and will include a clinical scientist, drug safety scientist, biostatistician, and statistical programmer from the Sponsor. The IMC members will not have direct contact with investigational staff or site monitors. The IMC may decide to unblind the study team to enable decision-making. The IMC may invite representatives from other functional areas on an ad-hoc basis when additional expertise is required (e.g., clinical pharmacology, research) or invite additional Sponsor scientists to participate in data analyses and review.

The IMC will meet at a frequency dictated by the IMC charter but no less frequently than once every 3 months. Additionally, ad-hoc IMC meetings may be convened immediately or expeditiously at any time to address potential safety concerns if periodic review of blinded safety data indicates 3 or more patients with serious or Grade 3 or higher adverse events (excluding asthma exacerbations) that the investigator or Sponsor determines to be related to study treatment, within the same MedDRA high level term.

The IMC will assess the severity, relatedness, and reversibility of adverse events, the degree of imbalance between treatment arms, the similarity and frequency of events under a single higher level term, the plausibility of a common mechanism, possible risk mitigation measures, and may recommend changes to study conduct (including termination of study) as appropriate.

At any time during the study, the Sponsor may choose to inactivate and suspend enrollment and further dosing or reduce the dose due to safety concerns as recommended by the IMC. Should an ad-hoc IMC meeting be convened, enrollment of patients may be temporarily halted if warranted by the frequency and severity of the blinded adverse events, until the IMC evaluates the unblinded data and decides whether resumption of dosing is safe to proceed, or until IMC-recommended changes to the conduct of the study are implemented.

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 or early termination visit, or have otherwise been discontinued from the study. The total duration of this study for each patient is approximately 62 weeks, including screening, run-in, treatment, and follow-up.

In addition, the Sponsor may decide to terminate *enrollment or* the *entire* study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 25 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for MTPS9579A Dose and Schedule

The dose of MTPS9579A in this study (1800 mg IV Q4W) has been selected by the Sponsor based on the totality of the following data: understanding of tryptase biology in healthy volunteers and patients with asthma, Phase Ia/b SAD/MAD clinical trial data, MTPS9579A properties, mechanism of action, nonclinical activity and safety, and prior clinical experience targeting tryptase. The selected Phase IIa dose is within the dose range previously evaluated in the Phase Ia/b study (GA40396). In that study, doses up to 3600 mg of MTPS9579A administered intravenously as a single dose or as a Q4W regimen (3 doses), which was the maximum dose tested, was well tolerated. The dose and regimen to be tested in this study (1800 mg IV Q4W) is projected to maximize the potential for clinical benefit based on the totality of data available to date. At steady-state concentrations, it is anticipated that this dose will reduce active tryptase levels by 95%, which accounts for the maximum concentration of active tryptase that may be present in the airway of patients with asthma while ensuring patient safety. More details on the safety, PK, and PD activity of MTPS9579A are available in the MTPS9579A Investigator's Brochure.

3.3.2 Rationale for Patient Population

The current high unmet medical need in asthma is for patients with uncontrolled disease despite adherence to guidelines-based, standard-of-care therapy. In this study, the target population is patients with moderate to severe asthma whose disease remains uncontrolled despite daily use of ICS therapy and at least one additional controller medication. Patients must have a diagnosis of asthma, an Asthma Control Questionnaire, 5-item version (ACQ-5) score ≥1.5 (Appendix 2), and have experienced at least two asthma exacerbations (as defined in Section 4.1.1.1) within the 12 months prior to screening as evidence of uncontrolled disease.

Patients with uncontrolled asthma despite treatment represent a high unmet medical need because they have exhausted conventional therapeutic options. A recent study has demonstrated that patients with a history of exacerbations are at the highest risk for future exacerbations (Bloom et al. 2018). Therapeutic options for these patients are limited because of 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, 2005; Adams and Jones 2006; Sears et al. 2009; Lemanske et al. 2010).

The National Heart, Lung, and Blood Institute Expert Panel Report 3 (2007) and Global Initiative for Asthma (2018) guidelines include several options for the addition of controller medications, including 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, LTM/LTRAs, and LAMAs. While individuals in this population with eosinophilic asthma respond favorably to treatment with biologic-based therapies modulating eosinophil-related signaling pathways (IL-5, IL-4/IL-13), these therapies are of limited benefit to patients with asthma who have lower levels of eosinophils.

3.3.3 Rationale for Control Group

A placebo-treated control group will be used in this study to assess differences in CompEx events, pulmonary function, asthma control, symptoms, PD biomarkers, and safety in patients who receive MTPS9579A compared with patients who receive placebo. The use of a control group is necessary to assess safety signals that may be attributable to MTPS9579A in a patient population and given the inherent variability in symptoms and lung function. Patients in the control group will undergo the same study assessments as patients treated with MTPS9579A. All patients will continue to receive standard-of-care treatment for asthma and other allowable medical conditions (with some restrictions; refer to Section 4.4) in addition to study drug (MTPS9579A or matching placebo) throughout the study.

3.3.4 Rationale for Biomarker Assessments

Biomarker assessments, before and at various timepoints after treatment, will be used to demonstrate evidence of the biologic activity of MTPS9579A in patients, identify biomarkers that may be predictive of response to MTPS9579A, define PK/PD relationships, support selection of a recommended dose regimen, advance the understanding of the mechanism of action of MTPS9579A in patients, and increase the knowledge and understanding of disease biology. During this study, urine samples, serum samples, blood samples, and upper airway samples will be collected. Nasosorption is an upper airway, non-invasive sampling method that uses a synthetic absorptive matrix to collect nasal mucosal lining fluid from the nose.

Blood samples will be collected for DNA extraction to enable identification of mutations in genes encoding tryptase (*TPSAB1* and *TPSB2*) that are associated with tryptase levels and activity in the airway or can increase the knowledge and understanding of disease biology.

3.3.5 Rationale for Optional Methacholine Challenge Test

Mast cell microlocalization within airway smooth muscle cell bundles is thought to contribute to airway hyper-responsiveness (Brightling et al. 2002). Methacholine challenge testing, a measure of airway hyper-responsiveness, will be used to demonstrate physiological activity of MTPS9579A in patients. This assay will be examined with PK/PD and biomarker data to understand the mechanism of action of MTPS9579A.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 160 patients with moderate to severe asthma *were originally planned to* be randomized in this study (80 patients in each of 2 treatment arms); *however, as of August 2021, study enrollment has been halted with 134 patients enrolled.*

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for Enrollment in the Run-In Period

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

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Age 18–75 years, inclusive, at the time of signing the Informed Consent Form
- Body mass index of 18–38 kg/m^2 and weight $\geq$ 40 kg at screening
- Documented physician-diagnosed asthma for at least 12 months prior to screening
- Pre-bronchodilator FEV_1 40%–80% predicted at screening

- Post-bronchodilator reversibility of FEV_1 (liters) $\geq$ 12% and $\geq$ 200 mL at screening

  Post-bronchodilator reversibility testing, including medication-withholding strategies and appropriate dosing of short-acting bronchodilators, should be performed per American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al. 2005).

  Alternative evidence demonstrating variable expiratory airway limitation may be considered after discussion with the Medical Monitor.

- Treatment with asthma controller therapy (daily ICS [$\geq$100 μg of fluticasone propionate or equivalent] and at least one additional controller therapy [LABA, LAMA, LTM/LTRA]) for $\geq$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 a total daily ICS dose of $<$500 μg fluticasone propionate or equivalent, one of their additional controller therapies must be LABA.

  For patients receiving a total daily ICS dose of $\geq$ 500 μg fluticasone propionate or equivalent, they must receive one or more of the following additional controller therapies: LABA, LTM/LTRA, LAMA, or long-acting theophylline preparations.

