Clinical Study Protocol

A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma

Study Number TV48574-AS-20031

NCT04545385

Protocol with Amendment 02 Approval Date: 28 April 2021

Clinical Study Protocol with Amendment 02

Study Number TV48574-AS-20031

A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma

Short title: **A Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of TEV-48574 in Adults with Severe Uncontrolled Asthma**

Title of the protocol for lay people: **A Study to Test if TEV-48574 is Effective in Relieving Asthma**

Proof of Concept Study (Phase 2a)

IND number: 133677; NDA number: NA; BLA number: NA;
EudraCT number: 2020-001927-15

EMA Decision number of Pediatric Investigation Plan: NA

Article 45 or 46 of 1901/2006 does not apply

Original Protocol Approval Date: 28 May 2020

Protocol with Amendment 01 Approval Date: 09 November 2020

Protocol with Amendment 02 Approval Date: 28 April 2021

Sponsor

Teva Branded Pharmaceutical
Products R&D, Inc.
145 Brandywine Parkway,
West Chester, Pennsylvania 19380
United States of America

Information regarding clinical laboratories and other departments and institutions is found in Appendix A

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study TV48574-AS-20031 (original protocol dated 28 May 2020) has been amended and reissued as follows:

Amendment 02	28 April 2021 12 patients randomized to date
Administrative Letter 02	02 December 2020 7 patients randomized to date
Amendment 01	09 November 2020 6 patients randomized to date
Administrative Letter 01	13 October 2020 2 patients randomized to date

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 15.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02 Dated 28 April 2021

Clinical Study Protocol with Amendment 01 Dated 09 November 2020

Original Protocol Dated 28 May 2020

IND number: 133677; NDA number: NA; BLA number: NA;
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A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, investigational medicinal products (IMP) shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]		

Executed signature pages are maintained separately within the Trial Master File.

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02 Dated 28 April 2021

Clinical Study Protocol with Amendment 01 Dated 09 November 2020

Original Protocol Dated 28 May 2020

IND number: 133677; NDA number: NA; BLA number: NA;
EudraCT number: 2020-001927-15

EMA Decision number of Pediatric Investigation Plan: NA

Article 45 or 46 of 1901/2006 does not apply

A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national and local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel:

Coordinating Investigator	**Signature**	**Date**

Executed signature pages are maintained within the Investigator Site File and Trial Master File.

CLINICAL STUDY PROTOCOL SYNOPSIS

With Amendment 02

Study TV48574-AS-20031

Title of Study: A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc

IND Number: 133677 **EudraCT Number:** 2020-001927-15

Name of Active Ingredient: TEV-48574

Name of Investigational Medicinal Product: Fully human monoclonal antibody to tumor necrosis factor (ligand) 1A (TL1A)

Type of Study: Proof of Concept, Phase 2a

Indication: T2-low/non-T2 Severe Uncontrolled Asthma

Is this study conducted to investigate the New Use of an approved, marketed product?

No

Number of Investigational Centers Planned: ~75

Countries Planned: United States and the European Union, ~5 countries

Planned Study Period: Q3 2020 to Q3 2022

Number of Patients Planned: Approximately 124 to 174 patients; the final number may be determined based on an interim analysis.

Study Population: Adult patients aged 18 years and older with T2-low and non-T2 uncontrolled severe asthma.

Primary Objective: The primary objective of the study is to evaluate the effect of TEV-48574 compared with placebo on loss of asthma control (LoAC) in adult patients with T2-low and non-T2 severe asthma uncontrolled on inhaled corticosteroids plus long-acting beta-agonists (ICS+LABA).

Secondary Objectives: The secondary efficacy objective is to evaluate the effect of TEV-48574 compared with placebo on a range of clinical measures of asthma control.

Other Objectives: Other objectives include the evaluation of the safety and tolerability, device-related events, pharmacokinetics, and immunogenicity of TEV-48574.

Exploratory Objectives: [redacted]

Study Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint is the proportion of patients who experience LoAC during the treatment period. LoAC is defined as any one of the following during the treatment period:

- Morning peak expiratory flow (PEF) decrease ≥30% from baseline on 2 consecutive days or morning handheld forced expiratory volume in the first second of exhalation (FEV_1) decrease ≥20% from baseline on 2 consecutive days
- Increase in short-acting beta agonist (SABA)/quick-relief medication ≥6 puffs over baseline use in 24 hours on 2 consecutive days
- Increase in ICS dose ≥4x most recent dose
- Systemic corticosteroid use

- Asthma ER visit or hospitalization

Key Secondary Efficacy Endpoints:

The key secondary efficacy endpoints are as follows:

- Time from randomization to LoAC during the treatment period
- Asthma Control Questionnaire 6-question version (ACQ-6) at end-of-treatment (EOT) and throughout the study
- FEV_1 (% predicted, L) at EOT and throughout the study
- Use of SABA quick relief medication at EOT and throughout the study

Other Secondary Efficacy Endpoints:

The other efficacy endpoints are as follows:

- Proportion of patients who have a clinical asthma exacerbation (CAE) during the treatment period
  CAE is defined as a worsening of asthma symptoms resulting in any of the following:
  - The use of systemic corticosteroids (oral or injectable)
  - An emergency department visit due to asthma treated with systemic corticosteroids
  - An inpatient hospitalization due to asthma.
    Note: CAEs are a subset of LoACs
- Time from randomization to first CAE during the treatment period
- Number of nighttime awakenings due to asthma during the treatment period
- Percent decrease in ICS dose during the treatment period
- Other lung function parameters as assessed by hand-held spirometry at end of treatment (EOT) and throughout the study
- Fractional exhaled nitric oxide (FeNO) throughout the study

Safety Endpoints

The safety endpoints for this study are as follows:

- Frequency of adverse events
- Change from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study
- Change from baseline in vital signs throughout the study
- Change from baseline in 12-lead electrocardiogram (ECG) findings throughout the study
- Use of concomitant medication
- Local tolerability
- Number (%) of patients who did not complete the study due to adverse events

Device-Related Events

- All device-related adverse events, malfunctions etc. will be recorded and evaluated for their impact relative to the safety and efficacy of the investigational medicinal product.

Pharmacokinetic Endpoints

The pharmacokinetic endpoints for this study are as follows:

- Trough serum TEV-48574 concentrations throughout the study (sparse sampling)
- Population pharmacokinetic analysis of pharmacokinetic data

Immunogenicity endpoints

The immunogenicity endpoints for this study are as follows:

- Assessment of treatment-emergent anti-drug-antibody (ADA) results and responses: change from baseline and throughout the study
- Impact of the presence of ADAs on pharmacokinetics and clinical safety (if possible)
- Assessment of neutralizing ADA in ADA positive patients throughout the study

Exploratory analyses

[redacted]

General Design: This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept (POC) study to evaluate the efficacy and safety of TEV-48574 administered subcutaneously (sc) every 2 weeks in adult patients aged 18 years and older with T2-low and non-T2 uncontrolled severe asthma. The primary efficacy endpoint is the proportion of patients who experience LoAC during the treatment period.

Eligibility requirements include: peripheral blood eosinophil counts of <250 cells/μL (at least 2 out of 3 measurements both <250 cells/μL separated by 2 weeks [± 3 days]); an ACQ-6 score ≥1.5 despite daily treatment with medium/high dose ICS+LABA for at least 3 months with a stable dose for at least 1 month prior to screening, with or without other asthma controller medications, and at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma, or an inpatient hospitalization due to asthma, or a 2-fold or higher increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit (Visit S1). Patients with asthma controller medications (excluding systemic corticosteroids and systemic immunomodulatory therapies) in addition to ICS+LABA may be eligible provided all eligibility criteria are met.

The study will consist of an approximate 4- to 5-week screening/run-in period, a 16-week treatment period, and an 8-week follow-up period. The initial 5-week period consisting of screening plus run-in may be extended for up to 14 days if needed for the shipment of investigational medicinal product (IMP) to the investigational site or to complete assessment of eosinophil counts. All inclusion and exclusion criteria, with the exception of the second eosinophil count, should be assessed within the first 2 weeks of Visit S1. If a patient contracted and recovered from coronavirus disease 2019 (COVID-19) more than 6 weeks prior to screening, and the patient was not admitted to a hospital's ICU during that COVID-19 infection, and if the patient's symptoms from COVID-19 completely resolved back to pre-COVID-19 status (no lingering anosmia, weakness, persistent dyslogia or feelings of dysphoria for many months after the infection resolved), then the patient may enroll in the trial. The principal investigator should determine whether or not the subject has truly recovered back to his/her usual pre-COVID-19 status and is eligible for enrollment in the study.

A hand-held spirometer and an e-diary will be dispensed at the second screening visit (Visit S2), 2 weeks (± 3 days) after the initial S1 screening visit, and will be trained on their use. Patients who meet all inclusion criteria (except for eosinophil counts if assessment is incomplete) and none of the exclusion criteria are eligible to enter the run-in and have their ICS+LABA standardized with study-provided ICS+LABA (background asthma controller therapy) at Visit S2; this should start at least 2 weeks prior to randomization and marks the start the of run-in. At the end of run-in, patients who continue to meet all of the inclusion criteria, none of the exclusion criteria, and all of the randomization criteria will be eligible to be randomized to TEV-48574 ([redacted] For patients who are randomized, the standardized ICS+LABA dose must be maintained and the patient held stable on that dose for the first 4 weeks of the treatment period, followed by a structured decrease in background asthma controller therapies for patients not meeting criteria for LoAC. Patients will be monitored via hand-held spirometry and e-diary daily, including between visits, throughout the study. Patients who experience an event of LoAC will be treated by the investigator, discontinue IMP, restart (or increase) background asthma controller therapies, and remain in the study and complete all remaining visits, procedures and assessments, except for IMP administration. The total duration of patient participation in the study is planned to be up to approximately 30 weeks.

Brief Summary of Study Design for the Trial Registry(ies): The main purpose of this study is to test if TEV-48574 is effective in preventing loss of asthma control when background therapies are decreased in a structured manner. Researchers will look at 2 different groups of patients: 1 group of patients who are administered the study drug and 1 group of patients who are administered a placebo. The study is "double-blind," which means

patients and researchers will not know who takes TEV-48574 or placebo. In addition to testing the efficacy of TEV-48574, the safety, pharmacokinetics, and immunogenicity of TEV-48574 will also be assessed.

Method of Blinding and Randomization: This is a randomized, double-blind, placebo-controlled study. Patients who meet all inclusion criteria, none of the exclusion criteria and all of the randomization criteria will be randomly assigned to receive TEV-48574 or placebo to match TEV-48574, in a 1:1 ratio. Patients will be randomly assigned to the treatment groups by means of a computer-generated randomization list using interactive response technology after confirmation of all eligibility criteria. The study patients and the clinical team at the site will be blinded to treatment assignment until the database is locked for analysis. Individuals who may not be blinded include (but are not limited to) the bioanalytical scientists, pharmacokineticists, and biostatisticians who are not directly involved in study conduct.

Study Drug Dose, Mode of Administration, and Administration Rate: TEV-48574 for sc injection is provided as a liquid solution with a concentration of 100 mg/mL. Placebo IMP is provided as a liquid solution in the same formulation as TEV-48574, except for absence of active protein. [redacted]

- [redacted]
- Placebo to match TEV-48574

[redacted]

Investigational Medicinal Product (IMP): TEV-48574

Reference IMP:

Placebo: matching placebo

Comparison Drug: None

Duration of Patient Participation: Approximately 30 weeks, including an approximate 4- to 5-week screening/ run-in period (that can be extended by 2 weeks where required), 16-week treatment period, and 8-week follow-up period.

End of Study: End of study (EOS) is defined as the last visit of the last patient at the follow-up visit (V11 EOS).

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: The investigator will discuss with the patient the return to appropriate medical care and medication as part of standard of care provided by the patient's primary physician and specialists.

Inclusion Criteria: Patients may be included in the study only if they meet all of the following criteria:

a. The patient is a man or woman of any ethnic origin, at least 18 years of age at the time of signature of the informed consent form (ICF).

b. The patient has a diagnosis of asthma for at least 12 months prior to the initial screening visit.

c. The patient must have an absolute eosinophil count <250 cells/μL (at least 2 measurements both <250 cells/μL separated by 14 days [± 3 days]). If one of the results is ≥250 cells/μL, samples may be collected at a third time point (Visit S3) provided that the third time point is 14 days (± 3 days) after the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/μL

d. The patient has an ACQ-6 score ≥1.5.

e. The patient has demonstrated ≥12% and ≥200 mL response to a bronchodilator from baseline FEV_1 within 30 minutes after 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex‑actuator) or equivalent (eg, Ventolin) at screening.

f. The patient has asthma with a FEV_1 ≥30% and <80% of the value predicted for age, height, sex, and race at screening. FEV_1 must be performed using the office-based spirometer provided for the study. One pulmonary function test retest during the screening visit(s) period (up to 2 weeks) is allowed to fulfill this criterion.

g. The patient is able to perform technically acceptable and repeatable spirometry, including with a hand-held spirometer, after training (applicable to FEV1, not PEF).

h. The patient's background asthma therapy includes daily medium- or high-dose ICS plus LABA for at least 3 months prior to the initial screening visit with or without other asthma controller medications. The dose of ICS may vary during these 3 months, but must remain at a stable daily dose for at least 1 month prior to Visit S1. Medium- and high-dose ICS classification will be based on the Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2019 update, Appendix C). Patients with asthma controller medications (excluding systemic corticosteroids and systemic immunomodulatory therapies) in addition to ICS+LABA may be eligible provided all eligibility criteria are met.

i. The patient has had at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit. Only clinical asthma exacerbations with historical documentation in the patient's medical or pharmacy records may count towards this criterion.

j. Patients must be able to replace their pre-study ICS+LABA with study-provided ICS+LABA

k. The patient is a non-smoker for ≥6 months with lifetime history ≤10 pack-years, with no current e-cigarette use. The patient must have a negative urine cotinine test at the screening visit.

l. The patient is able to communicate satisfactorily with the investigator and to participate in, and comply with, the requirements of the study.

m. The patient is able to understand the nature of the study and any potential hazards associated with participating in the study.

n. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and willing to return to the investigational center for further visits, as applicable, and the follow up procedures and assessments as specified in this protocol.

o. Women of non-childbearing potential who are either surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile as assessed by a physician, or 1-year postmenopausal (no menses for at least 12 months without an alternative medical cause plus an increased concentration of follicle stimulating hormone [FSH] of more than 35 U/L in women not using hormonal contraception or hormonal replacement therapy).
Women of childbearing potential must have a negative β-HCG test result and practice a highly effective method of birth control (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, see Section 5.9) prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer.
Male patients (including vasectomized) with women of childbearing potential (WOCBP) partners

(whether pregnant or not) must use condoms prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer.