- ACQ-5 score $\geq$1.5 at screening

- Documented history (e.g., medical report, pharmacy prescription assessed by investigator) of $\geq$2 asthma exacerbations within the 12 months prior to screening while on daily ICS maintenance therapy, defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) that result in at least one of the following:
  - Hospitalization or an emergency department or urgent care visit with systemic corticosteroid treatment
  - Use of systemic (IV, IM, or oral) corticosteroids for $\geq$ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of $\geq$ 3 days

- Demonstration of acceptable inhaler, peak flow meter, and spirometry techniques at screening

- Demonstrated compliance with required use of the eDiary, defined as completing all required assessments (answering questions related to asthma symptoms, PEFR measurements, and use of short-acting rescue therapy) on at least 5 of 7 days during each of 2 consecutive weeks within the screening period (12–28 days)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 60 days after the final dose of MTPS9579A.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of

amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of MTPS9579A to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

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

After completing the run-in period, patients must meet the following additional criteria for enrollment in the double-blind treatment period:

- Ongoing compliance with required use of the eDiary, defined as completing all required assessments (answering questions related to asthma symptoms, PEFR measurements, and use of short-acting rescue therapy) on at least 5 of 7 days during each of the 2 consecutive weeks of the run-in period
- No changes in ICS therapy or allowed controller medications (see Section 4.1.1.1) during the run-in period
- No new asthma exacerbation or infection (defined in Section 4.1.2) during the run-in period

4.1.1.3 Inclusion Criteria for the Optional Methacholine Challenge Test

Patients enrolled in the double-blind treatment period must meet the following additional criteria for enrollment into the optional methacholine challenge test:

- Signed Informed Consent Form for the Optional Methacholine Challenge Test
- Methacholine challenge at randomization ($PD_{20} \leq 200$ μg)
- FEV_1 60%–80% predicted

4.1.2 Exclusion Criteria

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

- History or evidence of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation associated with panic attacks, or other mimics of asthma
- History or evidence of significant respiratory disease other than asthma, including occupational asthma, aspirin-sensitive asthma, asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome, bronchiolitis, interstitial lung disease, or COPD
- Current smoker, electronic cigarette (e-cigarette) user, former smoker with smoking history of > 10 pack-years, former e-cigarette user with an e-cigarette history of at least daily use for ≥ 10 years, or unwillingness to abstain from smoking and/or e-cigarette use from the time of consent through the completion of the study

  A current smoker is defined as someone who has smoked tobacco or marijuana products (by way of a cigarette, pipe, cigar, or e-cigarette) on at least 30 days within the 24 months prior to screening.

  A patient who smokes or uses e-cigarettes occasionally (smoked or “vaped” a tobacco or marijuana product on fewer than 30 days within the 24 months prior to screening) and has a total smoking history of ≤ 10 pack-years may be permitted but must agree to abstain from all smoking or e-cigarette use during the study.

  For e-cigarette users, no use of electronic cigarettes for at least 28 days prior to screening.
- History or evidence of substance abuse that, in the investigator’s judgment, would affect the patient’s ability to participate in the study, pose a risk to patient safety, interfere with the conduct of the study, or have an impact on the study results
- History or evidence of any clinically significant medical condition/disease (e.g., psychiatric, neurologic, cardiovascular, renal, hepatic, gastrointestinal, endocrine, autoimmune) or abnormalities in laboratory tests that, in the investigator's judgment, precludes the patient’s safe participation and completion of the study, or interferes with the conduct and interpretation of 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 A_{1c} (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 chronic heart failure exacerbation within 12 months prior to screening or at risk for heart failure exacerbation in the investigator's opinion
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- QT interval corrected through use of Fridericia's formula (QTcF) $>$450 ms, if patient is male, or QTcF $>$470, if patient is female, demonstrated by at least two ECGs $>$30 minutes apart
- Active malignancy or history of malignancy within 5 years of screening, except for appropriately treated non-melanoma skin carcinoma, cervical carcinoma in situ, breast ductal carcinoma in situ, or Stage I uterine cancer
- Positive for hepatitis C virus (HCV) antibody at screening, unless HCV RNA $<$15 IU/mL (or undetectable) at screening and for 6 months if successfully completed HCV anti-viral treatment
- Positive hepatitis B surface antigen (HBsAg) at screening, or:

  Negative HBsAg and positive hepatitis B core antibody (HBcAb); with a positive hepatitis B virus (HBV) DNA test
- Positive HIV antibody at screening
- Positive for TB during screening, defined as either a positive purified protein derivative (PPD) test ($\geq$ 5 mm of induration 48–72 hours after injection) or a positive QuantiFERON® TB Gold (QFT-G) test during screening

  For patients with a history of bacille Calmette-Guérin (BCG) vaccination, the following criteria for the QFT-G apply:

  – An indeterminate QFT-G should be repeated.
  – A positive QFT-G or two successive indeterminate QFT-G results should be considered a positive diagnostic TB test.
  – An indeterminate QFT-G followed by a negative QFT-G test should be considered a negative diagnostic TB test.

  Patients with a positive PPD test or QFT-G are eligible if they meet all of the following criteria:

  – No symptoms consistent with TB (see TB worksheet; Appendix 3)
  – Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB per the treatment options as stated in the WHO guidelines; WHO 2018) 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

- Acute infection requiring either surgical intervention (e.g., drainage) or medical therapy (e.g., antibiotics) within 4 weeks prior to screening
- Active parasitic infection within 6 months prior to screening
- Planned surgical intervention during the course of the study
- History of any known immunodeficiency disorder
- History of documented immune complex disease (Type III hypersensitivity reactions) to monoclonal antibody administration
- History of anaphylaxis to any biologic therapy for any indication
- Known sensitivity to any of the active substances or their excipients to be administered during dosing
- Initiation of or change in allergen immunotherapy within 3 months prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with immunoglobulin or blood products within 4 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with any live or live, attenuated vaccines within 4 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with any licensed biologic agent (e.g., omalizumab, mepolizumab, reslizumab, dupilumab) within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening period, or anticipated need during the course of the study
- Treatment with any investigational therapy within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening period, or anticipated need during the course of the study
- 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 corticosteroids within 4 weeks (oral or IV) or 12 weeks (IM) prior to screening or during the screening period for any reason, including treatment for an acute exacerbation event
- Treatment with intra-articular corticosteroids within 4 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Maintenance oral or SC β-agonist therapy (e.g., terbutaline) within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with phosphodiesterase-4 inhibitors (e.g., roflumilast) within 4 weeks prior to screening, during the screening period, or anticipated need 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), during the screening period, or anticipated need for these medications during the course of the study

- Maintenance oral or inhaled antibiotic therapy within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with mast cell stabilizers (e.g., chromolyn) within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Treatment with homeopathic medications, herbal medications, acupuncture, or hypnosis for treatment of allergic disease within 2 weeks prior to screening, during the screening period, or anticipated need during the course of the study
- Intubation for respiratory failure due to asthma within 12 months prior to screening
- Maintenance intermittent positive pressure ventilation within 2 weeks prior to screening, 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, during the screening period, or anticipated need during the course of the study
- Bronchial thermoplasty treatment within 24 months prior to screening, during the screening period, or anticipated need during the course of the study
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of MTPS9579A

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After successful completion of the run-in period, at the Week 2 visit, patients will be randomly allocated to treatment with MTPS9579A or placebo at a 1:1 ratio through an interactive voice or web-based response system (IxRS). Randomization will be stratified by region (United States/Western Europe vs. Eastern Europe vs. Southern Hemisphere) and number of prior asthma exacerbations requiring use of systemic corticosteroids in the previous 12 months to balance patients across study arms. Enrollment caps for blood eosinophil level (Visit 1 $<$150 vs. 150–300 vs. $>$300 cells/μL) of approximately 35% per group during randomization will be utilized to ensure a natural distribution of patients in both study arms. A permuted block randomization method will be employed.

Patients, study site personnel, contract research organization personnel, and other Sponsor agents (with the exception of the IxRS provider, pharmacist, and bioanalytical labs for excluding placebo PK samples from testing) will remain blinded to individual treatment assignment.

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

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.

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is MTPS9579A and placebo. Methacholine is considered a non-investigational medicinal product (NIMP) for this study as it is a bronchial challenge agent.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 MTPS9579A and Placebo

MTPS9579A or placebo will be supplied by the Sponsor as a sterile liquid in 6-cc glass vials for injection. When diluted for IV administration, MTPS9579A and placebo are indistinguishable. For information on the formulation and handling of MTPS9579A or placebo, see the pharmacy manual.

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 local prescribing information for the formulation, packaging, and handling of these medications. Patients may not be on systemic (oral, IV, or IM) corticosteroids, biologic agents, or experimental therapeutics for the treatment of asthma (see Section 4.4.3 for details).