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results. Examples include but are not limited to: chronic obstructive pulmonary disease, chronic bronchitis or any respiratory condition that requires any chronic antibiotic use (some antibiotics can be immunomodulatory such as macrolides [eg, erythromycin, azithromycin, and clarithromycin]), bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, and interstitial lung disease (including eosinophilic granulomatosis with polyangiitis [EGPA] which is expressly prohibited), obstructive sleep apnea (sometimes referred to as sleep apnea or Pickwickian Syndrome), and gastroesophageal reflux disease that is not treated with a proton pump inhibitor on a scheduled treatment regimen (not as needed).

b. The patient has any concomitant conditions or treatments that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the study as judged by the investigator and/or the clinical study physician.

c. The patient has any of the following medical conditions:

- Conditions that may mimic asthma (eg, vocal cord dysfunction, hyperventilation, panic attacks, cardiac asthma, uncontrolled gastroesophageal reflux disease [gastroesophageal reflux disease controlled on a stable proton pump inhibitor regimen for at least 1 month may be allowed])
- Conditions of immunodeficiency, immunocompromise, and/or conditions requiring immunomodulatory therapy
- A history of malignancy within 5 years before screening (exception: basal cell carcinoma or in situ carcinoma of the cervix if successful curative therapy occurred at least 12 months prior to screening)
- Tested positive for tuberculosis (TB) at screening by the QuantiFERON® TB Gold Test, or had a history of untreated latent or active TB. If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, a repeat specimen shall be submitted; if the second test is also positive, the patient screen fails; if the second test is negative, a third test shall be submitted; if the third test agrees with the first test, the patient screen fails; if the third test agrees with second test, the patient is considered to be negative for TB; see Section 7.5.2 for details.
- Known history of, or a positive test result for, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) types 1 or 2 at screening
- A history of more than one herpes zoster episode or multimetameric herpes zoster
- A history of an opportunistic infection (eg, cytomegalovirus retinitis, *Pneumocystis carinii*, aspergillosis, *Clostridium difficile*)
- A history of or ongoing chronic or recurrent infectious disease (eg, infected indwelling prosthesis, osteomyelitis, chronic sinusitis)

- A suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the initial screening visit. Note: Patients who develop an upper respiratory infection/lower respiratory infection (URI/LRI) during the screening period may rescreen 2 weeks after symptoms resolve subject to local or regional public health directives.
- Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening/run-in, will be tested for active COVID-19 infection and will only be included if they test negative for COVID-19. Patients who were admitted to an ICU during a prior COVID-19 infection; or patients who contracted or recovered from COVID-19 less than 6 weeks prior to screening, or patients with COVID-19 symptoms (lingering anosmia, weakness, persistent dyslogia or feelings of dysphoria for many months) from a pre-study COVID-19 infection that have not completely resolved back to their pre-COVID-19 infection health status are excluded from the study.

d. The patient has taken any systemic corticosteroids within 30 days of screening, including but not limited to oral corticosteroids as maintenance therapy for asthma, and/or treatment for clinical asthma exacerbation (CAE) within 30 days of screening.

e. Intensive care unit (ICU) admission or intubation within the 3 months prior to screening.

f. CAE as defined by this protocol (see Section 6.1.2) within the 30 days prior to screening.

g. The patient is currently using any systemic immunosuppressive or immunomodulatory biologic or non-biologic. Note: Previous use of such agents that occurred ≥5 half-lives from the initial screening visit may be allowed, if approved by the clinical study physician.

h. The patient participated in a clinical trial within 30 days or 5 half-lives of the investigational drug before screening.

i. The patient has received investigational drugs targeted against TL1A.

j. Abnormality in laboratory values during screening that is considered clinically significant by the investigator, or could interfere with the objective of the study as determined by the sponsor. Any such laboratory abnormality may be retested at the investigator's clinical discretion and if within normal limits, accepted.

k. The patient is currently pregnant or lactating or is planning to become pregnant during the study or for at least 10 weeks after administration of the last dose of IMP in case of early withdrawal. Any woman becoming pregnant during the study will be withdrawn from the study.

l. The patient has a known hypersensitivity to the IMP and/or excipients.

m. Live and attenuated vaccines should be excluded 14 days before IMP dosing and throughout the study. Inactivated vaccines (including approved inactivated COVID 19 vaccines) should preferably be completed 14 days before first IMP dosing. If administered during the study it is recommended to be at least 3 days before and after IMP administration, or as required by local country regulations.

n. The patient has a positive urine drug test during screening for compounds of abuse, or for cotinine, the relevant metabolite from cigarette smoking, the use of which would make the patient ineligible. Repeat testing will not be permitted. A positive urine test for tetrahydrocannabinol, the psychoactive ingredient in marijuana, is permitted during the trial.

o. The patient has a history of alcohol or drug abuse within 2 years preceding the initial screening visit.

p. Initiation or dose escalation of allergen immunotherapy (administered by any route) is planned during the study period. However, patients who initiated immunotherapy 90 days or more before the initial screening visit and have been on a stable (maintenance) dose for 30 days or more before the initial screening visit may be considered for inclusion.

q. The patient is either an employee or an immediate relative of an employee of the sponsor or of any of the clinical investigational centers participating in the study.

Randomization criteria: The patients must meet the following randomization criteria prior to randomization:

a. The patient continues to meet all of the inclusion criteria (including ACQ-6 ≥1.5) and none of the exclusion criteria.

b. The patient has not had a clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit, or other need for systemic corticosteroids during the screening period.

c. The patient has at least 57% adherence (4 out of the 7 days prior to randomization) to hand-held spirometry and e-diary assessments.

Statistical Considerations:

Sample Size Rationale:

The primary efficacy analysis for this study will be the comparison between treatment groups of the proportion of patients experiencing a LoAC event during the 16-week treatment period. The study will be considered positive if the primary efficacy test indicates a statistically significant treatment effect versus placebo at the predefined significance level.

Sample size calculations were performed based on the following considerations:

In the Phase 2a study results for dupilumab, the observed LoAC rate in the placebo group was 44% (Wenzel et al 2013). The patients in that study had elevated peripheral blood eosinophil counts (≥300 cells/µL). To estimate the LoAC rate that would have been observed in patients with peripheral blood eosinophil counts <300 cells/µL the ratio of exacerbation rates observed between eosinophil count strata in the placebo groups of the dupilumab Phase 3 study were used (Castro et al 2018). This resulted in an estimated LoAC rate of 27% for the patients meeting the entrance criteria for the current study.

This study is designed to detect a 60% reduction in LoAC rate versus placebo; ie, a placebo group rate of 27% and a TEV-48574 group rate of 10.8%.

Based on the assumptions above, and assuming a 15% dropout rate during the study, 62 randomized patients per treatment group will provide 80% power to detect a treatment effect of 60% reduction in LoAC rate in the TEV-48574 group using a Chi-square test with one-sided alpha (Type I error rate) of 0.1.

An unblinded interim analysis is planned to re-assess the sample size and conduct a futility analysis as described in Section 9.13. If the sample size increases as a result of the interim analysis, the number of evaluable patients would be expected to increase proportionately.

Analysis of Primary Endpoint: The primary analysis will compare rates of LoAC between treatment groups using logistic regression with fixed effect for treatment, baseline FEV1, baseline weight, age group (<65 years vs ≥65 years), and gender as covariates. The primary analysis will be performed on the intent-to-treat (ITT) analysis set. Patients who withdraw from the study or discontinue treatment due to lack of efficacy or due to an asthma-related adverse event will be analyzed as having experienced LoAC. Patients who withdraw from the study for other reasons will be analyzed as not experiencing a LoAC. The treatment effect will be tested at a one-sided alpha of 0.1.

Analysis of Secondary Efficacy Endpoints: All efficacy variables will be summarized by treatment group. For continuous variables, the summary statistics will include n, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. For categorical variables, patient counts and percentages will be provided.

LoAC rates, 90% and 95% CIs for LoAC rates, estimated treatment effects (ie, the odds ratio of TEV-48574 versus placebo), and 90% and 95% CIs of the odds ratio will be provided.

The key secondary efficacy analysis of time to LoAC will use a one-sided log-rank test to compare the hazard rates between the TEV-48574 and placebo groups. The analysis will be performed on the ITT analysis set. Patients who withdraw from the study or discontinue treatment due to lack of efficacy or due to an asthma-related adverse event will be analyzed as having experienced LoAC at the time of the withdrawal or treatment discontinuation. Patients who withdraw from the study for other reasons will be analyzed as being right-censored at the time of withdrawal.

The Kaplan-Meier (KM) method will be used to estimate and compare the distributions of time to LoAC between treatment groups.

Analysis of ACQ-6 will use the mixed model repeated measures model with treatment group, baseline value, visit, treatment and visit interaction, and baseline value as fixed effects and patient as a random effect.

The on-site morning trough FEV1 throughout study will be analyzed using similar mixed model repeated measures (MMRM) method, as described for the analysis of ACQ-6.

Use of SABA quick relief medication will be derived from the e-diary data in monthly analysis intervals and will be analyzed using a similar MMRM method.

The efficacy endpoints defined at end-of-treatment (EOT) will take the last available assessment value in the treatment period, and will be analyzed using appropriate analysis of covariance models.

Additional covariates or factors may be added to the statistical models. These will be detailed in the SAP.

Multiple Comparisons and Multiplicity: As there are only 2 treatment groups and one primary analysis test in this study, no multiplicity correction is necessary. Secondary endpoints will be considered as hypothesis-generating, and multiple testing adjustment will not be made.

Planned Interim Analyses: An unblinded interim analysis is planned after the first 40 to 52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely. The main purposes of the interim analysis include sample size re-assessment and futility analysis.

Safety/Tolerability, PK, and Immunogenicity Analyses: Safety/tolerability, PK, and immunogenicity results will be summarized using descriptive statistics by treatment group. [redacted] may be addressed in a separate statistical analysis plan and report.

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LIST OF ABBREVIATIONS

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ACQ-6	Asthma Control Questionnaire (6-question)
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{0-t}	area under the serum concentration-time curve from time 0 to the time of the last measurable drug concentration
$AUC_{0-\infty}$	area under the serum concentration-time curve from time 0 to infinity
AUC_{τ}	AUC over one dosing interval
$AUC_{\tau,ss}$	AUC during dosing interval at steady state
CAE	clinical asthma exacerbation
CFR	code of federal regulations
CI	confidence interval
CL/F	apparent total clearance of the drug from serum after extravascular administration
C_{max}	maximum observed serum drug concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DcR3	Decoy Receptor 3
DoR	day of randomization
DR3	Death Receptor 3
ECG	electrocardiography, electrocardiogram
EGPA	eosinophilic granulomatosis with polyangiitis
EOS	end-of-study
EOT	end-of-treatment
ER	emergency room
ET	early termination
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration

Abbreviation	Term
$FEF_{25\%-75\%}$	forced expiratory flow at 25-75% of the pulmonary volume
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in the first second of exhalation
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GINA	Global Initiative for Asthma
GPSP	Global Patient Safety and Pharmacovigilance
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HFA	hydrofluoroalkanes
HIV	human immunodeficiency virus
IB	investigator's brochure
HSP	hysterosalpingogram
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
ICU	intensive care unit
IEC	Independent Ethics Committee
IL	interleukin
ILC2	innate lymphoid cells, type 2
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intention-to-treat
JDMC	Joint Data Monitoring Committee
KM	Kaplan-Meier
LABA	long-acting beta agonist
LoAC	Loss of asthma control
LRI	lower respiratory infection
MAD	multiple ascending dose
MDI	metered-dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
NF-κB	nuclear factor kappa-light chain enhancer of activated B cells
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no observed adverse effect level
NRS	numerical response scale
PAR	pharmacometrics analysis report
PDAESI	protocol-defined adverse events of special interest
PEF	peak expiratory flow
PK/PD	pharmacokinetic/pharmacodynamic
POC	proof-of concept
PP	per-protocol
QSP	quantitative systems pharmacology
SABA	short-acting beta agonist
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SD	standard deviation
SE	standard error
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	elimination half-life
t_{max}	time to maximum observed drug concentration
TB	tuberculosis
TC	teleconference
TL1A	tumor necrosis factor ligand 1A
TNF	tumor necrosis factor
TNFSF15	TNF superfamily member 15
T_{reg}	regulatory T cell
ULN	upper limit of the normal range
URI	upper respiratory infection
USA	United States of America
VC	videoconference
Vz/F	apparent volume of distribution after extravascular administration
WHO-DD	World Health Organization Drug Dictionary

Abbreviation	Term
WOCBP	women of childbearing potential

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Asthma Background

Asthma is a common chronic lung disorder characterized by inflammation and narrowing of the airways. Symptoms of asthma include cough, breathlessness, and wheezing. Recent estimates suggest that as many as 339 million people in the world have asthma (Global Asthma Network 2018).

Until recently, inhaled corticosteroids (ICS) have been considered the most effective treatment agents for the long-term control of asthma (see EPR-3 2007 and GINA 2014). For patients whose asthma was not adequately controlled on daily ICS alone, the addition of long-acting beta-agonists (LABAs) and/or other controller therapies was recommended to provide additional control. For some severely affected patients with asthma, daily oral corticosteroid or currently approved biologics help maintain asthma control. However, it has been observed that the aforementioned treatment paradigm is not effective for all asthma subpopulations and there is a growing understanding that efficacy is often associated with the underlying pathophysiological pathways driving patients' asthma. Currently there are no approved effective therapies for patients whose asthma is not well controlled by the above therapies.

1.1.2. T2 and Non-T2 Asthma

It is now generally acknowledged that a number of underlying pathophysiological processes can lead to asthma, and a number of phenotypes and endotypes have been characterized (Fajit and Wenzel 2014; Robinson et al 2017). Asthma has been dichotomized according to the presence and level of type 2 (T2) inflammation in the airways (Fahy 2016; Samitas et al 2017). T2 inflammation refers to inflammation driven by a particular set of cytokines including IL-4, IL-5 and IL-13. Originally described in relation to T helper 2 (Th2) cells and initially referred to as Th2 inflammation, it is now recognized that other types of cells also play a role and so the more general designation of T2 has come into use (Th2 inflammation represents a subset of T2 inflammation driven by Th2 cells). Cells (other than Th2 cells) that have been described as secreting T2 type cytokines include: type 2 innate lymphoid cells (ILC2); natural killer cells; other types of T cells and eosinophil-basophil progenitors.

T2 asthma has been divided into T2-high and T2-low subtypes based upon a variety of criteria including cytokine profiles and/or eosinophil counts. Non-T2 asthma is generally thought of as not driven by T2 inflammation and is often described relative to the absence of evidence of T2 inflammation. Non T2-asthma is poorly understood (Fajt and Wenzel 2014; Samitas et al 2017). The underlying causes of some T2-low asthma and non-T2 asthma might be attributable to several cellular signaling pathways, including: oxidative stress; neutrophilic inflammation caused by dysregulation of the Th17 pathway; Th1-related processes; and potentially Th2 components as well (Robinson et al 2017; Samitas et al 2017). Lack of responsiveness to corticosteroids has been described in patients with T2-low and non-T2 asthma (Pavord et al 1999; Fahy 2016; Schleich et al 2013). In addition, currently approved asthma biologics are only for the treatment of T2 asthma and often show increased efficacy for T2 high asthma (FitzGerald et al 2018, Castro et al 2018).

For practical purposes, T2-high, T2-low, and non-T2 status is often identified by peripheral blood eosinophil counts. Some investigators recommend adding fractional exhaled nitric oxide (FeNO) to peripheral blood eosinophil counts for categorization. Even though peripheral eosinophil counts are used to identify T2 patients, T2 asthma is not identical to the phenotype of eosinophilic asthma (although there is probably substantial overlap between the two populations).

While there is some debate as to what threshold(s) distinguishes T2-high from T2-low asthma, most studies have used a cutoff between 250 cells/μL and 300 cells/mL (Coverstone et al 2020). Examples of absolute eosinophil counts used to define T2-high, T2-low, and non-T2 include:

- T2-high ≥250 cells/μL
- T2-low ≥150 cells/μL to <250 cells/μL
- Non-T2 <150 cells/μL
- Non-T2-high refers to T2-low and non-T2 combined, i.e., patients with absolute eosinophil counts <250 cells/μL

1.1.3. TL1A as a Target

Tumor necrosis factor (TNF) (ligand) 1A (TL1A, also known as TNF [ligand]) superfamily member 15 [TNFSF15], VEGI) is a member of the TNF ligand superfamily and has a trimeric structure consisting of 3 noncovalently associated TL1A protein subunits. It is a single-pass type II membrane protein that can be cleaved by endogenous proteases to produce a soluble form. Both the membrane-bound and soluble forms are active. TL1A has been reported to be expressed by a number of cells including endothelial cells (Migone et al 2002), tissue macrophages, lamina propria lymphocytes, and $CD11c^{high}$ dendritic cells (Bamias et al 2003; Bamias et al 2006).

TL1A expression has also been reported to differ between steady state and inflammatory conditions and between healthy and diseased states (Migone et al 2002; Bamias et al 2003; Bamias et al 2006; Riley et al 2018; Schofield et al 2019; Pavlidis et al 2019).

TL1A has 2 identified receptors: Death Receptor 3 (DR3, TNFRSF25, APO-3, TRAMP, LARD, WSL-1) and Decoy Receptor 3 (DcR3,TNFRSF6B). DR3 is the cognate signaling receptor for TL1A and a member of the tumor necrosis factor receptor superfamily (TNFRSF25). DR3 expression by a number of cells including lymphocytes (eg, NK cells, T cells) has been reported (Pappu et al 2008). DcR3 is a soluble decoy receptor that is also bound by other TNF superfamily members FASL and LIGHT (Zhan et al 2011; Migone et al 2002). DcR3 binding of TL1A competes with DR3 binding thereby competitively inhibiting the results of TL1A-DR3 signaling (Migone et al 2002).

Under most circumstances, TL1A signaling through DR3 activates the NF-κB signaling pathway and has both costimulatory and anti-apoptotic effects on T cells (Migone et al 2002). Additionally, DR3 contains a canonical TNF receptor family death domain and may be pro-apoptotic in cells lacking the NF-κB signaling pathway or under conditions where this pathway is not activated, eg, under cellular stress (Wen et al 2003).

TL1A signaling is not a primary driver of immune responses but rather amplifies responses under certain conditions. It has been reported as amplifying type 1 helper T-cell (Th1) responses by synergizing with interleukin 12 (IL-12) (Bamias et al 2003; Papadakis et al 2004), Th17 responses by synergizing with IL-23 (Pappu et al 2008; Takedatsu et al 2008), and Th2 responses by both amplifying response to antigen (Kayamuro et al 2009) and inhibiting the production of inducible regulatory T cells (Tregs) and the function of natural Tregs (Meylan et al 2011). TL1A signaling through DR3 also enhances Th9 cell pathogenicity in allergic responses (Richard et al 2015), and is associated with type 2 innate lymphoid cells (ILC2) expansion and survival including in a murine model of asthma (Meylan et al 2014; Yu et al 2014). TL1A is an attractive target for therapeutic intervention because targeting TL1A should mitigate over-activation of immune responses while leaving baseline immunity intact.

1.1.4. TEV-48574

TEV-48574 is a highly potent, fully human immunoglobulin G (IgG) subclass 1 (IgG_1) (lambda) monoclonal antibody (mAb) that targets TL1A. TEV-48574 is a blocking antibody that inhibits the binding of TL1A to its cognate signaling receptor, DR3. By competitively inhibiting TL1A binding to DR3, the antibody prevents activation of the DR3 signaling pathway. TEV-48574 also inhibits the binding of TL1A to DcR3 although TEV-48574 preferentially inhibits the TL1A-DR3 interaction over the TL1A-DcR3 interaction. TEV-48574 has shown efficacy in nonclinical studies (Section 1.2.1) and was safe and well tolerated in the Phase 1 study TV48574-SAD-10126 (Section 1.2.2).

The purpose of this study is to establish proof-of concept (POC) through the evaluation of efficacy of TEV-48574, as well as to further evaluate safety, in patients with T2-low and non-T2 severe asthma that is uncontrolled on standard of care therapies (ICS+LABA).

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and the first in human study [redacted] are provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

1.2.1. Nonclinical Studies

[redacted]

A comprehensive set of in vitro and in vivo nonclinical studies was conducted to support TEV-48574 long-term therapeutic use in humans.

[redacted]

[redacted]

The nonclinical safety program conducted with TEV-48574 consisted of a [redacted]

The nonclinical safety program revealed no safety concerns. [redacted]

1.2.2. First-in-Human Clinical Study

The first-in-human study [redacted] was a Phase 1, randomized, double-blind, placebo-controlled, parallel-group study to determine the safety, tolerability, PK, and immunogenicity of TEV-48574 after:

- [redacted]
- [redacted]

[redacted]

High level summaries of data are provided below. Details can be found in the IB.

[redacted]

[redacted]

Safety

No deaths, serious adverse events, protocol-defined adverse events of special interest (severe hypersensitivity reactions or anaphylaxis) or withdrawals due to adverse events were reported during the study.

No adverse events consistent with immunosuppression (including opportunistic or unusual infections or malignancies), cytopenias, cytokine release syndrome, or systemic reactions were reported and no safety signal was observed with treatment-emergent ADA responses. The nature and incidence of the adverse events (AEs) were similar between doses and comparable to placebo. There were no dose-related trends and no clinically meaningful differences observed between the treatment groups for laboratory tests, vital signs, electrocardiogram (ECG), and physical examination findings.

[redacted]

Immunogenicity

Immunogenicity is considered a risk for all biologics including TEV-48574 and ADA responses are expected. [redacted] No safety signal with treatment-emergent ADA responses was observed. Details can be found in the IB.

1.3. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product

[redacted]

This Proof of Concept study will investigate the efficacy of TEV-48574 in patients with T2-low and non-T2 severe asthma uncontrolled on standard of care (ICS+LABA). As described in Section 1.1.2, such patients may benefit from the development of further therapy options. Management of the patients' safety during the study, including their asthma control, is detailed in Section 3 (study design), Section 7 (assessment of safety), and Appendix B (Joint Data Monitoring Committee [JDMC]).

Management of study activities during coronavirus disease 2019 (COVID-19) outbreaks is detailed in Appendix J.

Additional information regarding benefits and risks to patients may be found in the IB.

In summary, the benefit and risk assessment for TEV-48574 in this POC study is considered favorable following review of data from the completed Phase 1 clinical study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary, Secondary, and Other Study Objectives and Endpoints

The primary, secondary, and other study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the study is to evaluate the effect of TEV-48574 compared with placebo on loss of asthma control (LoAC) in adult patients with T2-low and non-T2 severe asthma uncontrolled on inhaled corticosteroids plus long-acting beta-agonists (ICS+LABA).	Primary efficacy endpoint: Proportion of patients who experience loss of asthma control (LoAC) during the treatment period. LoAC is defined as any one of the following during the treatment period: • Morning PEF decrease ≥30% from baseline on 2 consecutive days or morning handheld FEV_1 decrease ≥20% from baseline on 2 consecutive days • Increase in SABA/quick-relief medication ≥6 puffs over baseline use in 24 hours on 2 consecutive days • Increase in ICS dose ≥4x most recent dose • Systemic corticosteroid use • Asthma ER visit or hospitalization
The secondary efficacy objective is to evaluate the effect of TEV-48574 compared with placebo on a range of clinical measures of asthma control	Key secondary efficacy endpoints: • Time from randomization to LoAC during the treatment period • Asthma Control Questionnaire 6-question version (ACQ-6) at end of treatment (EOT) and throughout the study • Forced expiratory volume in the first second of exhalation (FEV_1) (% predicted, L) at EOT and throughout the study • Use of SABA quick relief medication at EOT and throughout the study Other secondary efficacy endpoints: • Proportion of patients who have a CAE during the treatment period • Time from randomization to first CAE during the treatment period • Number of nighttime awakenings due to asthma during the treatment period • Percent decrease in ICS dose during the treatment period • Other lung function parameters as assessed by hand-held spirometry at end of treatment (EOT) and throughout the study • Fractional exhaled nitric oxide (FeNO) throughout the study

Objectives	Endpoints
Other objectives include the evaluation of the safety and tolerability, device-related events, pharmacokinetics, and immunogenicity of TEV-48574	Safety and tolerability endpoints: • Frequency of adverse events • Change from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study • Change from baseline in vital signs throughout the study • Change from baseline in 12-lead electrocardiogram (ECG) findings throughout the study • Use of concomitant medication • Local tolerability • Number (%) of patients who did not complete the study due to adverse events Device-Related Events • All device-related adverse events, malfunctions etc. will be recorded and evaluated for their impact relative to the safety and efficacy of the investigational medicinal product. Pharmacokinetic endpoints: • Trough serum TEV-48574 concentrations throughout the study (sparse sampling) • Population pharmacokinetic analysis of pharmacokinetic data Immunogenicity endpoints: • Assessment of treatment-emergent ADA responses: change from baseline and throughout the study • Impact of the presence of ADAs on pharmacokinetics and clinical safety (if possible). • Assessment of neutralizing ADA in ADA positive patients throughout the study

2.1.1. Justification of Primary Endpoint

LoAC is a clinically relevant endpoint suited to proof of concept and shorter clinical trials that is related to annualized exacerbation rate, a well-established endpoint used to assess efficacy of asthma therapies, including in registration trials. In the past, LoAC has been referred to as asthma exacerbation (without requiring systemic corticosteroids): for clarification purposes and to distinguish this endpoint from clinical asthma exacerbations, the term LoAC will be employed for this clinical trial. Proof-of-concept will be evaluated by investigating the effect of TEV-48574 on the proportion of patients who experience a LoAC event in a population of patients with severe uncontrolled T2-low and non-T2 asthma who will undergo withdrawal of background asthma controller therapies.

2.2. Exploratory [redacted]

2.2.1. Exploratory [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

2.2.2. Exploratory [redacted]

[redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group POC study to evaluate the efficacy and safety of TEV-48574 administered sc every 2 weeks in adult patients aged 18 years and older with T2-low and non-T2 uncontrolled severe asthma. The primary efficacy endpoint is the proportion of patients who experience loss of asthma control (LoAC) during the treatment period.

Eligibility requirements include: peripheral blood eosinophil counts of <250 cells/µL (at least 2 out of 3 measurements both <250 cells/µL separated by 2 weeks [± 3 days]); an ACQ-6 score ≥1.5 despite daily treatment with medium/high dose ICS+LABA for at least 3 months with a stable dose for at least 1 month prior to screening, with or without other asthma controller medications, and at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma, or an inpatient hospitalization due to asthma, or a 2-fold or higher increase from the subject's usual maintenance ICS dose during the exacerbation period, documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit (Visit S1). Patients with asthma controller medications (excluding systemic corticosteroids and systemic immunomodulatory therapies) in addition to ICS+LABA may be eligible provided all eligibility criteria are met. Detailed inclusion and exclusion criteria can be found in Section 4.1 and Section 4.2.

The study will consist of an approximate 4- to 5-week screening/run-in period, a 16-week treatment period, and an 8-week follow-up period. The initial 5-week period consisting of screening plus run-in may be extended for up to 14 days if needed for the shipment of investigational medicinal product (IMP) to the investigational site or to complete assessment of eosinophil counts. All inclusion and exclusion criteria, with the exception of the second eosinophil count, should be assessed within the first 2 weeks of Visit S1.

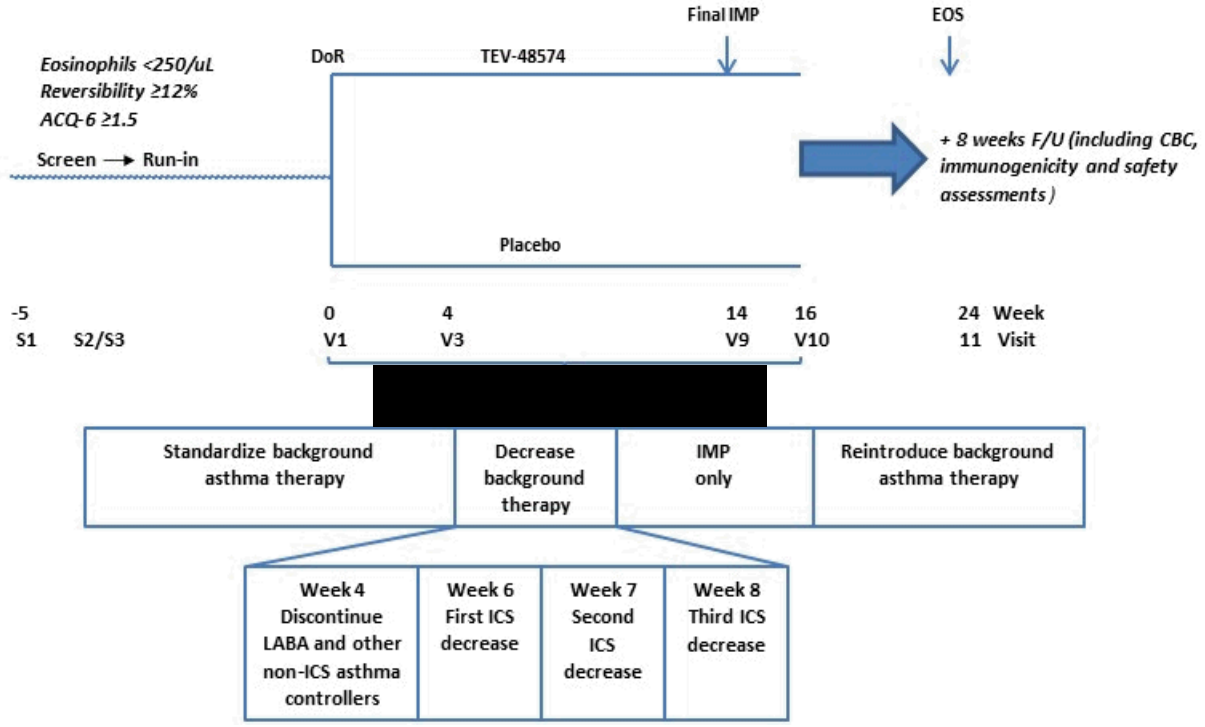
If a patient contracted and recovered from COVID-19 more than 6 weeks prior to screening, and the patient was not admitted to a hospital's ICU during that COVID-19 infection, and if the patient's symptoms from COVID-19 completely resolved back to pre-COVID-19 status (no lingering anosmia, weakness, persistent dyslogia or feelings of dysphoria for many months after the infection resolved), then the patient may enroll in the trial. The principal investigator should determine whether or not the subject has truly recovered back to his/her usual pre-COVID -19 status and is eligible for enrollment in the study.

An e-diary will be dispensed at the second screening visit (Visit S2), 2 weeks (± 3 days) after the initial S1 screening visit. Patients who meet all inclusion criteria (except for eosinophil counts if assessment is incomplete) and none of the exclusion criteria are eligible to enter the run-in and have their ICS+LABA standardized with study-provided ICS+LABA (background asthma controller therapy) at Visit S2; this should start at least 2 weeks prior to randomization and marks the start the of run-in. At the end of run-in, patients who continue to meet all of the inclusion criteria, none of the exclusion criteria, and all of the randomization criteria will be eligible to be randomized to TEV-48574 ([redacted]). For patients who are randomized, the standardized

ICS+LABA dose must be maintained and the patient held stable on that dose for the first 4 weeks of the treatment period, followed by a structured decrease in background asthma controller therapies for patients not meeting criteria for LoAC. Patients will be monitored via hand-held spirometry and e-diary daily, including between visits, throughout the study. Patients who experience an event of LoAC will be treated by the investigator, discontinue IMP, restart (or increase) background asthma controller therapies, and remain in the study and complete all remaining visits, procedures and assessments, except for IMP administration. The total duration of patient participation in the study is planned to be up to approximately 30 weeks.

The screening and run-in, treatment, and follow-up periods are described below; the study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



ACQ-6 = 6-question Asthma Control Questionnaire; CBC = complete blood count; DoR = day of randomization; EOS = end of study; EOT = end of treatment; F/U = follow up; IMP = investigational medicinal product.

Screening and Run-in (4- to 5- weeks)

Screening starts with the initial screening visit and will be followed by a run-in that proceeds through the day prior to the day of randomization. The duration of the screening and run-in period will be approximately 5 weeks and may be extended by up to 14 days to allow for IMP shipping and to complete assessments of peripheral blood eosinophil count. Screening assessments and procedures will be completed over at least 2 visits, including the initial screening visit, and may be completed over more than 2 visits. An effort should be made to complete screening assessments and procedures in the first 2 weeks following Visit S1, with the exception of obtaining the samples for the second (and if applicable third) peripheral blood eosinophil counts.

Samples for peripheral blood eosinophil counts should be collected at 2 time points. The first time point should be at Visit S1, if possible, and the second (Visit S2) 14 days (± 3 days) after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that the third time point is 14 days (± 3 days) after Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.

Patients will receive a hand-held spirometer and an e-diary at Visit S2 (14 days ± 3 days) after the initial screening Visit S1, and will be trained on their use. Patients will record spirometry and e-diary results daily throughout the study (screening and run-in through the end of the follow-up period/EOS).

Reversibility testing may be performed on another day if the patient has not withheld LABA and SABA for the requisite number of hours: reversibility testing should only be attempted after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Patients may only be asked to hold bronchodilators for reversibility once informed consent has been signed. However, if of their own volition, without being asked, patients have not taken any of the aforementioned bronchodilators for the requisite amount of time prior to the initial screening visit, reversibility may be performed at the initial screening visit.

When the e-diary is dispensed, or when reversibility is performed during screening (whichever comes first), the patient's pre-study quick relief rescue medication will be converted to study-provided albuterol/salbutamol inhalers. The subject's pre-study quick relief rescue medication will be converted to study-provided albuterol/salbutamol inhalers at Visit S1. At Visit S2, once all eligibility criteria (inclusion and exclusion) have been confirmed, with the exception of the second peripheral blood eosinophil count, eligible patients will have their ICS+LABA converted to study-provided ICS+LABA inhalers and commence run-in; this should be completed at least 2 weeks prior to randomization.

All patients will be provided with the strength of inhaled fluticasone propionate plus salmeterol closest to the equivalent of the patient's pre-screening ICS+LABA. This will include fixed-dose combination ICS+LABA and any additional ICS dose. Patients on additional asthma controller medication(s) except those excluded by the eligibility criteria (see Section 4.2) will continue those medications throughout the run-in period and will discontinue them at 4 weeks after randomization (Visit 3).

Treatment Period (16 weeks)

The treatment period begins with randomization and ends with the EOT visit (week 16). After the end of the screening period, patients who meet all of the inclusion criteria (Section 4.1), none of the exclusion criteria (Section 4.2), and all of the randomization criteria (Section 4.3) will be randomized in a 1:1 ratio to the following regimens administered sc every 2 weeks:

- TEV-48574 [redacted]
- Placebo to match TEV-48574

With randomization, patients enter the 16-week treatment period. The patients will receive the IMP loading dose on the day of randomization and the subsequent corresponding IMP maintenance dose every 2 weeks for a total of 8 doses (1 loading dose and 7 maintenance doses).