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

The MTPS9579A/placebo dose for IV administration will be prepared by diluting study drug/placebo with saline. Details regarding preparation instructions are provided in the pharmacy manual. For patients who experience mild infusion-related signs or symptoms (Grade $\leq$ 2), the infusion time may be modified. For patients with Grade 3 or higher infusion-related signs or symptoms requiring treatment, the infusion should be discontinued and the Sponsor should be notified immediately. Patients should not be medicated or premedicated in order to tolerate IV administration of study drug. Any changes in the rate of infusion or disruptions of infusion should be carefully documented. Infusions of MTPS9579A/placebo should be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

4.3.3 Investigational Medicinal Product Accountability

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from

the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Continued Access to MTPS9579A

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide the Genentech IMP (MTPS9579A) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing MTPS9579A in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to screening (for medications not intended for the treatment of asthma) or 3 months prior to screening (for medications intended for the treatment of asthma) to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Asthma Therapy

All patients will continue on a stable asthma treatment regimen, as outlined below:

- Daily ICS therapy plus at least one additional controller medication (LABA, LAMA, LTM/LTRA) 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 a total daily ICS dose of < 500 μg fluticasone propionate or equivalent, one of their additional controller medications must be LABA.

  For patients receiving a total daily ICS dose of ≥ 500 μg fluticasone propionate or equivalent, they must receive one or more of the following additional controller medications: LABA, LTM/LTRA, LAMA, or long-acting theophylline preparations.

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 (see the study manual for examples of ICS dose equivalence). 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. (Note: This only pertains to rescue use; ICS/LABA as a stable controller medication is permitted.)

Restrictions on the timing of administration of bronchodilators are described in Section 4.5.7.

4.4.1.1 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, an emergency department or 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 4.4.4.

4.4.1.2 Systemic Corticosteroid Use

Patients who require any systemic corticosteroids within 4 weeks (oral or IV) or 12 weeks (IM) 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 asthma management after randomization. Corticosteroids used for treatment of asthma (e.g., an acute exacerbation event as defined in Section 4.1.1.1) should be documented on the appropriate eCRF. Systemic corticosteroids should not be used other than for asthma exacerbations, but in the event that they are used to treat other medical conditions, this should be documented on the Concomitant Medications eCRF.

4.4.2 Cautionary Therapy

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

4.4.3 Asthma Therapy and Concomitant Restrictions

Asthma therapy and concomitant therapy restrictions are summarized in Table 1.

Table 1 Asthma Therapy and Concomitant Therapy Restrictions

Medication	Restrictions [a]
Asthma Therapies	
ICS therapy (≥100 μg of fluticasone propionate or equivalent)	On a stable regimen for ≥ 3 months prior to screening, with no changes within 4 weeks prior to screening, during the screening period, or during the treatment period If total daily ICS dose of <500 μg fluticasone propionate or equivalent: • One of the additional controller medications must be LABA. If total daily ICS dose of ≥ 500 μg fluticasone propionate or equivalent: • Must receive one or more of: LABA, LTM/LTRA, LAMA, or long-acting theophylline preparations
LABA therapy LTM/LTRA therapy LAMA therapy	On a stable regimen for ≥ 3 months prior to screening, with no changes within 4 weeks prior to screening, during the screening period, or during the treatment period
Allergen immunotherapy	No changes in dose or initiation of therapy within 3 months prior to screening, during the screening period, or during the treatment period
Maintenance oral corticosteroids (daily or every other day)	Prohibited within 3 months prior to screening and during the screening period
Systemic corticosteroids (oral, IV, or IM)	Prohibited within 4 weeks (oral or IV) or 12 weeks (IM) prior to screening and during the screening period Prohibited for treatment of any condition other than asthma exacerbations or life-threatening conditions (e.g., spinal cord compression, cerebral edema) during the study period
Bronchial thermoplasty	Prohibited within 24 months prior to screening, during the screening period, or during the treatment period
Maintenance intermittent positive pressure ventilation	Prohibited within 2 weeks prior to screening, during the screening period, or during the treatment period
Maintenance bilevel positive airway pressure therapy	
Mast cell stabilizers (e.g., chromolyn)	
Licensed biologic agents (e.g., omalizumab, mepolizumab, reslizumab, dupilumab)	Prohibited within 3 months or 5 drug half-lives prior to screening (whichever is longer), during the screening period, or during the treatment period
Homeopathic medications, herbal medications, acupuncture, or hypnosis	Prohibited within 2 weeks prior to screening, during the screening period, or during the treatment period

Table 1 Asthma Therapy and Concomitant Therapy Restrictions (cont.)

Other Therapies	
Intra-articular corticosteroids	Prohibited within 4 weeks prior to screening, during the screening period, or during the treatment period
Phosphodiesterase-4 inhibitors (e.g., roflumilast)	
Live or live, attenuated vaccines	
Immunoglobulin or blood products	
Maintenance oral or SC β-agonist therapy (e.g., terbutaline)	Prohibited within 2 weeks prior to screening, during the screening period, or during the 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 period, or during the treatment period
Immunomodulatory, immunosuppressive, or experimental anti-inflammatory therapy other than biologic agents or corticosteroids (see separate exclusions above)	
Maintenance oral or inhaled antibiotics	Prohibited within 2 weeks prior to screening, during the screening period, or during the treatment period

ICS = inhaled corticosteroids; IM = intramuscular; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; LTM = leukotriene modifier; LTRA = leukotriene receptor antagonist.

[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 (Section 5.1.2.1) should be considered.

4.4.4 Prohibited Medication Use Prior to Peak Expiratory Flow Rate and Spirometry Measurements

Patients will measure PEFR prior to taking their asthma controller medications (see Section 4.5.8.2 for details). At specified timepoints during the study, patients will undergo pre-bronchodilator spirometry measurements in the clinic (see Section 4.5.7 for details). Patients must comply with the following restrictions prior to PEFR and spirometry measurements:

- 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 spirometry
- SABA or SAMA: prohibited within 4 hours prior to spirometry

If the patient has not complied with the above restrictions prior to spirometry measurements, their visit should be rescheduled (see Section 4.5.7), with the exception of an unscheduled visit.

4.5 STUDY ASSESSMENTS

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

Patients will be closely monitored for safety and tolerability throughout the study.

4.5.1 Informed Consent Forms and Screening Log

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

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

4.5.2 Medical History, Concomitant Medications, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking/vaping history, and use of alcohol and drugs of abuse, will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient 7 days prior to screening (for medications not intended for the treatment of asthma) or 3 months prior to screening (for medications intended for the treatment of asthma) will be recorded. At the time of each follow-up limited physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and

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

Limited, symptom-directed physical examinations and examination for infusion-related reactions should be performed at specified visits during the placebo-controlled period and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position (resting for at least 5 minutes), and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Nasosorption

Nasosorption is a minimally invasive technique that samples the nasal mucosal lining fluid using the Nasosorption™ FX•i device (Hunt Developments), which has been used in humans. The aseptic device is inserted into the nostril with the absorbent strip held flat against the surface of the inferior turbinate for 60 seconds as described in the study pulmonary function testing (PFT) manual.

4.5.6 Fractional Exhaled Nitric Oxide

FeNO is a volatile marker of airway inflammation that decreases with ICS treatment. Standard nitric oxide machines (Circassia NIOX® VERO Nitric Oxide Monitor) will be provided to the site and should be used for all study-related FeNO measurements that will be performed in accordance with ATS published guidelines and described in the study PFT manual. 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 FeNO measurements. Patients must complete at least three (and up to six) separate measurements to obtain at least two nitric oxide plateau values that agree within 10% of each other according to ATS guidelines (training and guidance to be provided separately) (ATS 2005; Dweik et al. 2011).

4.5.7 Spirometry

Spirometry, including the procedure for bronchodilator testing, will be conducted as per the study PFT manual, which is based on the 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 (6600 VITALOGRAPH COMPACT™), including

software, will be dispensed to all sites. Training on equipment use, system calibration, and data storage and transfer will be provided.

Spirometric assessments will include FEV_1, FVC, percentage of predicted values for FEV_1 and FVC, FEV_1 to FVC ratio, and average forced 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. 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. The acceptability of the data, including graphic representations of the maneuvers, will be determined by blinded over-readers. Calculation for the reproducibility of the acceptable maneuvers will be programmed.

Pre-bronchodilator spirometry evaluations should be performed 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 an unscheduled visit, as detailed in Section 4.4.4. With the exception of an unscheduled visit, a patient's pre-bronchodilator spirometry testing must thus be rescheduled if the patient arrives for a scheduled study visit having used a bronchodilator within this restricted time window. 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 2, ±5 days for Week 3, and ± 6 days for all other visits.

Post-bronchodilator spirometry will be performed at screening. During this assessment, 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 per ATS/ERS guidelines (Miller et al. 2005).