[redacted]

Patients qualifying for randomization will continue the same background asthma controller regimen as used during run-in without change for the first 4 weeks of the treatment period; this regimen includes study-provided controller inhalers (ICS+LABA and additional ICS), plus any additional controller medications that met the eligibility criteria. After week 4, background asthma controller therapies will be decreased in a structured manner in patients not experiencing LoAC (see Section 6.1.1 for LoAC definition) (the patient will be aware of the dose decreases). The first step is implemented after the first 4 weeks of the treatment period and includes discontinuing LABA and any additional asthma controller medications, with the exception of study-provided additional ICS. The second step will be made 2 weeks later. The second and subsequent steps will consist of decreasing the ICS dose step-wise weekly, by ~50%. For patients on ICS doses greater than the high dose ICS+LABA twice a day, the total ICS dose should also be decreased step-wise weekly, by ~50%. Excluding patients who meet LoAC criteria during the structured withdrawal of background asthma controller therapies, the duration of treatment with IMP only will be approximately 8 or 9 weeks. Since study-provided asthma controller formulations may vary locally, Table 1 shows an example of the step-wise structured withdrawal. Eligibility assessment for structured withdrawal of background asthma controller therapies (between scheduled in-person visits) may be done by phone; if it is suspected that a patient meets the criteria for LoAC, the investigator may ask the patient to attend the site for an unscheduled visit.

Table 1: Examples of Schedule of Withdrawal of Background Asthma Controller Therapies

		Dose at start of treatment period	
Time point: Weeks after randomization (visit number)	**Action**	**Fluticasone/salmeterol 500/50 µg BID**	**Fluticasone/salmeterol 250/50 µg BID**
4 weeks (V3)	Discontinue LABA and other non-ICS asthma controllers*	FP 500 BID	FP 250 BID
6 weeks (V4)	First ICS decrease	500 decreased to 250 BID	250 decreased to 100 BID
7 weeks (Telephone, V5)	Second ICS decrease	250 decreased to 100 BID	100 BID decreased to 0
8 weeks (V6)	Third ICS decrease	100 BID decreased to 0	0

*Other asthma controllers (eg, LAMA, leukotriene antagonists) will also be discontinued.
Note: Last IMP administration 14 weeks after randomization (visit 9); end-of-treatment visit (EOT) 16 weeks after randomization
BID=twice daily; FP=fluticasone propionate; ICS=inhaled corticosteroids; LABA=long-acting beta-agonists; LAMA= long-acting muscarinic antagonist; V = visit.

Patients will be monitored for worsening of asthma and potential LoAC (and CAE) both at scheduled visits and in between visits via hand-held spirometry and e-diary. Asthma specific alerts will be sent for the following:

- Decrease in morning FEV_1 ≥20% from baseline on 2 consecutive days OR decrease in morning PEF ≥30% from baseline on 2 consecutive days
- Increase in rescue medication use/SABA of 4 or more puffs over baseline for 2 or more consecutive days OR ≥12 puffs in any single day
- Increase of 2 nighttime awakenings due to asthma over baseline on 2 consecutive days

In the event of an alert, the site will follow-up with the patient. An alert does not mean that the patient's medications need to be changed or that study drug should be discontinued, only that the patient should be contacted and evaluated by phone or at an unscheduled visit according to investigator judgment. If, in the investigator's judgment, LoAC is suspected, every effort to have the patient evaluated at an unscheduled visit should be made.

Definitions of LoAC and Clinical Asthma Exacerbation (CAE) are presented in Section 6.1.1 and Section 6.1.2. LoAC events and CAEs will be treated by the investigator according to local standard of care. In the event of a LoAC or CAE, IMP will be discontinued and background asthma controller therapy will be restarted or increased per investigator judgment. Patients who experience LoAC or CAE will remain in the study for assessments. (Note: CAEs are a subset of LoAC events; see Section 6.1.1 and Section 6.1.2 for definitions).

Study procedures and assessments are described in detail Section 3.6.

The last dose will be administered 14 weeks after the start of the treatment period (randomization). The EOT visit that takes place 2 weeks after the last dose (ie, 16 weeks after the start of the treatment period) marks the end of the treatment period. After EOT, patients may restart the background asthma controller therapy regimen that they started at randomization.

Patients have the right to withdraw from the study completely or to discontinue treatment with IMP while remaining in the study at any time. Patients who withdraw from the study before completing the treatment period are encouraged to complete EOT/early termination (ET) visit as soon as possible after receiving their last dose of IMP (Section 4.4.3). Patients who discontinue treatment with IMP for reasons other than a protocol defined LoAC or CAE while remaining in the study are encouraged to complete ET visit procedures as soon as possible after receiving their last dose of IMP (Section 4.4.2) and to complete the remaining study visits and assessments (with the exception of administration of IMP).

Follow-up Period (8 weeks)

After the end of the 16-week treatment period, the patient will enter the 8-week follow-up period for continued assessments. During the follow-up period, patients may resume their study-provided background controller therapies. This follow-up visit marks the end of study (EOS). Patients who complete the EOS visit will be considered to have completed the study.

The end of trial for notification purposes will be the last patient last EOS visit.

The study duration will be approximately 18 months. The study is expected to start in Q3 2020 and last until approximately Q1 2022. The expected duration of the study may also be extended dependent on enrollment, sample size adjustment, and other factors.

The principal investigator is the main investigator at each site; the responsibilities of the principal investigator are outlined in Section 11.

Detailed information about study procedures and assessments are presented in Section 6 (efficacy), Section 7 (safety), and Section 8 (pharmacokinetics, immunogenicity, exploratory measures including [redacted]).

Details about the timing of study procedures and assessments are presented in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up).

Management of study activities during COVID-19 outbreaks is detailed in Appendix J.

3.2. Planned Number of Patients and Countries

Approximately 310 patients will be screened to achieve approximately 62 randomized patients per arm (124 in total). An unblinded interim analysis (described in Section 9.12) is planned, which could result in a sample size increase, from the initially planned 124 to up to 174 total randomized patients (87 per arm), which would require up to 435 patients screened.

Assuming a dropout rate of approximately 15%, the number of evaluable patients is planned to be approximately 52 per arm (104 in total). If the sample size increases as a result of the interim analysis, the number of evaluable patients would be expected to increase proportionately (eg, approximately 148 evaluable patients for a sample size of 174 patients randomized). Details on definition of evaluable patients and sample size are given in Section 8.4.

The study is planned to be conducted in the United States and the European Union across approximately 75 investigational centers in approximately 5 countries. Additional geographic locations and investigational centers may be added, if needed.

3.3. Justification for Study Design and Selection of Population

This is a placebo-controlled POC study to evaluate the efficacy and safety of TEV-48574 in adult patients with uncontrolled severe asthma of the T2-low and non-T2 type. As is typical after Phase 1, the efficacy of TEV-48574 has not yet been established. The purpose of this POC study is to investigate the efficacy and safety of TEV-48574 in patients with T2-low and non-T2 severe asthma uncontrolled on standard of care (ICS+LABA). The primary and secondary efficacy objectives have been designed to test POC with a TEV-48574 loading dose of [redacted] sc followed by maintenance doses of [redacted] sc every 2 weeks over a treatment period of 16 weeks (with structured decreases in background asthma controller therapies starting 4 weeks after randomization). The study has also been designed to protect the safety of the participating patients. The results of this study may support the development of TEV-48574, with potential benefits for patients with uncontrolled severe asthma, especially with T2-low and non-T2 endotypes.

[redacted]

To mitigate other potential risks to patients, in addition to every-two-weeks in-person evaluations, daily measures of asthma control including FEV_1 and rescue medication use will be

collected between visits and decreases in background asthma controller therapies will be structured. Patients who experience loss of asthma control, as defined by this protocol (Section 6.1.1), will stop the IMP, receive appropriate treatment by the investigator and resume background asthma controller therapy.

The sample size calculation is provided in Section 9.1. The TEV-48574 dose to be evaluated in this study was selected [redacted] (Section 5.5.1). A placebo control arm will be used to establish efficacy and safety (Section 5.5.2). Randomized treatment allocation (Section 5.13.1) and double-blinding (Section 5.13.2) will be used to prevent bias in the assessment of efficacy and safety.

3.4. Stopping Rules for the Study

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor may terminate the study in the event of:

- new toxicological or pharmacological findings or safety issues that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of TEV–48574 for treatment of asthma

If the whole study or arms of the study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.4).

3.5. Joint Data Monitoring Committee

There will be a JDMC in this study. The data will be reviewed in a blinded fashion. The JMDC will recommend whether to continue the study as designed, conduct protocol/informed consent form (ICF) modifications, temporarily suspend enrollment and/or study intervention until some uncertainty is resolved, or discontinue the study. Details for the JDMC are given in Appendix B.

3.6. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). Detailed descriptions of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetics, immunogenicity, and exploratory measures including [redacted]). Study procedures and assessments by visit are listed in Section 3.6.1.

Table 2: Study Procedures and Assessments: Screening and Run-In

Note: Screening will include at least 2 visits and may be completed over more than 2 visits. The screening assessments and procedures for the first screening visit may be completed over more than one visit: sites should make every effort to complete the screening assessments and procedures in the first 2 weeks following the initial screening visit, with the exception of the second eosinophil count. If the screening assessments and procedures are divided over more than one visit, each additional screening visit should include the following: prior/concomitant medication inquiry; adverse event inquiry, LoAC/CAE inquiry, daily e-diary and handheld spirometry review including adherence, vital signs, and brief physical exam. Once all inclusion and exclusion criteria have been assessed, with the exception of the second eosinophil count, and it has been confirmed that patients meet all of the inclusion criteria and none of the exclusion criteria (with the exception of incomplete assessment of eosinophil count), the run-in will commence at Visit S2 with the provision of study-provided ICS+LABA.

Samples for peripheral blood eosinophil counts will be collected at a minimum of 2 time points. The first time point should be at the initial screening visit (Visit S1), if possible, and the second (Visit S2) 14 days (± 3 days) after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that the third time point is 14 days (± 3 days) after the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.

Study period	**Screening and Run-In**	
Visit number	**S1** Screening (may be completed over more than one visit)	**S2/3** At least 1 other visit for peripheral eosinophil count (blood draw)
Procedures and assessments, weeks before randomization	**-5**[a]	
Informed consent	X	
Inclusion and exclusion criteria	X	X
Demography	X	
Medical history	X	
Asthma and allergy history	X	
Prior/concomitant medication inquiry	X	X
Adverse events inquiry	X	X
Perform COVID-19 symptoms inquiry[b]	X	X
LoAC and CAE inquiry	X	X
ACQ-6	X	
ECG[c]	X	
Vital signs measurement[d]	X	X
Full physical examination, including height and weight[e]	X	
Brief physical examination[e]		X

Study period	**Screening and Run-In**	
Visit number	**S1** Screening (may be completed over more than one visit)	**S2/3** At least 1 other visit for peripheral eosinophil count (blood draw)
Procedures and assessments, weeks before randomization	**-5**[a]	
FeNO[f]	X	
Distribute e-diary and handheld spirometer		X
Review e-diary for SABA/quick-relief medication usage, and nighttime awakenings/asthma symptoms, including adherence		X (S3)
Review hand-held spirometry, including for adherence		X (S3)
Spirometry with reversibility testing[g]	X	X (if not completed prior to this visit)
Distribute albuterol/quick-relief medication	X	
Infectious serologies[h]	X	
TB screening[i]	X	X (at S3 if needed)
Urine drug screen including cotinine	X	
Hormone testing (FSH, for confirmation in females reporting postmenopausal status)	X	
Serum pregnancy test (women of childbearing potential)	X	
Urine pregnancy test (women of childbearing potential)		X
Serum Chemistry	X	
CBC with differential count	X	
Peripheral eosinophil count	X	X (at S3 if needed)
Coagulation	X	
Urinalysis	X	
Run-in		Distribute study-provided controller inhalers at S2 and commence run-in once all inclusion and exclusion criteria, with the exception of the second eosinophil count, have been fulfilled (see text in Section 3.6.1.1)

[a] Run-in may be extended for up to 14 days if needed for the shipment of IMP to the investigational site or to complete assessment of eosinophil counts.

[b] Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening/run-in, will be tested for active COVID-19 infection. Patients who were hospitalized in the intensive care unit for COVID-19 are excluded.

[c] ECGs should be performed before scheduled blood draws and after the subject has been in a supine position for 5 minutes.

[d] Vital signs measurements include blood pressure, pulse, body temperature, and respiratory rate. Patients are to remain in a supine position for at least 5 minutes prior to measuring blood pressure and pulse. If possible, blood pressure measurements should be completed on the same arm at each visit. Vital signs should be measured before scheduled blood draws.

[e] For details on full/brief physical examinations, see Section 7.7.

[f] FeNO should be completed before reversibility testing.

[g] Patients need to have signed the ICF before being asked to hold medications for reversibility testing. Therefore, initial reversibility testing may take place at a visit after the initial screening visit (see Section 3.6.1.1 for additional details). Reversibility testing should only be attempted after withholding short acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Patients who do not meet reversibility criteria (≥12% and ≥200 mL), may be re-tested once during the initial 2 weeks (±3 days) of the screening period.

[h] Serology includes hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (HCV), and human immunodeficiency virus (HIV) types 1 or 2.

[i] QuantiFERON® TB Gold Test (If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, additional samples will be tested to confirm diagnosis; see Section 7.5.2 for details.)

ACQ-6=Asthma Control Questionnaire 6-question version; CAE=clinical asthma exacerbation; COVID-19= coronavirus disease 2019; ECG=electrocardiogram; FSH=follicle-stimulating hormone; ICF=informed consent form; ICS+LABA=inhaled corticosteroids + long acting beta-agonists; IMP=investigational medical product; LoAC=loss of asthma control; SABA=short-acting beta agonist; TB=tuberculosis

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Table 3: Study Procedures and Assessments: Treatment Period (Visits 1 – 10)

Study period	**Treatment Period – Visits 1 – 10**									
Visit number	**V1 DoR**	**V2**	**V3**	**V4**	**V5 Phone[a]**	**V6**	**V7**	**V8**	**V9**	**V10 EOT[b]**
Procedures and assessments weeks after random. *study day*	**0** *-*	**2** *15*	**4** *29*	**6** *43*	**7** *50*	**8** *57*	**10** *71*	**12** *85*	**14** *99*	**16** *113*
Allowed time windows, ±days	**-**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Inclusion and exclusion criteria	X									
Randomization criteria	X									
LoAC and CAE inquiry[c]	X	X	X	X	X	X	X	X	X	X
Review e-diary for SABA/quick-relief medication usage[d] and nighttime awakenings, including for adherence	X	X	X	X	X	X	X	X	X	X
Review hand-held spirometry, including for adherence	X	X	X	X	X	X	X	X	X	X
ACQ-6	X	X	X	X		X	X	X	X	X
Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.	X	X	X	X		X	X	X	X	X
Check supply of study-provided SABA. Collect returned inhalers.	X	X	X	X		X	X	X	X	X

Study period	**Treatment Period – Visits 1 – 10**									
Visit number	**V1** **DoR**	**V2**	**V3**	**V4**	**V5** **Phone**[a]	**V6**	**V7**	**V8**	**V9**	**V10** **EOT**[b]
Procedures and assessments **weeks after random.** ***study day***	**0** ***-***	**2** ***15***	**4** ***29***	**6** ***43***	**7** ***50***	**8** ***57***	**10** ***71***	**12** ***85***	**14** ***99***	**16** ***113***
Allowed time windows, ±days	**-**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X
Adverse events inquiry	X	X	X	X	X	X	X	X	X	X
Perform COVID-19 symptoms inquiry[e]	X	X	X	X	X	X	X	X	X	X
ECG[f]	X		X			X		X		X
Vital signs measurement[g]	X	X	X	X		X	X	X	X	X
Full physical examination, including weight[h]	X									X
Brief physical examination		X	X	X		X	X	X	X	
FeNO[i]	X	X	X	X		X	X	X	X	X
Background asthma controller therapies withdrawal (other than ICS/LABA)	X									
Background asthma ICS/LABA controller therapies withdrawal evaluation[j]			X	X	X	X	X	X	X	

Study period	**Treatment Period – Visits 1 – 10**									
Visit number	**V1 DoR**	**V2**	**V3**	**V4**	**V5 Phone**[a]	**V6**	**V7**	**V8**	**V9**	**V10 EOT**[b]
Procedures and assessments weeks after random. ***study day***	**0** ***-***	**2** ***15***	**4** ***29***	**6** ***43***	**7** ***50***	**8** ***57***	**10** ***71***	**12** ***85***	**14** ***99***	**16** ***113***
Allowed time windows, ±days	**-**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
In-office spirometry (full flow-volume loop)	X	X	X	X		X	X	X	X	X
Urine pregnancy test[k]	X	X	X	X		X	X	X	X	X
Serum chemistry	X		X			X		X		X
CBC with differential count	X		X			X		X		X
Urinalysis[l]	X									X
Serum drug concentration[m]	X	X	X			X		X		X
ADA[m]	X	X	X			X		X		X
[redacted] (exploratory)[m]	X		X			X				X
Pharmacogenomics – Blood in PaxGene DNA tube (optional)[n]	X									
IMP administration[op]	X	X	X	X		X	X	X	X	
Local tolerability assessment[q]	X	X	X	X		X	X	X	X	

[a] For patients who have not withdrawn completely from their background asthma controller therapies due to the patient entering the study on higher background asthma controller therapy doses, further phone visits will be performed between in-person visits after V6, V7 etc. (see Section 3.6.1.2.7)

[b] In case of early termination the procedures outlined in Section 3.6.1.2.9 should be followed.