4.5.8 Assessments Completed by the Patient at Home

At the initial screening visit, patients will receive an eDiary and a peak flow meter to measure PEFR. Patients will be instructed in eDiary use and asked to use the eDiary twice per day (morning/evening) to record asthma-related symptoms, PEFR, and use of short-acting rescue therapy. The eDiary will remind patients twice daily to complete their entries and will provide a time window during which the entry must be completed at approximately the same time each day. Patients will use the eDiary during screening and through Week 50.

Compliance with the required use of the eDiary and PEFR measurements (see Section 4.1.1.1) must be demonstrated on 5 of 7 days during each of 2 consecutive weeks during the screening period and also during the 2 week run-in period. eDiary compliance less than 70% (fewer than 5 out of 7 days/week) during the screening period

will result in screen failure. eDiary compliance less than 70% (fewer than 5 out of 7 days/week) during the run-in period will result in study discontinuation. Site staff will review daily diary compliance at each subsequent visit and provide refresher training if compliance is consistently less than 70% between study visits.

4.5.8.1 Daily Diary Symptom-Related Asthma Assessments

The daily diary (see Appendix 4 and Appendix 5) comprises:

- Daytime/nighttime asthma symptoms
- Nighttime awakenings
- Number of doses of short-acting rescue therapy

4.5.8.2 Peak Expiratory Flow Rate

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. Patients will be given instructions on how to measure PEFR and record information in the eDiary.

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

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study's central laboratory for analysis or analyzed at point of care, except where noted for pregnancy tests:

- Pregnancy tests

  All women of childbearing potential will have serum pregnancy tests at central lab at screening. Urine pregnancy tests will be performed at sites' local lab or clinic prior to each administration of study drug, and at other specified visits after treatment discontinuation. Serum pregnancy tests will be confirmed at central labs and performed at subsequent visits if a urine pregnancy test is positive. Study drug will not be administered if a patient has a positive pregnancy test.
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, calcium, magnesium, phosphate, total protein, albumin, total and direct bilirubin, ALP, ALT, AST, urate, LDH, creatine kinase, and HbA_{1c}
- HIV serology: HIV-1/2 antibody
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.

- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

- TB: QFT-G test or PPD test
- Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, bilirubin, nitrite, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If urinalysis is abnormal, reflex testing for culture and antibiotic sensitivity should be performed per local standard of care, if clinically indicated.
- Urine drug screen, including, but not limited to, amphetamines, barbiturates, benzodiazepines, cocaine, cotinine, marijuana/cannabinoids (tetrahydrocannabinol), methadone, methamphetamines, methylenedioxymethamphetamine, opiates, and phencyclidine

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for PK analysis
- Serum samples for immunogenicity analysis
- Serum, blood, urine, and nasal mucosal lining fluid samples for exploratory research on biomarkers

Exploratory biomarker research may include, but will not be limited to, active tryptase, total tryptase, urea, and inflammatory lipids. Research may involve extraction of DNA and genomic profiling through use of single nucleotide polymorphism analyses and next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics. NGS methods may include whole genome sequencing (WGS), but only at participating sites (see Section 4.5.13).

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 or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

- Serum, urine, blood, and nasal mucosal lining fluid samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

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

4.5.10 Electrocardiograms

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

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. ECGs should not be obtained within 3 hours after any meal. 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 the study sites. The following should be recorded in the appropriate eCRF: 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 on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the QTcF is $>$500 ms and $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs.

The 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).

4.5.11 Chest X-Rays

Patients with a positive PPD test (without a history of BCG vaccination) or a QFT-G that is positive or indeterminate 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 scan may be substituted 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.

4.5.12 Asthma Exacerbations

At each study visit, the investigator will ask directed questions to assess whether the patient experienced any asthma exacerbations as defined in Section 2.1.1 since the last study visit.

Given that asthma exacerbations comprise part of 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 5.3.5.10 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. Additional evaluations will be performed as outlined in the schedule of activities (see Appendix 1).

4.5.13 Blood Samples for Whole Genome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this section of the protocol (Section 4.5.13) will not be applicable at that site.

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 or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. 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 and characterization of important biomarkers and pathways to support future drug development.

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

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

Refer to Section 4.5.9 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.14 Optional Methacholine Challenge Test

Consenting patients who meet additional inclusion criteria (Section 4.1.1.3) will undergo an optional methacholine challenge test, which should be performed before study drug dosing and within the visit windows for randomization and the Week 30 visit. Methacholine challenge will be performed using standard techniques (Coates et al. 2017) and as described in the study PFT manual.

The Informed Consent Form will contain a separate section that addresses this optional test. A separate, specific signature will be required to document a patient's agreement to undergo optional testing. The investigator should document whether the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Methacholine Challenge Test Informed Consent eCRF.

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 biological specimens, including body fluids,

solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- 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, storage, and analysis of RBR samples 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 MTPS9579A, diseases, or drug safety:

- Leftover blood, serum, nasal mucosal lining fluid, and urine samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

RBR samples 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

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

Patient medical information associated with RBR samples 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 of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples 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 consent 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 samples. 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 samples 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 samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.15.7 Monitoring and Oversight

RBR samples 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 samples 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 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Any Grade 4 adverse event that the investigator or Sponsor determines to be related to study treatment. This excludes asthma exacerbations, unless they meet one of the other criteria for study treatment discontinuation.

- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Suspicion of hypersensitivity or anaphylactic reaction to study drug (i.e., generalized urticaria or angioedema [WHO Grade 3 allergic reaction] or anaphylaxis [Grade 4 allergic reaction] related to study drug, or Grade 3 or 4 infusion related reaction)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced and should continue follow-up for all other study procedures and measurements through the end of the study (Week 58).

4.6.2 Patient Discontinuation from the Study

Patients who discontinue the study prematurely will return to the clinic for a safety follow-up visit at Week 54 or for the early termination visit.

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

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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

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

4.6.3 Study Discontinuation

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

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

- Any emerging aggregate safety signals from serious or Grade 3 or higher adverse events evaluated by the unblinded IMC (as specified in Section 3.1.3) that indicates a potential health hazard
- Patient enrollment is unsatisfactory

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MTPS9579A is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with MTPS9579A in studies with healthy volunteers. The anticipated important safety risks for MTPS9579A are outlined below. Refer to the MTPS9579A Investigator's Brochure for a complete summary of safety information.

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

5.1.1 Risks Associated with MTPS9579A

MTPS9579A is a monoclonal antibody, and like all protein-based therapeutics, it carries a potential for immunogenicity leading to hypersensitivity and injection-site or infusion-related reactions. Tryptase is not thought to play a role in homeostatic function, and at this time, neither nonclinical nor clinical data indicate any important potential risks based on its mechanism of action. Clinical and nonclinical data do not suggest additional potential risks. Inclusion and exclusion criteria for this study are designed such that comorbidities are minimized and would not place patients at additive risk.

5.1.1.1 Immunogenicity

The development of ADAs is a potential risk for all protein therapeutics (such as monoclonal antibodies). Administration of MTPS9579A, a monoclonal antibody against tryptase, may lead to the development of anti-MTPS9579A antibodies. Patients who develop ADAs may experience adverse events or reduced efficacy.

Serum samples will be collected at protocol-defined intervals (see Appendix 1) to monitor for the development of ADAs. Patients who test positive for antibodies against MTPS9579A and have clinical sequelae that are considered related to ADAs may be asked to return for additional follow-up testing.

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

Hypersensitivity reactions and anaphylaxis have been described with SC or IV 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). See Appendix 6 for anaphylaxis precautions and management.

No hypersensitivity/hypersensitivity-like reactions or anaphylaxis/anaphylactoid reactions associated with MTPS9579A were observed following a single IV dose or repeat IV and SC doses in cynomolgus monkeys. The potential for hypersensitivity to MTPS9579A in humans is unknown. However, to date, there have been no reports of anaphylaxis or systemic hypersensitivity among subjects enrolled in the Phase I clinical trial of MTPS9579A in healthy volunteers, even among those who developed ADAs.

Systemic allergic reactions have also not been observed in the Phase I clinical study in healthy volunteers. However, as with any large-molecule therapeutic, administration of MTPS9579A may result in systemic reactions. Systemic reactions to large-molecule therapeutics can be IgE mediated; however, they may also be non-IgE mediated or due to cytokine release. Systemic reactions are generally characterized by signs and symptoms that include 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 drug administration, or within several hours of administration, but they may be delayed.

Patients with a history of anaphylaxis, hypersensitivities, or drug allergies to antibody therapeutics will be excluded from studies with MTPS9579A.