[c] If, in the investigator's judgment, LoAC is suspected, every effort to have the patient evaluated at an unscheduled visit should be made. Procedures and assessments to be performed if an unscheduled visit occurs are described in Section 3.6.1.4. An effort should be made to collect blood samples for TEV-48574 serum concentration and ADA testing at (or as close to) the time of LoAC as possible in addition to the scheduled assessments.

[d] At the visits it should be determined if the patient has adequate rescue medication remaining.

[e] If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from IMP and will need to visit the clinical site again for an early termination visit. Remote assessment of safety via teleconference and/or videoconference, with videoconference being the preferred method, is recommended until the patient is able to visit the clinical site for the early termination visit.

[f] ECG assessments should precede vital sign assessments. ECGs should be performed in a supine position after 5 minutes rest. At DoR, ECG will be performed in triplicate, with each ECG taken within 1 to 5 minutes of the previous one.

[g] Vital signs measurements include blood pressure, pulse, body temperature, and respiratory rate. Patients are to remain in a supine position for at least 5 minutes prior to measuring blood pressure and pulse. If possible, blood pressure measurements should be completed on the same arm at each visit. Vital signs should be measured before scheduled blood draws and after the ECG assessment when applicable.

[h] For details on full/brief physical examinations, see Section 7.7.

[i] FeNO should be completed before in-office spirometry.

[j] A structured decrease in background asthma controller therapies will performed as described in Section 3.1 in patients without LoAC. Further details can be found in the pharmacy manual.

[k] Only for women of childbearing potential.

[l] When sampling urine, menstruation status should be recorded for women of childbearing potential.

[m] In cases of a suspected severe systemic hypersensitivity reaction (eg, anaphylaxis), CAE, LoAC, serious adverse event or immunogenicity-related adverse event, efforts should be made to collect additional sample(s) for immunogenicity, serum total and free TL1A and serum concentration of TEV-48574. In cases of suspected or confirmed anaphylaxis, efforts should be made to collect samples for ADA determination as close to the onset of the event as possible, at resolution, and 30 days after onset of the event.

[n] On signing the appropriate ICF, an optional blood sample may be collected for pharmacogenomics analysis.

[o] If during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6. IMP will be discontinued in patients who experience LoAC and background therapy will be restarted/increased; these patients will stay in the study.

[p] All device-related adverse events, malfunctions etc. will be recorded and evaluated for their impact relative to the safety and efficacy of the IMP.

[q] Administration site findings and pain will be assessed 1 hour after the completion of IMP administration. Additionally after the loading dose and first maintenance dose, assessments will also be performed 2 hours after the completion of administration. Allowed time windows for the local tolerability assessments are ±15 minutes.

ADA=anti-drug antibody; ACQ-6=Asthma Control Questionnaire 6-question version; β-HCG=beta human chorionic gonadotropin; CAE=clinical asthma exacerbation; COVID-19=coronavirus disease 2019; DoR=day of randomization; ECG=electrocardiogram; EOT=End of Treatment; FeNO=fractional exhaled nitric oxide; ICF=informed consent form; ICS+LABA=inhaled corticosteroids + long acting beta-agonists; IMP=investigational medicinal product; LoAC=loss of asthma control; PK=Pharmacokinetic; random=randomization; SABA=short-acting beta agonist; V=visit.

Table 4: Study Procedures and Assessments: Follow-up Period

Study period	**Follow-up**
Visit number	**V11** **EOS**
Procedures and assessments **week after randomization -** ***study day***	**24** ***169***
Allowed time window, ±days	**7**
Concomitant medication inquiry	X
Adverse events inquiry	X
Perform COVID-19 symptoms inquiry[a]	X
LoAC and CAE inquiry	X
Review e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence	X
Review hand-held spirometry, including for adherence	X
Collect e-diary and hand-held spirometer	X
ACQ-6	X
Collect any study-provided inhalers	X
ECG[b]	X
Vital signs measurement[c]	X
Full physical examination, including weight[d]	X
FeNO	X
Urine pregnancy test (women of childbearing potential)	X
Serum chemistry	X
CBC with differential count	X
Urinalysis[e]	X
Serum drug concentration	X
ADA	X
[redacted] (exploratory)	X

[a] If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection.

[b] ECG assessments should precede vital sign assessments. ECGs should be performed in a supine position after 5 minutes rest.

[c] Vital signs measurements include blood pressure, pulse, body temperature, and respiratory rate. Patients are to remain in a supine position for at least 5 minutes prior to measuring blood pressure and pulse. If possible, blood pressure measurements should be completed on the same arm at each visit. Vital signs should be measured before scheduled blood draws and after the ECG assessment when applicable.

[d] For details on full physical examinations, see Section 7.7.

[e] When sampling urine, menstruation status should be recorded for women of childbearing potential.

ACQ-6=Asthma Control Questionnaire 6-question version; ADA=anti-drug antibody; CAE=clinical asthma exacerbation; COVID-19=coronavirus disease 2019; ECG=electrocardiogram; EOS=End-of-study; FeNO=fractional exhaled nitric oxide; LoAC=loss of asthma control; V=visit.

3.6.1. Study Procedures and Assessments By Visit

3.6.1.1. Assessments and Procedures for Screening and Run-in

A signed and dated ICF will be obtained from all patients before screening assessments and procedures commence.

After informed consent is obtained, patients who are screened will be assigned a permanent identification number such that all patients from each investigational center are given consecutive identification numbers in successive order of inclusion.

Note: Screening will include at least 2 visits and may be completed over more than 2 visits. The screening assessments and procedures for the first screening visit may be completed over more than one visit: sites should make every effort to complete the screening assessments and procedures in the first 2 weeks following the initial screening visit, with the exception of the second eosinophil count. It is recommended that the site consider consenting the subject and completing the first peripheral eosinophil count at the initial S1 screening visit in order to determine if the subject meets the eosinophil criteria for enrollment. If the subject is eligible, the remaining S1 assessments and procedures may be performed within two weeks of the initial S1 screening visit. However, sites may elect to conduct the entire S1 screening assessments and procedures at one visit only.

If the screening assessments and procedures are divided over more than one visit, each additional screening visit should include the following: review inclusion/exclusion criteria, prior/concomitant medication inquiry; adverse event inquiry, COVID-19 symptoms inquiry, LoAC/CAE inquiry, vital signs, and brief physical exam. Once all inclusion and exclusion criteria have been assessed, with the exception of the second eosinophil count (see below), and it has been confirmed that patients meet all of the inclusion criteria and none of the exclusion criteria (with the exception of incomplete assessment of eosinophil count), the run-in will commence with the provision of study-provided ICS+LABA at Visit S2.

Samples for peripheral blood eosinophil counts should be collected at 2 time points. The first time point should be at Visit S1, if possible, and the second (Visit S2) 14 days (± 3 days) after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/μL. If one of the results is ≥250 cells/μL, samples may be collected at Visit S3 provided that the third time point is 14 days (± 3 days) after the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/μL.

Efforts to perform the following assessments and procedures in the order listed should be made and may be divided over more than one visit:

3.6.1.1.1. Visit S1

- Obtain written informed consent before any other study-related assessments or procedures are performed.
- Review inclusion/exclusion criteria.
- Document demography and review medical history, including asthma and allergy history.

- Perform prior/concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Perform LoAC and CAE inquiry.
- Complete the ACQ-6.
- Perform ECG.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform full physical examination, and measure height and weight.
- Measure FeNO.
- Perform reversibility testing
  - Patients need to have signed the ICF before being asked to hold medications for reversibility testing. Reversibility testing should only be attempted after withholding short acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Therefore, initial reversibility testing may take place at a visit after the first screening visit.

    Perform reversibility testing if long-acting and short-acting inhaled bronchodilators were held for the specified time; if not, the patient should be brought back on another day to complete. If of their own volition, without being asked, patients have not taken any of the aforementioned bronchodilators for the requisite amount of time prior to the initial screening visit, reversibility may be performed at the initial screening visit. If the inclusion criterion for reversibility is not met, testing may be repeated once within the initial 2-weeks (±3 days) of the screening period. SABAs, such as salbutamol or albuterol, administered via a metered dose inhaler should be used for reversibility testing. Four separate puffs (eg, albuterol 90 μg or salbutamol 100 μg ex-valve, or equivalent) should be given by metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be performed a minimum of 15 minutes after SABA is taken and within 30 minutes after SABA.
- Distribute albuterol/quick-relief medication at Visit S1.
- Obtain sample for infectious serologies.
- Perform tuberculosis screen.
- Perform urine drug screen.
- Perform hormone testing (FSH, for confirmation in females reporting postmenopausal status) and serum pregnancy testing (women of childbearing potential).

- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, coagulation, urinalysis), including peripheral blood eosinophil counts. As described below, a second peripheral blood eosinophil count will be required to fulfil the inclusion criteria.

3.6.1.1.2. Visit S2 (14 days [± 3 days] after Visit S1)

- Review inclusion/exclusion criteria.
- Perform prior/concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Perform LoAC and CAE inquiry.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform brief physical examination.
- Distribute e-diary, instruct the patient on how to perform the respective assessments, and perform first assessments.
- Distribute hand-held spirometer.
- Perform reversibility testing (if not completed prior to this visit).
- Perform urine pregnancy testing (women of childbearing potential).
- Repeat testing of peripheral blood eosinophil counts.
- If all inclusion and exclusion criteria, with the exception of the second eosinophil count, are fulfilled within the first 2 weeks, distribute study-provided controller inhalers to standardize the patient's ICS+LABA and commence run-in. This should start at least 2 weeks prior to randomization.

3.6.1.1.3. Visit S3 (14 days [± 3 days] after Visit S2) (if required)

If required, to meet the eosinophil count inclusion criterion, efforts should be made to perform the following assessments and procedures in the order listed:

- Perform prior/concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Perform LoAC and CAE inquiry.
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.

- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform brief physical examination.
- Repeat testing of peripheral blood eosinophil counts.
- Perform urine pregnancy testing (women of childbearing potential).
- Review inclusion/exclusion criteria.
- If the patient has not already started run-in and all inclusion and exclusion criteria are now fulfilled, distribute study-provided controller inhalers to standardize the patient's ICS+LABA and commence run-in. This should start at least 2 weeks prior to randomization.

3.6.1.2. Assessments and Procedures During the Treatment Period

3.6.1.2.1. Assessments and Procedures for the Day of Randomization (Visit 1): Pre-Study Drug Administration; Randomization, and Administration of the Loading Dose

Patients who have been on study-provided controller inhalers for at least 2 weeks and who meet all of the inclusion criteria, none of the exclusion criteria, and all of the randomization criteria proceed to the Day of Randomization (DoR) visit (Visit 1).

Efforts should be made to perform the following procedures in the order listed, at the Day of Randomization visit before IMP administration:

- Review inclusion/exclusion criteria.
- Review randomization criteria.
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Complete the ACQ-6.
- Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.
- Check supply of study-provided SABA. Collect returned inhalers.
- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Perform ECG in triplicate.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).

- Perform full physical examination and document body weight.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop).
- Perform urine pregnancy testing (women of childbearing potential).
- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, peripheral eosinophil count, urinalysis).
- Collect blood sample for serum TEV-48574 concentration determination (PK assessment) from all patients before IMP administration.
- Collect blood sample for immunogenicity (ADA) assessment.
- Collect blood for [redacted] assessment.
- Collect optional blood sample in PaxGene DNA tube for pharmacogenomics analysis.
- Withdraw all controller medications with the exception of ICS/LABA.

Patients who continue to meet all of the inclusion criteria, none of the exclusion criteria, and all of the randomization criteria will be assigned a permanent unique randomization number and a treatment number generated by interactive response technology (IRT). These two newly assigned numbers will be entered into the CRF, and study drug will be dispensed. During the double-blind treatment period, patients will return to the study center every 2 weeks for administration of IMP, assessments and procedures.

The following procedures/assessments will be performed during and after administration of study drug:

- Administer IMP [redacted] using the [redacted]
- [redacted]
- Evaluation of local tolerability at the administration site at 1- and 2-hours post-administration.
- If, during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.

3.6.1.2.2. Treatment Visit 2 (Week 2)

At this visit, background asthma controller therapies remain unchanged.

Efforts should be made to perform the following assessments and procedures in the order listed, before administration of study drug:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.

- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Complete the ACQ-6.
- Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.
- Check supply of study-provided SABA. Collect returned inhalers.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform brief physical examination.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop).
- Perform urine pregnancy testing (women of childbearing potential).
- Collect blood for serum TEV-48574 concentration determination (PK assessment) from all patients.
- Collect blood sample for immunogenicity (ADA) assessment.

The following procedures/assessments will be performed during and after administration of study drug:

- Administer IMP [redacted] using the [redacted]
- [redacted]
- Evaluation of local tolerability at the administration site at 1- and 2-hours post-administration.
- If, during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.

3.6.1.2.3. Treatment Visit 3 (Week 4)

At this study visit, patients who have not had LoAC will begin the structured withdrawal of their background asthma controller therapies.

Efforts should be made to perform the following assessments and procedures in the order listed:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.

- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Patients who have not had LoAC will commence the structured withdrawal of their background asthma controller therapies (see Section 3.1).
- Complete the ACQ-6.
- Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.
- Check supply of study-provided SABA. Collect returned inhalers.
- Perform ECG.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform brief physical examination.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop).
- Perform urine pregnancy testing (women of childbearing potential).
- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, peripheral eosinophil count).
- Collect blood for serum TEV-48574 concentration determination (PK assessment) from all patients.
- Collect blood sample for immunogenicity (ADA) assessment.
- Collect blood sample for [redacted] assessment.

The following procedures/assessments will be performed during and after administration of study drug:

- Administer IMP [redacted] using the [redacted]
- [redacted]
- Evaluation of local tolerability at 1-hour post-administration.
- If, during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.

3.6.1.2.4. Treatment Visit 4 (Week 6)

At this study visit, patients who have not had LoAC will continue the structured withdrawal of their background asthma controller therapies.

Efforts should be made to perform the following assessments and procedures in the order listed:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Patients who have not had LoAC will continue the structured withdrawal of their background asthma controller therapies (see Section 3.1).
- Complete the ACQ-6.
- Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.
- Check supply of study-provided SABA. Collect returned inhalers.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform brief physical examination.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop).
- Perform urine pregnancy testing (women of childbearing potential).

The following procedures/assessments will be performed during and after administration of study drug:

- Administer IMP [redacted] using the [redacted]
- [redacted]
- Evaluation of local tolerability at the administration site at 1-hour post-administration.
- If, during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.

3.6.1.2.5. Telephone Enquiry, Visit 5 (Week 7)

The patient will be contacted by telephone. The following assessments will be performed:

- Perform prior/concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Review uploaded daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review uploaded daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Patients who have not had LoAC will continue the structured withdrawal of their background asthma controller therapies (see Section 3.1).

If, in the investigator's judgment, LoAC is suspected, every effort to have the patient evaluated at an unscheduled visit should be made.

For patients who have not withdrawn completely from their background asthma controller therapies by visit 5, additional phone visits (P1, P2 etc) should be performed between in-person visits until the withdrawal of background therapies is complete or the patient experiences a LoAC.

As noted Section 3.3, daily measures of asthma control including FEV_1 and rescue medication use will be collected between visits and decreases in background asthma controller therapies will be structured. Patients who experience loss of asthma control at any time, as defined by this protocol, will stop the IMP, receive appropriate treatment by the investigator, and resume background asthma controller therapy.

3.6.1.2.6. Treatment Visit 6 (Week 8)

At this study visit, patients who have not had LoAC will continue the structured withdrawal of their background asthma controller therapies, or IMP only if that had already been reached.