Investigators and healthcare professionals administering MTPS9579A should be trained to recognize and manage the signs and symptoms of a potential anaphylactic,

anaphylactoid, or hypersensitivity reaction and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 6).

Investigators and healthcare professionals should also be trained to accurately and appropriately report these events immediately to the Sponsor as adverse events of special interest, and as serious adverse events if appropriate (see Section 5.2). Healthcare professionals should also instruct patients on how to recognize the symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction and to contact a healthcare provider or seek emergency care in case of any such symptoms. Patients will need to be clinically stable prior to each dose of study drug as assessed by clinical evaluations, including vital signs and spirometry/PEF measurements.

5.1.1.3 Infusion-Related Reactions

In patients who receive study drug intravenously, infusion-related reactions may occur. These may be acute—often overlapping in symptoms with a hypersensitivity or anaphylactic reaction. Should such an acute reaction take place, the patient should be managed following the scheme as for anaphylaxis (see Appendix 6). Infusion-related reactions may also be delayed, occurring hours to days (up to 14 days) after administration. These delayed symptoms are frequently similar to those of serum sickness: rash, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Corominas et al. 2014). If a delayed infusion-related reaction is suspected, the patient should discontinue study drug, and appropriate clinical management should be applied.

In the Phase I clinical study in healthy volunteers, no subjects have had any infusion-related reactions.

5.1.1.4 Injection-Site Reactions

Injection-site reactions have been described with SC administration of monoclonal antibodies (Corominas et al. 2014). If SC exposure occurs at the IV infusion site, 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 variability of incidence relating primarily to the specific drug administered. Injection-site reactions may be self-limited but may require local and/or systemic therapy for severe reactions.

No clinically significant injection-site reactions associated with MTPS9579A were observed following single or repeat doses in cynomolgus monkeys.

In Phase I clinical trials of MTPS9579A in healthy volunteers, approximately 29% of participants developed injection-site erythema, and approximately 11% of subjects developed injection-site or administration-site pallor. These reactions were mild (WHO Grade 1) and self-limited, typically appearing 1 hour after administration and resolving within 2 hours.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Treatment Interruption

Reduction in dosing for adverse events is not permitted. Patients who experience certain adverse events considered to be related to study drug should be discontinued from treatment as described in Section 4.6.1.

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 Management Guidelines for Hepatotoxicity

Table 2 provides specific guidelines for withholding or discontinuing study drug for patients who experience hepatotoxicity.

Table 2 Guidelines for Treatment Interruption or Discontinuation for Patients Who Experience Hepatotoxicity

Event	Actions to Be Taken
Hepatotoxicity	
ALT or AST increase that meets Hy's Law criteria: ALT or AST $>3\times$ ULN in combination with TBILI $>2\times$ ULN or clinical jaundice	Discontinue MTPS9579A
If criteria for Hy's Law are not met: ALT or AST increase that meets at least one of the following criteria: • $>8\times$ ULN • $>5\times$ ULN for ≥ 2 weeks • $>3\times$ ULN with clinical signs or symptoms that are consistent with hepatitis (e.g., right upper quadrant pain or tenderness, fever, nausea, vomiting, jaundice)	Withhold MTPS9579A. 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 MTPS9579A.
If criteria for Hy's Law are not met: TBILI $>3\times$ ULN or Alkaline phosphatase $>3\times$ ULN	Withhold MTPS9579A. 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 MTPS9579A.

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 absolute (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms or >60 ms longer than the baseline value
- 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. The Medical Monitor should be notified as soon as possible. In more complicated or severe occurrences, hospitalization should be considered.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., methacholine challenge)

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 WHO Toxicity Grading Scale; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- 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.

- Grade ≥3 allergic reaction within 24 hours of infusion or suspected to be due to study drug

  Grade ≥3 allergic reactions include generalized urticaria and angioedema (Grade 3) and anaphylaxis (Grade 4).

5.2.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Adverse event information related to the predose optional methacholine challenge test should only be collected if it is a serious adverse event (see Section 5.3.1).
- Adverse event information related to the optional Week 30 methacholine challenge test should be collected and the relatedness to the procedure should be captured in the appropriate eCRF.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 12 weeks after the final dose of study drug or until discontinuation from the study, whichever occurs later. However, for patients who receive placebo during run-in but fail to be randomized, adverse events will be reported only 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).

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 WHO Toxicity Grading Scale (see Appendix 7) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the WHO Toxicity Grading Scale.

Table 3 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 4):

- 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 4 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 rechallenge.
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 Infusion-Related or Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related or anaphylactic reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related or 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., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [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., dosage modification, 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 solely to exacerbation 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. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to asthma exacerbation, "asthma exacerbation" 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 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., "asthma exacerbation").

Asthma exacerbation is defined as an acute worsening of asthma that requires a burst of systemic corticosteroids (refer to Section 2.1.1).

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.

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

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

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease (for example, progressive osteoarthritis necessitating a hip replacement surgery).

  The patient has not experienced an adverse event.

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

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours
- Hospitalization that was pursued for convenience to efficiently carry out multiple outpatient tests

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For MTPS9579A, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with MTPS9579A, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

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

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

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

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from patient-reported outcome (PRO) data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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

Genentech Medical Monitor contact information:

Medical Monitors and Telephone Nos:

[redacted], M.D., Ph.D. (Primary)
Office: [redacted] (United States)
Mobile: [redacted] (United States)

[redacted], M.D. (Secondary)
Office: [redacted] (United States)
Mobile: [redacted] (United States)

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 (including single-blinded placebo during the run-in), only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 84 days after the final dose of study drug or until end of study (Week 58) for patients who discontinue study drug but remain on study. For patients who receive placebo during run-in but fail to be randomized, serious adverse events and adverse events of special interest will be reported until 6 weeks after the placebo dose. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

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

EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur following completion of the adverse event reporting period described above 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 60 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 60 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.4 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, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 84 days after the final dose of study drug or end of study (Week 58) for patients who discontinue study drug but remain on study, or 6 weeks following the placebo dose for patients who failed to be randomized), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- MTPS9579A 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.

An IMC will monitor the incidence of the above-listed anticipated events during the study (see Section 3.1.3).

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary and secondary efficacy analyses will be based on a modified intent-to-treat (mITT) approach. All patients randomized who received at least one dose of study drug will be included in the mITT analysis set and be included in the analysis, with patients grouped according to the treatment assigned at randomization.

All safety analyses will include all randomized patients who received any study drug. For these analyses, patients will be grouped according to the treatment actually received.

An interim efficacy analysis is planned to be performed after approximately 51 patients have experienced a CompEx event in the 48-week, double-blind treatment period. For the interim analysis, the treatment assignments will be unblinded to relevant Sponsor study team members performing the analyses. The other parties who are involved in the conduct of the study (e.g., patients, site monitors, investigators) will remain blinded to patient-specific treatment assignments until the final database lock after the completion of the study.

The final analysis of data will be performed when all patients have either completed the study completion/early termination visit or discontinued early from the study. In addition, all data collected from the study will be cleaned, verified, and locked in a database.

All primary and secondary hypotheses tests will be two-sided with a type I error rate of 0.2. To aid the interpretation and understand the clinically significant differences from the formal hypothesis testing, two-sided 95% confidence intervals will be provided. There will be no adjustment made for any multiple comparisons. In addition, there will be no type I error control methods triggered as a result of the interim analysis.

Detailed specifications of all statistical methods (including scoring of PRO instruments and missing data handling) will be provided in the Data Analysis Plan (DAP).

6.1 DETERMINATION OF SAMPLE SIZE

The primary goal of this trial is estimation rather than hypothesis testing. This is largely due to the uncharacterized distribution of CompEx in the placebo arm. The interim analysis based upon 51 events will yield reasonable precision for estimating the true underlying hazard ratio. [redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), or complete the study will be summarized. Reasons for early discontinuation of treatment or premature study withdrawal will be listed and summarized by treatment group. 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 overall and 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 an mITT population, consisting of all randomized patients who received at least one dose of study drug during the 48-week double-blind treatment period, with patients grouped according to the treatment assigned at randomization.

Unless otherwise noted, analyses of efficacy outcome measures will be adjusted by blood eosinophil level (Visit 1 $<$150 cells/μL, 150–300 cells/μL, $>$300 cells/μL) and geographic region (United States/Western Europe, Eastern Europe, Southern Hemisphere).

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is time to first CompEx event, defined as time from randomization to first asthma exacerbation or diary worsening during the 48-week double-blind treatment period. Asthma exacerbations and diary worsening are defined as follows:

- Asthma exacerbations are assessed by the investigator and 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 or urgent care visit requiring administration of systemic corticosteroid treatment
  - Treatment with systemic (IV, IM, or oral) corticosteroids for $\geq$ 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of $\geq$ 3 days
- Diary worsening is based on the occurrence of prespecified changes (deteriorations) in the following six parameters: morning PEFR, evening PEFR, morning symptom score, evening symptom score, morning short-acting rescue therapy use, and evening short-acting rescue therapy use. Deterioration criteria, defined as either a change from baseline (threshold) or worsening of a certain magnitude (slope) over 5 consecutive days, are presented for each parameter in Appendix 8. Diary worsening is defined as occurrence of one or both of the following scenarios:

- Patient meets threshold deterioration criterion (i.e., prespecified change from baseline) for PEFR (morning and/or evening) and at least one other parameter (i.e., morning symptom score, evening symptom score, morning rescue therapy use, and/or evening rescue therapy use) on 2 consecutive days.
- Patient meets threshold deterioration criterion (i.e., prespecified change from baseline) for one parameter on 2 consecutive days and slope deterioration criterion (i.e., prespecified change over 5 consecutive days calculated via univariate linear regression) for all six parameters.

For the purposes of determining whether the threshold deterioration criteria are met, baseline levels are calculated for each individual as the mean over the 10 planned sessions conducted prior to time of randomization for each of the diary variables.

In the event that the first diary worsening scenario is met (i.e., threshold met in two parameters), the diary worsening event will start on the first of the 2 consecutive days (defined as Event Days 0 and 1).

In the event that the second diary worsening scenario is met (i.e., threshold in one parameter and slope in all six parameters), the diary worsening event will start on the first of the 2 consecutive days that the threshold was met (Event Days 0 and 1), and the slope criteria for the six parameters must be met on Day 0 and the 4 consecutive days prior to that day (i.e., Event Day −4 through Event Day 0).

To qualify for the second diary worsening scenario, data from at least 3 of the 5 consecutive days must be available for calculation of the slope for each parameter. Analyses will be based on observed asthma exacerbations and diary worsenings, with no imputation for premature discontinuation or missing diary entries.

The primary endpoint will be analyzed through use of a Cox proportional hazards regression model comparing MTPS9579A with placebo with respect to time to first CompEx event, with adjustment for baseline covariates as described in Section 6.4. Estimated hazard ratios and their associated 95% confidence intervals will be provided. Further details regarding the primary endpoint and the analysis will be described in the DAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Rate of asthma exacerbations (as defined in Section 2.1.1) during the 48-week double-blind treatment period
- Time to first asthma exacerbation during the 48-week double-blind treatment period
- Absolute and relative change from randomization in pre-bronchodilator FEV_1 (liters) at Week 50
- Absolute and relative change from randomization in FeNO at Week 50

The secondary endpoints will be evaluated in the mITT population. Statistical models will be adjusted for baseline covariates, as described in Section 6.4. The annualized exacerbation rate will be estimated for each arm as the total number of protocol-defined asthma exacerbations observed over the treatment period divided by total patient-years at risk. For each individual patient, years 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 365.25 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. In addition, a patient's time at risk, as defined above, will be computed and used as an offset term in the model.

Continuous endpoints will be analyzed using mixed-model repeated measures. Time-to-event endpoints will be analyzed using a Cox proportional hazards regression model. For the categorical variables, appropriate statistical methods, such as Cochran-Mantel-Haenszel test or Fisher's exact test, will be used. Descriptive summaries for continuous endpoints will include mean, standard deviation, median, and range. Descriptive summaries for categorical endpoints will include counts and proportions.

Descriptive summaries for continuous endpoints will include mean, standard deviation, median, and range. Descriptive summaries for categorical endpoints will include counts and proportions. Further details will be described in the DAP.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Rate of severe asthma exacerbations during the 48-week double-blind treatment period, defined as asthma symptoms requiring hospitalization or resulting in death attributed to asthma
- Absolute change from randomization in pre-bronchodilator FEV_1 (percentage predicted) at Week 50
- Absolute change from randomization in patient-reported daytime asthma symptom severity, as measured by a daily symptom diary (as defined in primary efficacy objective), at Week 50
- Absolute change from randomization in patient-reported nighttime asthma symptom severity, as measured by a daily symptom diary (as defined in primary efficacy objective), at Week 50
- Absolute change from randomization in patient-reported number of puffs of short-acting rescue inhaler or number of times nebulizer was used at Week 50
- Absolute and relative change from randomization visit in PD_{20} as a measure of airway hyper-responsiveness at Week 30, in patients who consent to this optional assessment at select sites

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

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug during the 48-week double-blind treatment period, with patients grouped according to treatment received (MTPS9579A or placebo). Safety analysis of run-in patients will consist of all patients who received the single-blind placebo dose during the run-in period, regardless of whether or not the patient is randomly allocated into the double-blind treatment period. For this safety analysis, only events that occur during the 2-week run-in period will be included and grouped together since all patients will have received placebo.

Safety will be assessed through summaries of adverse events, laboratory test results, ECG parameters, physical examination findings, and vital signs. Verbatim descriptions of treatment-emergent adverse events will be coded using the MedDRA thesaurus terms and their severity by WHO Toxicity Grading Scale (see Appendix 7), 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 48-week double-blind treatment period. In addition, separate summaries will be generated for serious adverse events, adverse events of special interest, deaths, pregnancies, malignancies, anaphylaxis events, adverse events leading to discontinuation from the study, and adverse events leading to discontinuation of study drug.

Clinical laboratory data (serum chemistry, hematology evaluations, and urinalysis values) and vital signs will be summarized by descriptive statistics for each treatment group.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will include patients with sufficient data to enable estimation of key parameters (e.g., peak serum concentration and predose trough concentrations). Serum study drug concentrations at selected timepoints will be tabulated and summarized by descriptive statistics. The extent of interpatient variability will be evaluated, and potential sources of variability will be assessed. Relationships between exposure and PD, efficacy, and safety endpoints will be explored.

Additional PK analyses will be conducted during and/or at the end of study as appropriate.

6.7 IMMUNOGENICITY ANALYSES

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

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

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

6.8 BIOMARKER ANALYSES

Biomarkers will be assessed to determine pharmacological activity and mechanism of action of MTPS9579A. Data will be summarized by absolute levels of the biomarker, as well as absolute and relative changes from randomization (defined as predose), for each treatment group. Additional PD analyses will be conducted as appropriate.

Potential predictive biomarkers of MTPS9579A response will be assessed in primary and key secondary endpoints (e.g., CompEx, asthma exacerbation rate) to assess if a subset of patients derives enhanced clinical benefit from MTPS9579A. Predictive biomarker candidates include, but are not limited to, blood eosinophils and germline mutations in the genes encoding tryptase (*TPSAB1* and *TPSB2*).

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

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analysis

An interim analysis will take place after approximately 51 patients have experienced a CompEx event in this study. The expected timing of the interim analysis will be approximately 60 weeks after the first patient is randomized. No formal stopping rules or decision criteria have been defined for the result of the interim analysis.

The interim analysis will be performed and interpreted *for potential enrollment decisions (e.g., temporary or permanent enrollment halt, change to number of total randomized patients), for early study termination, or* for administrative purposes *(e.g., planning of future studies)* by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level.

Access to treatment assignment information will follow the Sponsor's standard procedures.

6.9.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two additional interim efficacy analyses (i.e., beyond what is specified in Section 6.9.1). The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted *for potential enrollment decisions (e.g., temporary or permanent enrollment halt, change to number of total randomized patients), for early study termination, or for administrative purposes (e.g., planning of future studies)* by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory 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.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data at home. 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 data will be transmitted to a centralized database maintained by the electronic device vendor.

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

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

7.4 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable 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) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an 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 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures,

prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 55 sites globally will participate to enroll approximately 160 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.9.