Efforts should be made to perform the following assessments and procedures in the order listed:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Confirm that structured withdrawal of background asthma controller therapy occurred, as discussed during visit 5 (telephone enquiry) (if applicable).
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.

- Patients who have not had LoAC will continue the structured withdrawal of their background asthma controller therapies if not already fully withdrawn (see Section 3.1).
- Complete the ACQ-6.
- Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.
- Check supply of study-provided SABA. Collect returned inhalers.
- Perform ECG.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform brief physical examination.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop)
- Perform urine pregnancy testing (women of childbearing potential).
- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, peripheral eosinophil count).
- Collect blood for serum TEV-48574 concentration determination (PK assessment) from all patients.
- Collect blood sample for immunogenicity (ADA) assessment.
- Collect blood sample for [redacted] assessment.

The following procedures/assessments will be performed during and after administration of study drug:

- Administer IMP [redacted] using the [redacted]
- [redacted]
- Evaluation of local tolerability at the administration site at 1-hour post-administration.
- If, during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.

3.6.1.2.7. Further Telephone Enquiries, Phone 1, 2 etc.

For patients who have not withdrawn completely from their background asthma controller therapies by visit 5, additional phone visits (P1, P2 etc) should be performed between in-person visits until the withdrawal of background therapies is complete or the patient experiences a LoAC.

The patient will be contacted by telephone. The following assessments will be performed:

- Perform prior/concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Review uploaded daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review uploaded daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Patients who have not had LoAC will continue the structured withdrawal of their background asthma controller therapies (see Section 3.1).

If, in the investigator's judgment, LoAC is suspected, every effort to have the patient evaluated at an unscheduled visit should be made.

3.6.1.2.8. Treatment Visits 7 (Week 10), 8 (Week 12) and 9 (Week 14)

At these study visits, most patients who have not had LoAC will have fully withdrawn their background asthma controller therapies and will continue on IMP only.

Patients who have not had LoAC and are not yet on IMP only (due to the initial ICS dose) will continue the structured withdrawal of their background asthma controller therapies.

Efforts should be made to perform the following assessments and procedures in the order listed at each of these visits, unless otherwise indicated:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Confirm that all background asthma controller therapies have been discontinued, as scheduled.
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Patients who have not had LoAC will continue either on IMP only (Section 3.1) or with structured withdrawal of their background asthma controller therapies.
- Complete the ACQ-6.
- Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.
- Check supply of study-provided SABA. Collect returned inhalers.
- Perform ECG (visit 8 only).

- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform brief physical examination.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop).
- Perform urine pregnancy testing (women of childbearing potential).
- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, peripheral eosinophil count; visit 8 only).
- Collect blood for serum TEV-48574 concentration determination (PK assessment) from all patients (visit 8 only).
- Collect blood sample for immunogenicity (ADA) assessment (visit 8 only).

The following procedures/assessments will be performed during and after administration of study drug:

- Administer IMP [redacted] using the KORU [redacted]
- [redacted]
- Evaluation of local tolerability at the administration site at 1-hour post-administration.
- If, during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.

3.6.1.2.9. Early Termination (ET) Visit

Patients who discontinue treatment with IMP for reasons other than the occurrence of LoAC/CAE in the study are encouraged to complete early termination (ET visit) procedures as soon as possible after receiving their last dose of IMP and to complete the remaining study visits and assessments (with the exception of administration of IMP) including EOT and EOS within the original time frames based on day of randomization (DoR). These patients are not considered to have withdrawn from the study.

Patients who decide to withdraw completely from the study are encouraged to complete early termination (ET visit) procedures as soon as possible after receiving their last dose of IMP.

At the ET visit the following procedures/assessments will be performed:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.

- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Complete the ACQ-6.
- Check supply and, if required, dispense study-provided controller therapies (for patients who remaining in the study). Collect returned inhalers.
- Check supply of study-provided SABA (for patients who are remaining in the study). Collect returned inhalers.
- Perform ECG.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform full physical examination.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop).
- Perform urine pregnancy testing (women of childbearing potential).
- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, peripheral eosinophil count, urinalysis).
- Collect blood for serum TEV-48574 concentration determination (PK assessment) from all patients.
- Collect blood sample for immunogenicity (ADA) assessment.
- Collect blood sample for [redacted] assessment.

3.6.1.2.10. End of Treatment (EOT) Visit (Visit 10, Week 16)

Two weeks after the final administration of IMP in the double-blind treatment period, patients will return to the study center for the EOT visit and efforts should be made to perform the following assessments and procedures in the order listed:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Complete the ACQ-6.
- Review background asthma controller therapies to be restarted after EOT visit.

- Check supply and, if required, dispense study-provided controller therapies. Collect returned inhalers.
- Check supply of study-provided SABA. Collect returned inhalers.
- Perform ECG.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform full physical examination.
- Measure FeNO.
- Perform in-office spirometry (full flow-volume loop)
- Perform urine pregnancy testing (women of childbearing potential).
- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, peripheral eosinophil count, urinalysis).
- Collect blood for serum TEV-48574 concentration determination (PK assessment) from all patients.
- Collect blood sample for immunogenicity (ADA) assessment.
- Collect blood sample for [redacted] assessment.

The follow-up period starts after the EOT visit. Patients will restart background asthma controller therapy after this visit.

3.6.1.3. Assessments and Procedures During Follow-up

3.6.1.3.1. Assessments and Procedures at the End of Study Visit

At 24 weeks after randomization (±7 days), patients will return to the study center for the EOS visit.

All patients, including those who discontinued treatment whether for protocol-defined LoAC or other reasons, should complete the End of Study (EOS) visit. Patients who complete the EOS visit are considered to have completed the study.

The monitoring of patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) at the EOS is described in Section 7.1.2.

Efforts should be made to perform the following assessments and procedures in the order listed at the EOS visit (week 24):

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review daily hand-held spirometry, including for adherence.

- Collect e-diary and hand-held spirometer
- Perform LoAC and CAE inquiry.
- Complete the ACQ-6.
- Collect any study-provided inhalers.
- Perform ECG.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform full physical examination and document body weight.
- Measure FeNO.
- Perform urine pregnancy testing (women of childbearing potential).
- Collect samples for clinical laboratory tests (serum chemistry, CBC with differential count, peripheral eosinophil count, urinalysis).
- Collect blood for serum TEV-48574 concentration determination (PK assessment) from all patients.
- Collect blood sample for immunogenicity (ADA) assessment.
- Collect blood sample for [redacted] assessment.

3.6.1.4. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. If, in the investigator's judgment, LoAC is suspected, every effort to have the patient evaluated at an unscheduled visit should be made. The date and reason for the unscheduled visit, as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests), should be documented in the patient's source records and be recorded on the CRF.

Assessments and procedures performed during unscheduled visits include, but are not limited to, the following:

- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Perform COVID-19 symptoms inquiry.
- Review e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.
- Review hand-held spirometry, including for adherence.
- Perform LoAC and CAE inquiry.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform physical exam (brief or full, at the discretion of the investigator).

Other procedures may be performed at the discretion of the investigator. Details for ET visits for patients who withdraw completely from the study and for patients who discontinue treatment for reasons other than per protocol for LoAC events (including CAEs) and remain in the study may be found in Section 4.4.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva (Appendix D). To be eligible for the study, patients must meet all of the inclusion criteria and none of the exclusion criteria. To be eligible for randomization, patients must continue to meet all of the inclusion criteria, none of the exclusion criteria, and all of the randomization criteria.

4.1. Patient Inclusion Criteria

Inclusion Criteria: Patients may be included in the study only if they meet all of the following criteria:

a. The patient is a man or woman of any ethnic origin, at least 18 years of age at the time of signature of the ICF.

b. The patient has a diagnosis of asthma for at least 12 months prior to the initial screening visit.

c. The patient must have an absolute eosinophil count <250 cells/µL (at least 2 measurements both <250 cells/µL separated by 14 days [± 3 days]). If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that the third time point is 14 days (± 3 days) after the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.

d. The patient has an ACQ-6 score ≥1.5.

e. The patient has demonstrated ≥12% and ≥200 mL response to a bronchodilator from baseline FEV_1 within 30 minutes after 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent (eg, Ventolin) at screening.

f. The patient has asthma with a FEV_1 ≥30% and <80% of the value predicted for age, height, sex, and race at screening. FEV_1 must be performed using the office-based spirometer provided for the study. One pulmonary function test retest during the screening visit(s) period (up to 2 weeks) is allowed to fulfill this criterion.

g. The patient is able to perform technically acceptable and repeatable spirometry, including with a hand-held spirometer, after training (applicable to FEV1, not PEF).

h. The patient's background asthma therapy includes daily medium- or high-dose ICS plus LABA for at least 3 months prior to the initial screening visit with or without other asthma controller medications. The dose of ICS may vary during these 3 months, but must remain at a stable daily dose for at least 1 month prior to Visit S1. Medium- and high-dose ICS classification will be based on the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2019 update, Appendix C). Patients with asthma controller medications (excluding systemic corticosteroids and systemic immunomodulatory therapies) in addition to ICS+LABA may be eligible provided all eligibility criteria are met.

i. The patient has had at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit

due to asthma, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit. Only clinical asthma exacerbations with historical documentation in the patient's medical or pharmacy records may count towards this criterion.

j. Patients must be able to replace their pre-study ICS+LABA with study-provided ICS+LABA

k. The patient is a non-smoker for ≥6 months with lifetime history ≤10 pack-years, with no current e-cigarette use. The patient must have a negative urine cotinine test at the screening visit.

l. The patient is able to communicate satisfactorily with the investigator and to participate in, and comply with, the requirements of the study.

m. The patient is able to understand the nature of the study and any potential hazards associated with participating in the study.

n. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and willing to return to the investigational center for further visits, as applicable, and the follow up procedures and assessments as specified in this protocol.

o. Women of non-childbearing potential who are either surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile as assessed by a physician, or 1-year postmenopausal (no menses for at least 12 months without an alternative medical cause plus an increased concentration of follicle stimulating hormone [FSH] of more than 35 U/L in women not using hormonal contraception or hormonal replacement therapy).
Women of childbearing potential must have a negative β-HCG test result and practice a highly effective method of birth control (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, see Section 5.9) prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer.
Male patients (including vasectomized) with WOCBP partners (whether pregnant or not) must use condoms prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results. Examples include but are not limited to: chronic obstructive pulmonary disease, chronic bronchitis or any respiratory condition that requires any chronic antibiotic use (some antibiotics can be immunomodulatory such

as macrolides [eg, erythromycin, azithromycin, and clarithromycin]), bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, and interstitial lung disease (including eosinophilic granulomatosis with polyangiitis [EGPA] which is expressly prohibited), obstructive sleep apnea (sometimes referred to as sleep apnea or Pickwickian Syndrome), and gastroesophageal reflux disease that is not treated with a proton pump inhibitor on a scheduled treatment regimen (not PRN).

b. The patient has any concomitant conditions or treatments that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the study as judged by the investigator and/or the clinical study physician.

c. The patient has any of the following medical conditions:

- Conditions that may mimic asthma (eg, vocal cord dysfunction, hyperventilation, panic attacks, cardiac asthma, uncontrolled gastroesophageal reflux disease [gastroesophageal reflux disease controlled on a stable proton pump inhibitor regimen for at least 1 month may be allowed])
- Conditions of immunodeficiency, immunocompromise, and/or conditions requiring immunomodulatory therapy
- A history of malignancy within 5 years before screening (exception: basal cell carcinoma or in situ carcinoma of the cervix if successful curative therapy occurred at least 12 months prior to screening)
- Tested positive for tuberculosis (TB) at screening by the QuantiFERON® TB Gold Test, or had a history of untreated latent or active TB. If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, a repeat specimen shall be submitted; if the second test is also positive, the patient screen fails; if the second test is negative, a third test shall be submitted; if the third test agrees with the first test, the patient screen fails; if the third test agrees with second test, the patient is considered to be negative for TB; see Section 7.5.2 for details.
- Known history of, or a positive test result for, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) types 1 or 2 at screening
- A history of more than one herpes zoster episode or multimetameric herpes zoster
- A history of an opportunistic infection (eg, cytomegalovirus retinitis, *Pneumocystis carinii*, aspergillosis, *Clostridium difficile*)
- A history of or ongoing chronic or recurrent infectious disease (eg, infected indwelling prosthesis, osteomyelitis, chronic sinusitis)
- A suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the initial screening visit. Note: Patients who develop an upper respiratory

infection/lower respiratory infection (URI/LRI) during the screening period may rescreen 2 weeks after symptoms resolve subject to local or regional public health directives.

- Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening/run-in, will be tested for active COVID-19 infection and will only be included if they test negative for COVID-19. Patients who were admitted to an ICU during a prior COVID-19 infection; or patients who contracted or recovered from COVID-19 less than 6 weeks prior to screening, or patients with COVID-19 symptoms (lingering anosmia, weakness, persistent dyslogia or feelings of dysphoria for many months) from a pre-study COVID-19 infection that have not completely resolved back to their pre-COVID-19 infection health status are excluded from the study.

d. The patient has taken any systemic corticosteroids within 30 days of screening, including but not limited to oral corticosteroids as maintenance therapy for asthma, and/or treatment for clinical asthma exacerbation (CAE) within 30 days of screening.

e. Intensive care unit (ICU) admission or intubation within the 3 months prior to screening.

f. CAE as defined by this protocol (see Section 6.1.2) within the 30 days prior to screening.

g. The patient is currently using any systemic immunosuppressive or immunomodulatory biologic or non-biologic. Note: Previous use of such agents that occurred ≥5 half-lives from the initial screening visit may be allowed, if approved by the clinical study physician.

h. The patient participated in a clinical trial within 30 days or 5 half-lives of the investigational drug before screening.

i. The patient has received investigational drugs targeted against TL1A.

j. Abnormality in laboratory values during screening that is considered clinically significant by the investigator, or could interfere with the objective of the study as determined by the sponsor. Any such laboratory abnormality may be retested at the investigator's clinical discretion and if within normal limits, accepted.

k. The patient is currently pregnant or lactating or is planning to become pregnant during the study or for at least 10 weeks after administration of the last dose of IMP in case of early withdrawal. Any woman becoming pregnant during the study will be withdrawn from the study.

l. The patient has a known hypersensitivity to the IMP and/or excipients.

m. Live and attenuated vaccines should be excluded 14 days before IMP dosing and throughout the study. Inactivated vaccines (including approved inactivated COVID 19 vaccines) should preferably be completed 14 days before first IMP dosing. If

administered during the study it is recommended to be at least 3 days before and after IMP administration, or as required by local country regulations.

n. The patient has a positive urine drug test during screening for compounds of abuse, or for cotinine, the relevant metabolite of tobacco abuse, the use of which would make the patient ineligible. Repeat testing will not be permitted. A positive urine test for tetrahydrocannabinol, the psychoactive ingredient in marijuana, is permitted during the trial.

o. The patient has a history of alcohol or drug abuse within 2 years preceding the initial screening visit.

p. Initiation or dose escalation of allergen immunotherapy (administered by any route) is planned during the study period. However, patients who initiated immunotherapy 90 days or more before the initial screening visit and have been on a stable (maintenance) dose for 30 days or more before the initial screening visit may be considered for inclusion.

q. The patient is either an employee or an immediate relative of an employee of the sponsor or of any of the clinical investigational centers participating in the study.

4.3. Randomization Criteria

The patients must meet the following randomization criteria prior to randomization:

a. The patient continues to meet all of the inclusion criteria (including ACQ-6 ≥1.5) and none of the exclusion criteria.

b. The patient has not had a clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but within 30 days of) the initial screening visit, or other need for systemic corticosteroids during the screening period.

c. The patient has at least 57% adherence (complete and acceptable data for 4 out of the 7 days prior to randomization) to hand-held spirometry and e-diary assessments.

4.4. Withdrawal Criteria and Procedures for the Patient

4.4.1. Withdrawal Criteria

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance) patients may completely withdraw from the study (ie, with no further study participation or contact) at any time for any reason. Patients may also voluntarily discontinue IMP and remain in the study for assessments. The investigator and/or sponsor may also discontinue a patient from IMP and/or withdraw a patient from the study, eg,

- in the event of intercurrent illness, adverse events, pregnancy, or any other reason concerning the health or well-being of the patient that indicates to the investigator that continued participation is not in the best interest of the patient, or

- if the patient is noncompliant with the study procedures and assessments or protocol-defined study restrictions or prohibited concomitant medication

Investigators are to discuss patients who may be considering discontinuing IMP or withdrawing completely from the study with the sponsor as soon as the site becomes aware of the situation.