The Sponsor will monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been

met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.7 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

	Screening[a]	Run-In[b]	Rand.[c]	Treatment												EOT[d]	Safety Follow -Up	Safety T/C[e]	UV[f]	ET[g]
Day (Window)	–28 to –1	1	15 (±2)	23 (±2)	44 (±3)	72 (±3)	100 (±3)	128 (±3)	156 (±3)	184 (±3)	212 (±3)	240 (±3)	268 (±3)	296 (±3)	324 (±3)	352 (±4)	380 (±3)	408 (±3)		
Week	–4 to 0	0	2	3	6	10	14	18	22	26	30	34	38	42	46	50	54	58		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Informed consent[h]	x																			
Demographic data	x																			
Medical history and baseline conditions	x																			
eDiary and peak flow meter distribution	x																			
Weight	x																x		x	x
Height	x																			
Complete physical examination[i]	x																x			x
Limited physical examination[j]			x	x	x	x	x		x		x		x			x			x	
Review eligibility criteria	x	x	x[k,u]																	
Vital signs[l]	x	x[m]	x[m]	x	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x	x		x	x
Concomitant medications[n]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Urine drug screen[o]	x		x																x	

Appendix 1: Schedule of Activities

	Screening[a]	Run-In[b]	Rand.[c]	Treatment												EOT[d]	Safety Follow -Up	Safety T/C[e]	UV[f]	ET[g]
Day (Window)	–28 to –1	1	15 (±2)	23 (±2)	44 (±3)	72 (±3)	100 (±3)	128 (±3)	156 (±3)	184 (±3)	212 (±3)	240 (±3)	268 (±3)	296 (±3)	324 (±3)	352 (±4)	380 (±3)	408 (±3)		
Week	–4 to 0	0	2	3	6	10	14	18	22	26	30	34	38	42	46	50	54	58		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Hematology[p]	x		x[q]		x	x	x		x		x		x			x	x		x	x
Chemistry[r]	x				x	x	x		x		x		x			x	x		x	x
Urinalysis[s]	x		x							x							x		x	x
Pregnancy test[t]	x		x[u]		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Viral serology[v]	x																			
TB test[w]	x																			
ECG (single record)	x		x	x						x						x	x		x	x
FeNO[x]	x	x	x[u]	x	x	x	x		x		x		x			x			x	x
Pre-bronchodilator spirometry[y]	x	x	x[u]	x	x	x	x		x		x		x			x			x	x
Post-bronchodilator spirometry (reversibility)	x																			
Optional methacholine challenge test			x								x									
Asthma exacerbation		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
eDiary retrieve/review	x[a]	x	x[k,u]	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
eDiary and PEFR[z]	Twice Daily																			

Appendix 1: Schedule of Activities

	Screening[a]	Run-In[b]	Rand.[c]	Treatment												EOT[d]	Safety Follow -Up	Safety T/C[e]	UV[f]	ET[g]
Day (Window)	–28 to –1	1	15 (±2)	23 (±2)	44 (±3)	72 (±3)	100 (±3)	128 (±3)	156 (±3)	184 (±3)	212 (±3)	240 (±3)	268 (±3)	296 (±3)	324 (±3)	352 (±4)	380 (±3)	408 (±3)		
Week	–4 to 0	0	2	3	6	10	14	18	22	26	30	34	38	42	46	50	54	58		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
ACQ-5	x																			
Serum PK sample [aa]			x [q]	x	x	x	x		x		x		x			x	x		x	x
Serum sample for biomarkers [bb]		x	x [q]	x	x		x				x					x				x
Nasosorption for biomarkers [bb]		x	x [q]	x	x		x				x					x				x
Urine sample for biomarkers [bb]		x	x [q]		x											x				
Serum ADA sample [bb, cc]			x [q]		x		x		x		x		x				x		x	x
Blood for SNP [bb]			x [q]																	
Blood for WGS [bb, dd]			x [q]																	
Adverse events [ee]		x	x [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration [ff]		PBO	x [q]		x	x	x	x	x	x	x	x	x	x	x					
Inspection for infusion reaction(s)			x [m,q]	x	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x	x		x	x

Appendix 1: Schedule of Activities

ACQ-5 = Asthma Control Questionnaire (5 items); ADA = anti-drug antibody; eDiary = electronic diary; EOT = end of treatment; ET = early termination; FeNO = fractional exhaled nitric oxide; PBO = placebo; PEFR = peak expiratory flow rate; PK = pharmacokinetic; PPD = purified protein derivative; Rand. = randomization; SNP = single nucleotide polymorphism; TB = tuberculosis; UV = unscheduled visit; WGS = whole genome sequencing.

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

[a] The screening period may last up to 4 weeks. The earliest a patient can qualify for the run-in period is after 12 days, when eDiary compliance criteria are met. Patients are allowed one attempt to re-screen.

[b] Run-in takes place from Day 1 through Day 14 to assess baseline eDiary symptoms; however, these assessments must be performed on Day 1 (±2 days).

[c] Note that these tests occur on the same day, before (left column) or after (right column) the patient has been randomized.

[d] Patients who complete the treatment period will return to the clinic for a treatment completion visit at Week 50. Patients who discontinue study drug for any reason should continue follow-up for all remaining study visits through the end of the study.

[e] Final safety follow-up will be conducted by telephone call.

[f] Patients who experience symptoms consistent with an asthma exacerbation will be asked to come to the clinic for an unscheduled visit for additional evaluations. Assessments should be performed as clinically indicated.

[g] Patients who are randomly allocated to the 48-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, except for collection of serum and nasosorption samples for biomarkers.

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

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

[j] Limited, symptom-directed physical examinations should be performed at specified visits during the placebo-controlled period and as clinically indicated. The examination should include, at a minimum, evaluation of the heart, lungs, and appropriate evaluations based on reported adverse events or symptoms. At the time of each follow-up limited physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

[k] eDiary compliance must be demonstrated on 5 of 7 days during each of the 2 consecutive weeks of the run-in period. eDiary compliance less than 70% (fewer than 5 out of 7 days/week) during the run-in period will result in study discontinuation. Patients must meet additional eligibility criteria for the double-blind treatment period as outlined in Section 4.1.1.2.

[l] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position (resting for at least 5 minutes), and temperature.

[m] Vital signs and a focused physical examination (e.g., for signs of hypersensitivity reaction) will be monitored serially (every 15 [±3] minutes) during both study drug administration and for the first hour immediately after dosing. Thereafter, vital signs and a focused physical examination will be performed every hour (±10 minutes) ending at the investigator's discretion.

[n] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to screening (for medications not intended for the treatment of asthma) or 3 months prior to screening (for medications intended for the treatment of asthma) to the study completion/discontinuation visit.

[o] Urine drug screen includes, but is not limited to, amphetamines, barbiturates, benzodiazepines, cocaine, cotinine, marijuana/cannabinoids (tetrahydrocannabinol), methadone, methamphetamines, methylenedioxymethamphetamine, opiates, and phencyclidine.

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

[q] Only to be performed after the patient is randomized.

[r] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, calcium, magnesium, phosphate, total protein, albumin, total and direct bilirubin, ALP, ALT, AST, urate, LDH, creatinine kinase, and hemoglobin A1c.

[s] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, bilirubin, nitrite, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If urinalysis is abnormal, reflex testing for culture and antibiotic sensitivity should be performed if clinically indicated.

[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, dosing should be held and a serum pregnancy test performed for confirmation.

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

[v] Includes hepatitis B surface antibody, hepatitis B surface antigen, total hepatitis B core antibody, hepatitis B DNA (if hepatitis B surface antigen test is negative and total hepatitis B core antibody test is positive), hepatitis C virus antibody, hepatitis C virus RNA (if hepatitis C virus antibody test is positive), and HIV1/2 antibody.

[w] Patients with a positive PPD test or a QuantiFERON® TB Gold test that is positive or indeterminate will require a chest X-ray to review for evidence of active TB as described in Section 4.5.11.

[x] Refer to Section 4.5.6 for FeNO procedure restrictions.

[y] Prohibited medication use prior to spirometry is described in Section 4.4.4. If the patient has used a bronchodilator within the time window defined in Section 4.4.4, then the visit must be rescheduled. To accommodate the rescheduled visit, the usual visit window during the treatment period may be extended to ±4 days for Week 2, ±5 days for Week 3, and ± 6 days for all other visits.

[z] Patients will use an eDiary to record asthma symptoms, PEFR, and use of short-acting rescue therapy twice daily prior to taking asthma controller medications. Refer to Section 4.5.8 for compliance requirements. The eDiary will remind patients twice daily to complete their entries and will provide a time window during which the entry must be completed at approximately the same time each day. On the days of study visits, if the patient has not performed the morning PEFR measurement before arrival at the clinic, the PEFR should be measured at the clinic (see Section 4.5.8.2).

[aa] On all study drug administration days that require PK serum sampling, PK samples will be obtained pre-dose and post-dose (2 hours ±30 minutes *after the end of the dose*). On clinic visit days where study drug is not administered and PK serum sampling is required, only one PK sample is to be obtained.