Investigators should attempt to obtain information on patients in the case of withdrawal from the study or discontinuation from IMP. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study or discontinuation from IMP, should be recorded in the source documents. The case report form (CRF) should document the primary reason for withdrawal from the study or discontinuation from IMP.

Discontinuation of IMP as described above and below does not include patients who discontinue IMP due to a LoAC event, as LoAC events are part of the planned conduct of the study.

If an adverse event is the primary reason for discontinuation of IMP or withdrawal from the study, this should be documented in the source and in the CRF including test results if applicable. Under these circumstances, monitoring should be continued until the event has resolved or stabilized, or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The investigator should inform the sponsor as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports should be provided when requested.

If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from IMP and will attend for an ET visit. Remote assessment of safety via teleconference (TC) and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends for the ET visit.

4.4.2. Discontinuation of IMP

Patients who discontinue treatment with IMP while remaining in the study are encouraged to complete early termination (ET visit) procedures as soon as possible after receiving their last dose of IMP and to complete the remaining study visits and assessments (with the exception of administration of IMP) including EOT and EOS within the original time frames based on date of randomization (DoR). The investigator should determine the reason for and the date of discontinuation of study treatment and record this information in both the source documentation and the CRF. The patient should not be considered withdrawn from the study due to interruption or discontinuation of IMP.

4.4.3. Withdrawal from the Study

If a patient decides to completely withdraw from the study (ie, refuses any further study participation or contact), all study participation for that patient will cease and all data to be collected at subsequent visits will be considered missing. If a patient decides to completely withdraw from the study, the patient should be encouraged return to the clinic as soon as possible to complete EOT/ET visit procedures. A complete final evaluation at the time of the patient's withdrawal should be made, including an explanation of why the patient is withdrawing from the

study. The reason for and date of withdrawal from the study should be recorded in the source documentation and the CRF.

4.4.4. Lost to follow-up

For patients who are lost to follow-up (ie, patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should make appropriate efforts to re-establish contact with the patient; attempts to contact the patient should be documented in the source documents. The investigator should attempt to reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study. Efforts should still be made to locate the patient and obtain information regarding serious adverse events, asthma exacerbation events, and survival status at the end of the 16-week treatment period. Whether or not contact is reestablished with the patient, every effort should be made to ascertain survival status at the end of the treatment period.

4.5. Replacement of Patients

A patient who is randomized but does not complete the treatment period will not be replaced.

4.6. Rescreening

A subject may be rescreened up to 2 times in the study. Rescreening for urine test found positive for illicit drugs or cotinine, or failure to meet inclusion criterion “e” (ACQ-6 score ≥1.5, Section 4.1) will not be allowed. A subject may be rescreened for all other inclusion and exclusion criteria that are not fulfilled.

4.7. Screen Failure

Screen failure occurs when a patient who consents to participate in the clinical study is not subsequently randomized into the study because that patient did not meet inclusion criteria, did meet exclusion criteria, and/or did not meet randomization criteria. Patients will be allowed to screen fail twice before no longer being considered for enrollment in the clinical study.

Selected information about patients who screen-fail will be collected to comply with reporting and publishing requirements. This information may include, but is not limited to, demography, detailed reasons for screening failure, eligibility criteria, and any serious adverse events.

5. TREATMENTS

Investigational Medicinal Products in this study include TEV-48574 (test IMP) and matching placebo (placebo IMP). [redacted]

- TEV-48574 [redacted]
- Placebo to match TEV-48574

Detailed information about the composition of the test IMP and placebo IMP can be found in the following sections.

Other study-provided medications (ICS+LABA, ICS and short-acting bronchodilators) are not considered IMPs in this study (see Section 5.6 for details).

5.1. Test Investigational Medicinal Product

TEV-48574 for subcutaneous administration is provided as a liquid solution with a nominal concentration of 100 mg/mL. Refer to Table 5 for specific details regarding TEV-48574. Additional details may be found in the Pharmacy Manual and in the IB for TEV-48574.

5.2. Placebo Investigational Medicinal Product

Placebo IMP for subcutaneous administration is provided as a liquid solution in the same formulation as TEV-48574, except for absence of active protein. Refer to Table 5 for specific details regarding placebo IMP.

5.3. Test and Placebo Investigational Medicinal Product Administration

TEV-48574 or placebo IMP will be administered sc using the [redacted]

The test and placebo IMP administration procedures are outlined in the Pharmacy Manual.

Table 5: Investigational Medicinal Products Used in the Study

	Test IMP	**Placebo IMP**
Trade name and INN, if applicable, or company-assigned number	TEV-48574	-
Formulation	[redacted]	[redacted]
Unit dose strength(s)/Dosage level(s)	[redacted]	-
Route of Administration	Subcutaneous administration	Subcutaneous administration
Dosing instructions	Refer to details in the Pharmacy Manual	Refer to details in the Pharmacy Manual
Packaging	[redacted]	[redacted]
Manufacturer	[redacted]	[redacted]

IMP=Investigational Medicinal Product.

5.4. Preparation, Handling, Labeling, Storage, and Accountability for IMPs

5.4.1. Storage and Security

The investigator or designee must confirm appropriate temperature conditions have been maintained for all IMPs received and any discrepancies are reported and resolved before use of the IMPs.

[redacted] The site should have a process for monitoring the storage temperature or unused IMP.

5.4.2. Labeling

Supplies of IMPs will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

5.4.3. Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the CFR or national and local regulations, and used in accordance with this protocol.

Only patients enrolled (ie, randomized) in the study may receive IMPs and only authorized staff at the investigational center may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies.

Further guidance and information are provided in the Pharmacy Manual.

5.5. Justification for Investigational Medicinal Products

5.5.1. Justification for Dose of Test Investigational Medicinal Product

The TEV-48574 dose to be evaluated in this study is a [redacted] loading dose sc followed every 2 weeks by a [redacted] maintenance dose sc (7 maintenance doses in total).

This dose was selected on the basis of pharmacokinetic and safety data from the Phase 1 Study [redacted] (Section 1.2.2), [redacted]

5.5.2. Justification for Use of Placebo Investigational Medicinal Product

A placebo-controlled design is scientifically appropriate as the use of a placebo-controlled design in this POC study will allow robust evaluation of any treatment effect of TEV-48574 and characterization of any potential adverse drug reactions.

Patients will have close medical observation throughout the study and will be provided with rescue medication. In addition, only patients for whom it is considered safe to participate in the study, in the opinion of the investigator, will be permitted to participate.

5.6. Other Medicinal Products

Note that other medicinal product is mandated for use in this study; however, for the purposes of this study it is not considered an IMP.

The study-provided ICS+LABA and ICS will consist of fluticasone propionate plus salmeterol and fluticasone propionate with strengths closest to the equivalent of the patient's pre-study ICS+LABA, plus additional ICS if applicable initially and per the structured withdrawal (see Section 3.1) subsequently. Locally approved formulations of fluticasone propionate plus salmeterol and fluticasone propionate will be used if available. Any other controller medications will not be study-provided.

The study-provided SABA/quick-relief bronchodilator medication will be albuterol/salbutamol.

5.7. Treatment after the End of the Study

No additional extension or compassionate use of TEV-48574 is planned after completion of this study. At the EOS visit, the investigator will discuss with the patient the return to appropriate medical care and medication as part of standard of care provided by the patient's primary physician and specialists.

5.8. Restrictions

Patients will be required to comply with the following restrictions:

5.8.1. Activity

Patients should avoid strenuous exercise for at least 4 hours prior to any clinic visit and for at least 4 hours after IMP administration.

5.8.2. Tobacco and illicit drugs

Smoking or use of tobacco products (eg, cigarettes, e-cigarettes, cigars, chewing tobacco, pipe tobacco), and use of illicit drugs is strictly forbidden in this study, and objective tests that indicate the use of and/or exposure to these drugs will be administered at the screening visit. Positive tests will result in an irrevocable screen failure of the subject, and retesting is not permitted. In addition, these drugs may not be used or taken at any time during the trial (from Screening Visit S1 through EOS visit). A positive urine test for tetrahydrocannabinol, the psychoactive ingredient in marijuana, is however, permitted during the trial.

5.8.3. Blood Donation

Patients may not donate blood during the study.

5.9. Effective Methods of Birth Control

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening
- Bilateral tubal occlusion/ligation
- Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical success
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the study period.

5.10. Prior and Concomitant Medication or Therapy

Any prior or concomitant therapy, medication, or procedure a patient has had 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug). In addition, prior biologics and immunomodulatory therapies (biologics and non-biologics should also be recorded in the source documents and in the CRF even if the end date was greater than 4 weeks prior to the initial screening visit.

The following medications will not be allowed during this study:

- Any systemic immunosuppressive or immunomodulatory agents (biological and non-biological excluding systemic maintenance allergen immunotherapy and

systemic corticosteroids for the treatment of LoAC events including clinical asthma exacerbations).

Examples include but are not limited to:

- systemic corticosteroids (except for the treatment of LoAC/CAE during the study)
- methotrexate
- cyclosporine
- interferon
- omalizumab
- dupilumab
- mepolizumab
- benralizumab
- reslizumab
- anti-tumor necrosis factor monoclonal antibodies

- Non-protocol specified ICS+LABA
- Any investigational drug (biologic or non-biologic)
- Investigational drugs targeted against TL1A
- Live and attenuated vaccines

Note:

- Stable maintenance allergen immunotherapy will be allowed. Starting or build-up phase allergen immunotherapy will not be allowed.
- Completion of inactivated vaccination (including available inactivated COVID-19 vaccinations) is preferable at least 14 days before the first IMP dose, if possible. Inactivated vaccination during the study is recommended to be at least 3 days before and after IMP administration, if possible, or as required by local country regulations.

5.11. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance with this protocol from the start of the screening period through the EOS visit.

If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study (Section 4.4). The IEC/IRB/competent authorities should be notified if required by local regulation.

5.12. Randomization and Blinding

This is a randomized, double-blind study. Patients who meet all inclusion criteria, none of the exclusion criteria, and all of the randomization criteria will be randomly assigned to receive TEV-48574 or placebo to match TEV-48574 in a 1:1 ratio.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

The study patients and the clinical team at the site will be blinded to treatment assignment until the database is locked for analysis. Individuals who may not be blinded include (but are not limited to) the bioanalytical scientists, pharmacokineticists, and biostatisticians who are not directly involved in study conduct.

The randomization list will be assigned to the relevant treatment groups through a qualified service provider, eg, via the Randomization and Trial Supply Management (RTSM) system. The generation of the randomization list and management of the RTSM system will be done by a qualified service provider under the oversight of the responsible function at Teva.

5.13. Maintenance of Randomization and Blinding

5.13.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

5.13.2. Blinding and Unblinding

Blinded pharmacokinetic and immunogenicity data may be assessed during the study. For patients who have pharmacokinetic or immunogenicity sample bioanalysis or data analysis conducted, the individuals responsible for sample bioanalysis and other responsible personnel will know who received test IMP and who received placebo IMP during the study (of those patients only). Personnel responsible for bioanalysis will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetic data analysis will not have access to clinical safety and efficacy data, and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to the concentration data of an individual patient).

Pharmacokinetic sample analysis by the bioanalytical laboratory and pharmacokinetic parameter calculations by pharmacokineticists will be performed during the course of the study. The population pharmacokinetic model for TEV-48574 may be updated with new pharmacokinetic data emerging from the ongoing study. The process to ensure study integrity, maintenance of the double blind, and the responsibilities of the relevant study personnel will be described in a pharmacokinetic analysis plan that will be approved prior to any data transfer, per the sponsor's relevant SOP(s) (eg, GBP-RD-502 [Performing Pharmacokinetic Analyses While Maintaining

the Blind]). A similar process could be implemented for the pharmacokinetic/pharmacodynamic model with updated pharmacokinetic and pharmacodynamic data, based on availability of the appropriate SOP.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, both via telephone and internet. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified following the breaking of the treatment code. The patient's IMP assignment should not be revealed to the sponsor.

When a blind is broken, the patient will be withdrawn from the study and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

For an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

The JDMC will review data in a blinded fashion, as outlined in Appendix B.

An interim analysis (Section 9.12) will be conducted by an independent, unblinded statistician who is not a part of the study team. A group of the sponsor's management team who are not a part of the study team may have access to the unblinded interim analysis results. A communication plan to ensure the maintenance of the study blind among the blinded personnel involved in the conduct of the study will be put in place prior to the interim analysis.

5.14. Total Blood Volume

The estimated maximum blood volume to be collected for each patient in this study is approximately 23 mL per visit. With a maximum number of 6 scheduled visits during any 8-week period of the study, the maximum volume within such a period would be 138 mL. Details on blood volumes to be collected during the study are provided in the ICF and Laboratory Manual.

6. ASSESSMENT OF EFFICACY

6.1. Assessments of Efficacy

Refer to Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up) for the timing of assessments and procedures. See Section 3.6 for a detailed description of assessments and procedures.

6.1.1. Loss of Asthma Control (Primary Efficacy Endpoint)

The primary efficacy endpoint is the proportion of patients who experience LoAC during the treatment period.

LoAC is defined as any one of the following during the treatment period:

- Morning PEF decrease ≥30% from baseline on 2 consecutive days or morning handheld FEV_1 decrease ≥20% from baseline on 2 consecutive days
- Increase in SABA/quick-relief medication ≥6 puffs over baseline use in 24 hours on 2 consecutive days*
- Increase in ICS dose ≥4x most recent dose*
- Systemic corticosteroid use
- Asthma ER visit or hospitalization

A patient who meets criteria for LoAC will discontinue IMP, and resume or increase background asthma controller therapies, but will remain in the study. LoAC events will be treated by the investigator according to local standard of care. An effort should be made to collect blood samples for TEV-48574 serum concentration and ADA testing at (or as close to) the time of LoAC as possible in addition to the scheduled assessments (see Table 3 [treatment period] and Table 4 [follow-up]).

In addition to the primary efficacy endpoint of the proportion of patients who experience LoAC, time to LoAC will be a key secondary endpoint (see Section 9.5.2).

*Once background asthma controller therapy has been standardized per protocol, the asthma controller regimen is to remain stable throughout the treatment period until the structured withdrawal per protocol or treatment of LoAC/CAE (Section 6.1.2). Patients who experience LoAC, including CAEs, during the treatment period will discontinue IMP and resume/increase background asthma controller therapy for the remainder of the study.

6.1.2. Clinical Asthma Exacerbation

CAEs are a subset of LoAC events (Section 6.1.1).

Asthma exacerbation during the study is defined as a worsening of asthma symptoms (examples are described below) resulting in any of the following:

- The use of systemic corticosteroids (oral or injectable).
- An emergency department visit due to asthma treated with systemic corticosteroids
- An inpatient hospitalization due to asthma.

Worsening asthma includes new or increased symptoms or signs that either worry the patient, or are related to an asthma-specific alert (if available through the e-diary/hand-held spirometer [see Section 3.1]).

A patient who meets criteria for a CAE will be treated per the local standard of care. Additional medication and/or medical intervention that would satisfy the definition of CAE occurring within 7 days of the last day of a prior CAE event will be considered as part of the same event for analysis purposes.

CAEs will be assessed at the time points specified in Table 2 (screening and run-in), Table 3 (treatment period) and Table 4 (follow-up).

6.1.3. e-Diary

Patients will be trained in using the e-diary to ensure proper use and to ensure rigorous data is collected throughout the study.

6.1.4. Asthma Control Questionnaire (ACQ-6)

The ACQ-6 is a validated asthma assessment tool that has been widely used (Juniper et al, 1999). Six questions are self-assessments (completed by the patient). Each item on the ACQ-6 has a possible score ranging from 0 to 6, and the total score is the mean of all responses (Appendix F). ACQ-6 results at screening and at DoR are part of the study inclusion criteria and randomization criteria respectively.

ACQ-6 will be administered at the sites at the time points in Table 2 (screening and run-in), Table 3 (treatment period) and Table 4 (follow-up).

6.1.5. Spirometry/FEV_1

Spirometry will be performed both at the site and by hand-held spirometer. On-site spirometry will include full-flow volume loops (FVC, FEV_1, FEV_1/FVC, $FEF_{25\%-75\%}$ and PEF) and reversibility testing at the time points in Table 2 (screening and run-in), Table 3 (treatment period) and Table 4 (follow-up). On site spirometry will be done according to American Thoracic Society/European Respiratory Society procedural guidelines (Graham, 2019). The National Health and Nutrition Survey (NHANES) III reference equations will be used.

Hand-held spirometry (FEV_1, PEF) will be performed daily. Every effort should be made to complete hand-held spirometry at approximately the same time each day, preferably in the morning. Patients will be trained in appropriate hand-held spirometry technique prior to dispensing the hand held spirometer. FEV_1 and PEF values will be monitored for data quality.