[bb] To be collected predose.

[cc] Samples will also be used for PK and biomarker analyses.

[dd] Not applicable for a site that has not been granted approval for WGS.

[ee] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 84 days after the final dose of study drug or end of study (Week 58) for patients who discontinue study drug but remain on study, whichever occurs later, or 6 weeks following the placebo dose for patients who failed to be randomized. 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).

[ff] Patients should be administered the study drug over 1 hour, and observed for 1 hour post-infusion, with observation ending at the investigator's discretion (as described in footnote "m").

Appendix 2
Asthma Control Questionnaire, 5-Item Version

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

For further information:

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DECEMBER 2002

Revised September 2010
ACQ-SA North American English Version

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

Revised September 2010
ACQ-SA North American English Version

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

Appendix 3
Tuberculosis Worksheet

Patient: _____ Visit: 1 (Screening)

Person completing form: _____ Date: _____

Patient must have either a purified protein derivative (PPD) or QuantiFERON TB Gold test per exclusion criteria in protocol Section 4.1.2. Please answer the following for potential patients **per the information recorded in the source document.**

1.1 Does the patient have active tuberculosis?

- ☐ No. Continue to 2.1.
- ☐ Yes. **Stop** – this patient must be excluded from the study.

2.1 If the patient had a PPD test, is the result negative (< 5 mm induration at 48 to 72 hours after the test was placed) or positive (≥ 5 mm induration at 48 to 72 hours after the test was placed)?

- ☐ Negative. Patient is eligible per exclusion criterion in protocol Section 4.1.2.
- ☐ Positive. Continue to 2.2.
- ☐ N/A. Patient had QuantiFERON TB Gold test instead of a PPD. Continue to 2.3.

2.2 Does patient have a history of bacille Calmette-Guérin (BCG) vaccination?

- ☐ Yes. Patient should have a QuantiFERON TB Gold test performed. After QuantiFERON results are available, continue to 2.3.
- ☐ No/Unknown. Continue to 3.1.

2.3 What is the result of the QuantiFERON TB Gold test?

- ☐ Negative. Patient is eligible per exclusion criterion in protocol Section 4.1.2.
- ☐ Indeterminate or Positive. Continue to 3.1.

3.1 Does the patient currently have any of the following symptoms?

- Productive, prolonged cough (> 3 weeks)
- Coughing up blood
- Fever
- Night sweats
- Unexplained appetite loss
- Unintentional weight loss

- ☐ No. Continue to 3.2.
- ☐ Yes. **Stop** – this patient must be excluded from the study.

_____	_____	_____
Person assessing item 3.1	Signature	Date

3.2 Does the patient have a documented history of adequate prophylaxis (**completed course** for latent tuberculosis per the treatment options as stated in the WHO guidelines; WHO 2018)?

- ☐ Yes. Continue to 3.3.

- ☐ No. **Stop** – this patient must be excluded from the study.

3.3 Has the patient had any known exposure to a case of active tuberculosis since their most recent prophylaxis?

- ☐ Yes. **Stop** – the patient must be excluded from the study.
- ☐ No. Continue to 3.4.

3.4 Has the patient had a chest radiograph or CT scan within 3 months prior to screening?

- ☐ No. A chest radiograph should be performed per protocol Section 4.5.12, and continue to 3.5.
- ☐ Yes. Continue to 3.5.

3.5 Is there evidence of active tuberculosis on the chest radiograph or CT?

- ☐ No. Patient is eligible per exclusion criterion in protocol Section 4.1.2.
- ☐ Yes. **Stop** – this patient must be excluded from the study.

Appendix 4
Daytime eDiary

Please answer the following questions first thing in the morning. These questions ask about your asthma after you went to sleep last night.

1. How severe were your asthma symptoms after going to sleep last night (shortness of breath, cough, wheeze, or chest tightness)?

☐ I had no asthma symptoms after going to sleep last night

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

2. After going to sleep last night, did you wake up because of your asthma symptoms (shortness of breath, cough, wheeze, or chest tightness)?

☐ No

☐ Yes

3. 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

How many puffs of a rescue inhaler did you take? _____ puffs

☐ Yes, I used a nebulizer (breathing machine)

How many times did you use a nebulizer (breathing machine)?
_____ times

Appendix 5
Nighttime eDiary

Please answer the following questions in the evening, just before bedtime. These questions ask about your asthma today, from waking up until now.

1. How severe were your asthma symptoms today (shortness of breath, cough, wheeze, or chest tightness)?

☐ I had no asthma symptoms today

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

2. 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

How many puffs of a rescue inhaler did you take? _____ puffs

☐ Yes, I used a nebulizer (breathing machine)

How many times did you use a nebulizer (breathing machine)?
_____ times

Appendix 6
Anaphylaxis Precautions and Diagnosis

Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, or other medications as required by patient status and as directed by the physician in charge.
- Continue to observe the patient and document observations.
- Draw serum/plasma samples for immunogenicity testing.
- Ask patient to return for washout immunogenicity sample if appropriate.

Criteria for Anaphylaxis Diagnosis

Anaphylaxis is highly likely when any one of the following criteria are fulfilled (adapted from Sampson et al. 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritis or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting)

Reference:

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

Appendix 7
WHO Toxicity Grading Scale

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	< 6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	<500/mm^3
Platelets	75,000–99,000/mm^3	50,000–74,999/mm^3	20,000–49,000/mm^3	<20,000/mm^3
PT	1.01–1.25×ULN	1.26–1.5×ULN	1.51–3.0×ULN	>3×ULN
aPPT	1.01–1.66×ULN	1.67–2.33×ULN	2.34–3×ULN	> 3×ULN
Fibrinogen	0.75–0.99×LLN	0.50–0.74×LLN	0.25–0.49×LLN	< 0.25×LLN
Fibrin split product	20–40 µg/mL	41–50 µg/mL	51–60 µg/mL	> 60 µg/mL
Methemoglobin	5%–9.9%	10.0%–14.9%	15.0%–19.9%	> 20%
LIVER ENZYMES				
AST (SGOT)	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	> 10×ULN
ALT (SGPT)	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	> 10×ULN
GGT	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	> 10×ULN
ALP	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	> 10×ULN
Amylase	1.1–1.5×ULN	1.6–2.0×ULN	2.1–5.0×ULN	> 5.1×ULN
CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required	< 2.0 mEq/L or paresis or ileus or lifethreatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	> 7.0 mEq/L or lifethreatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)			251–500 mg/dL	> 500 mg/dL or ketoacidosis or seizures

Appendix 7: WHO Toxicity Grading Scale

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

Appendix 7: WHO Toxicity Grading Scale

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

Appendix 7: WHO Toxicity Grading Scale

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

ADL=activities of daily living; FEV_1=forced expiratory volume in 1 second; LLN=lower limit of normal; Rx=treatment; ULN=upper limit of normal.

Appendix 8
Detailed Definition of Diary Worsening Events

Diary events are based on objective measures of deterioration of peak expiratory flow rate (PEFR), rescue therapy use, and asthma symptoms assessed morning and evening (overall, six parameters) recorded twice-daily in an eDiary. Deterioration is defined as either reaching a predefined change from baseline (threshold), for at least 2 consecutive days, or deterioration in all six parameters over a 5-day period plus at least one parameter reaching a threshold criterion for 2 consecutive days. Seven deteriorating criteria are used to construct the diary events. Deterioration of at least two concurrent criteria is needed to fulfill the criteria for a diary event. The light grey cells represent the 14 different two-criteria diary event combinations.

	Threshold Minimum change from baseline in PEFR (%), rescue therapy use (doses), and asthma symptoms score, morning or evening, for at least 2 consecutive days				**Slope** Deterioration over 5 days in all six parameters
	Rescue therapy: 1.5× increase from baseline		**Symptom score:** Increase of 1 from baseline or absolute maximum score		**PEFR**: 3% reduction rate/day **Rescue therapy**:0.3 × increase in dose rate/day **Symptoms**: 0.2 × increase in score rate/day
	morning	**evening**	**morning**	**evening**	
PEFR, morning 15% reduction from baseline					
PEFR, evening 15% reduction from baseline					
Rescue therapy, morning 1.5 × increase from baseline					
Rescue therapy, evening 1.5 × increase from baseline					
Symptom score, morning Increase of 1 from baseline or absolute maximum score					
Symptom score, evening Increase of 1 from baseline or absolute maximum score					