Reversibility testing will involve pre- and post-bronchodilator spirometry. For reversibility testing, SABAs, ie, salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate puffs (eg, albuterol 90 µg/puff or salbutamol 100 µg ex-valve/puff, or equivalent) should be given by metered-dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA and within 30 minutes after SABA.

FEV_1 is the volume of air that can be forcibly exhaled from the lungs in the first second, measured in liters. FVC is the volume of air that can be forcibly blown out after full inspiration,

measured in liters. The $FEF_{25\%-75\%}$ is the forced expiratory flow from 25% to 75% of forced vital capacity.

6.1.6. Asthma Rescue Medication Use

The number of inhalations/puffs of SABA/quick-relief inhaler will be recorded in the e-diary daily. Note: SABA therapy used for exercise pretreatment or for reversibility testing as described in Section 3.6.1.1 should not be recorded in the e-diary. Study sites should monitor rescue medication use during the study visits at the time points in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). Study sites are also responsible for responding to asthma specific alert criteria related to SABA/quick-relief inhaler use (see Section 3.1).

6.1.7. Nighttime Awakenings

Patients will record nighttime awakenings due to asthma in the e-diary daily, in the morning. Sites should check the records of nighttime awakenings during the study visits at the time points in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). Study sites are also responsible for responding to asthma specific alert criteria related to nighttime awakenings (see Section 3.1).

6.1.8. Fractional Exhaled Nitric Oxide

The concentration of NO in exhaled breath (FeNO) will be measured at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). FeNO should be performed prior to spirometry (if spirometry is performed during the visit).

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings, and use of concomitant medication. Refer to Table 2 (screening and run-in), Table 3 (treatment period), Table 4 (follow-up) for the timing of assessments and procedures, and Appendix B (JDMC).

7.1. Adverse Events and Adverse Device Effects

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product: adverse events do not necessarily have to have a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study. Development of a new condition or the worsening of a pre-existing condition will be considered an adverse event, whether or not considered related to TEV-48574. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of pre-existing conditions
- drug or drug/device or device/device interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant.

  (Note: Abnormal laboratory or diagnostic test results at the screening visit(s) that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

LoAC and CAEs are efficacy variables for this study and should be captured on the relevant specific CRF; accordingly, neither LoAC events nor CAEs should be recorded as adverse events unless assessed as more severe than the patient's usual disease course. LoAC events, including CAEs that are more severe than the patient’s usual course of disease and meet the criteria for a serious adverse event should be reported as a serious adverse event.

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF through the EOS visit. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered and until the EOS visit.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. Serious adverse events (Section 7.1.5) and/or PDAESI requiring reporting to GPSP (Section 7.1.6) must be reported within 24 hours from the investigator's awareness, using the SAE/PDAESI form (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for new adverse events after the study period defined above.

All device-related adverse events, malfunctions etc. will be recorded and evaluated for their impact relative to the safety and efficacy of the IMP.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking open-ended questions such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” A precise diagnosis should be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form. Reported or observed signs and symptoms that are not manifestations of a known diagnosis should be reported individually.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the IMP or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to the IMP and to the device, as well as the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

The relationship of adverse events will be captured separately for the relationship to the IMP and/or to the device. The relationship of an adverse event to the IMP and/or to the device will be determined according to the criteria in Table 6.

Table 6: The Relationship of an Adverse Event to the IMP and/or Device Suspects

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP/device.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP/device. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP/device. • It does not reappear or worsen when the IMP/device is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP/device cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP/device. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP/device, yet an IMP/device relationship clearly exists. • It follows a known pattern of response to the IMP/device.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events unless there was worsening of the preexisting condition during

the patient's participation in this study. Hospitalization due to asthma exacerbation that is consistent with the patient's known course of asthma should not be reported as an adverse event/serious adverse event.

- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3x the upper limit of normal (ULN)
- total bilirubin increase of >2x ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is included in the IB.

The sponsor's GPSP will determine the expectedness for all serious adverse events.

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. This applies also to Protocol Defined Adverse Events of Special Interests (PDAESI) requiring reporting to GPSP (Section 7.1.6). Completing the SAE/PDAESI form and reporting the event must not be delayed, even if not all the information is available. If any of the

information listed below is not immediately available, it should be provided to the sponsor as soon as possible but the initial reporting to the Sponsor must not be delayed.

Serious adverse events occurring to a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them.

The SAE/PDAESI form should be sent to the Local Safety Officer (LSO) or designee (a CRO in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided on the SAE/PDAESI form:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility, as described in Table 6)
- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including study-provided inhalers, doses, routes of administration, dates, and regimens)
- treatment for the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by both the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP.

In addition, the investigator will assess whether the etiology of the event is associated with the patient's primary condition, concomitant medications (including study-provided inhalers), or any other condition.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file or MedWatch of SAEs to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations. Submission of MedWatch forms to FDA is made by Regulatory Affairs upon receipt from the LSO.

The sponsor's GPSP will submit the XML of SUSARs to the EMA in an unblinded manner, when applicable and according to local regulations.

Blinding will be maintained for all study site personnel. Therefore, in case of a SUSAR, only the LSO/unblinded personnel from the CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Further details regarding reporting of SAE/PDAESI will be given in the SAE management plan (SMP).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is suspected to be related to the IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TEV-48754 and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing ICF and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-48574

7.1.6. Protocol-Defined Adverse Events of Special Interest

For purposes of this protocol, the following are considered protocol-defined adverse events of special interest:

- systemic severe reactions (including anaphylaxis)
- opportunistic infections
- malignancies (including non-melanoma skin cancer)

- administration site reactions

The process of reporting the above mentioned adverse events, except for administration site reactions, is the same as that for reporting serious adverse events (Section 7.1.5.3). Protocol-defined adverse events of special interest should be reported to GPSP regardless of seriousness or causality assessment, according to the criteria outlined in Section 7.1.5.1.

Administration site reactions will be evaluated and reported as described in Section 7.6.

In the event of suspected anaphylaxis while the patient is at the site, vital signs, including blood pressure, oxygen saturation, and respiration rate, should be measured. FEV_1 and PEF measurements should be obtained if it is safe to do so in the investigator's opinion. Blood samples to test TEV-48574 serum concentration, ADA, and free and total serum TL1A levels should be collected if possible. Collection of blood samples to test tryptase and/or histamine levels are encouraged if available locally at the time of the suspected hypersensitivity event. Other assessments may be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation medication/equipment nearby. In addition, information about all suspected anaphylaxis and hypersensitivity events will be recorded on the Suspected Anaphylaxis CRF, which is based on the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al, 2006).

A list of opportunistic infections is included in Appendix I.

7.1.7. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, the investigator should take the actions necessary to ensure patient safety. After the event has stabilized; treatment has been administered or both, the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Adverse Device Effects

An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device.

7.2.1. Adverse Device Effect Reporting

Adverse device effects (Figure 2) must be recorded on both the source documentation and the CRF.

All adverse device effects shall be reviewed by the investigator, the medical monitor, and the sponsor. The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and device deficiency and will categorize each as guided in Section 7.2.

The investigator should make an initial determination whether the adverse event may be related to a device deficiency (Section 7.1.4).

Adverse device effects and device deficiencies will be listed in the clinical study report (CSR).

7.2.2. Serious Adverse Device Effects

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.5.1).

7.2.2.1. Serious Adverse Device Effect Reporting

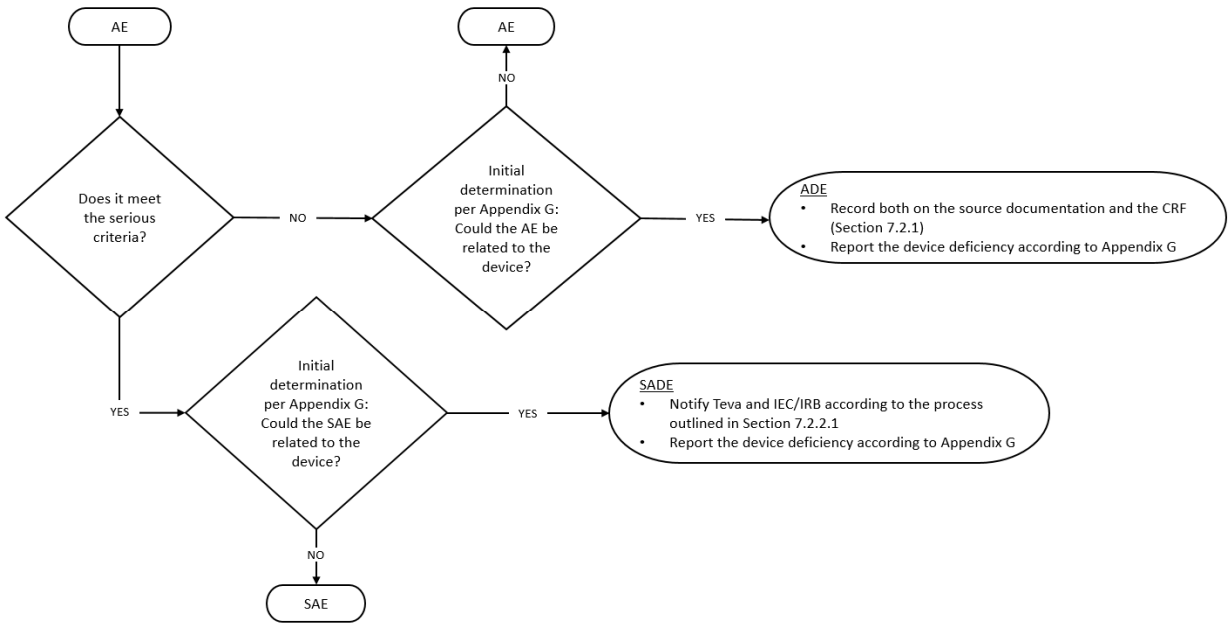
The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours); this information shall be promptly followed by detailed written reports as described below.

The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.5.3.

Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to national and local regulations.

The investigator should make an initial determination whether the serious adverse event may be related to a device deficiency.

Figure 2: Decision Tree for Adverse Events and Adverse Device Effects Classification



AE=adverse event; ADE=adverse device effect; CRF=case report form; IEC=Independent Ethics Committee; IRB=Institutional Review Board; SADE=serious adverse device effect; SAE=serious adverse event.

7.3. Pregnancy

Any female patient becoming pregnant during the screening period will be considered a screen failure and will not be allowed to rescreen.

Any female patient becoming pregnant during the study will discontinue IMP.

All pregnancies of women participating in the study and female partners of men participating in the study, if applicable, that occur during the study, or within 5 half-lives (~10 weeks) of the last IMP administration, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

All female patients and female partners of men participating in the study (female partners of men participating in the study who become pregnant will be asked to sign an ICF) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the woman participating in the study and/or the female partners of men participating in the study does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.4. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported in the patients' source documents, regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

2. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
3. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information/study protocol. Clinical judgment should always be

applied. Any dose of IMP (whether the test IMP or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

4. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information/study protocol.
5. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
6. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information/study protocol.
7. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
8. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

7.5. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2. A laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study; the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up may be considered adverse events. If further diagnostic work-up of abnormal laboratory result leads to the investigator concluding that the initial abnormality was not clinically significant, it is at the investigator's discretion whether or not the laboratory result triggering the work-up is an adverse event. (Note: Abnormal laboratory or diagnostic test results at the screening visit(s) that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

Table 7: Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation	Urinalysis
Calcium Phosphate Sodium Potassium Chloride Creatinine Glucose Blood urea nitrogen (BUN) Urate Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Lactate dehydrogenase (LDH) Gamma-glutamyl transpeptidase (GGT) Alkaline phosphatase Protein Albumin Bilirubin Direct bilirubin	Hemoglobin Hematocrit Erythrocytes Platelets Leucocytes (including differential count, presented in absolute values and percentages) – Neutrophils – Lymphocytes – Eosinophils – Monocytes – Basophils – Lymphocytes atypical Prothrombin International Normalized Ratio (INR)	Protein Glucose Ketones Hemoglobin pH Specific gravity Microscopic tests – Bacteria – Erythrocytes – Leucocytes – Crystals – Casts

7.5.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis) will be performed at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). Tests can be performed in either a fasting or non-fasting state. Clinical laboratory tests will be performed using the central laboratory. Details of laboratories to be used in the study are provided in Appendix A.

7.5.2. Other Clinical Laboratory Tests

At screening, patients will be tested for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (HCV), human immunodeficiency virus (HIV) types 1 or 2, and TB test (QuantiFERON® TB Gold Test). Patients with confirmed positive results will not be eligible to participate in the study.

If the QuantiFERON® TB Gold Test is negative at screening, then the patient may proceed in the screening period. However, if the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive at screening, then a second sample should be drawn and the following steps taken:

- If the second QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure.
- If the second QuantiFERON® TB Gold Test is negative (ie, results do not match the first test), then a third sample should be drawn.

  - If the third QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure.
  - If the third QuantiFERON® TB Gold Test is negative (ie, results match the second test), then the patient may proceed in the screening period.
- Note that sites may choose to split the second and third samples and send one to the central laboratory and one to a local laboratory. However, the local laboratory result may not be used for decision making.

COVID-19 testing will be available at the central laboratory. Locally performed COVID-19 testing results will also be accepted.

7.5.2.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin (HCG) tests in serum and in urine will be performed for women of childbearing potential at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up).

7.5.2.2. Follicle Stimulating Hormone

At screening, women who have been amenorrheic for at least 1 year without an alternative medical cause will have a serum follicle stimulating hormone (FSH) assessment to confirm postmenopausal status (an increased concentration of FSH of more than 35 IU/L in women not using hormonal contraception or hormonal replacement therapy).

7.6. Local Tolerability

Local tolerability assessments should be performed after each administration of IMP (Table 3) and include administration site findings and pain. Administration site findings (erythema, ecchymosis, induration, tenderness, warmth, and swelling) will be assessed using the scales provided in Table 8. Pain at the administration site will be reported using a standardized 11-point pain intensity numerical response scale (NRS-11) where 0 is “No pain” and 10 is “Worst possible pain”. Patients will be asked to respond to the following question: “How much pain do you feel at the drug injection site?”

Both administration site findings and pain will be assessed 1 hour after the completion of IMP administration. Additionally after the loading dose and first maintenance dose, assessments will also be performed 2 hours after the completion of administration. Allowed time windows for the local tolerability assessments are ±15 minutes.

Severity of local tolerability symptoms should be assessed as described in Table 8. The surface diameter in millimeters should be recorded and erythema, induration, and ecchymosis at the administration site will be graded according to the diameter measurements: Absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Erythema, ecchymosis, and induration under 5 mm in diameter should be assessed as absent. Care should be taken to avoid pressuring or squeezing the administration site while assessing induration via careful superficial palpation.

In the case that findings do not resolve while the patient remains at the study center, additional evaluation should take place thereafter at each visit until resolution occurs. Administration sites

may be photographed, including between visits to the study center, to provide visual representation in addition to comments in the source documents. Any features that could be used to identify the patient will not be captured on the photograph. Appropriate treatment for administration site finding or pain may be provided if necessary, in which case such treatments must be recorded as concomitant medication(s).

Table 8: Administration Site Finding Severity Assessment

Test	Response
Erythema	- Absent - Erythema surface diameter 5 mm to ≤50 mm (mild) - Erythema surface diameter >50 to ≤100 mm (moderate) - Erythema surface diameter >100 mm (severe)
Ecchymosis	- Absent - Ecchymosis surface diameter 5 mm to ≤50 mm (mild) - Ecchymosis surface diameter >50 to ≤100 mm (moderate) - Ecchymosis surface diameter >100 mm (severe)
Induration	- Absent - Induration surface diameter 5 mm to ≤50 mm (mild) - Induration surface diameter >50 to ≤100 mm (moderate) - Induration surface diameter >100 mm (severe)
Tenderness Warmth Swelling	- None - Mild - Moderate - Severe

Administration site findings described in Table 8 and administration site pain will not be captured as adverse events. Administration site findings with characteristics that are not described in Table 8 or this section (eg, lipoatrophy, necrosis, abscess) or fulfill seriousness criteria must be recorded and reported as specified in Section 7.1.2 and Section 7.1.5.

7.7. Physical Examinations

Physical examinations, will be performed at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). Any physical examination finding that is judged by the investigator as clinically significant (except at the initial screening visit, which will be captured as medical history) may be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2. Physical exam findings that are attributable to another adverse event or to LoAC/CAEs would not be reported as separate adverse events.

A full physical examination will include at a minimum the following organ systems:

- General appearance;
- Head, eyes, ears, nose, mouth, and throat;
- Chest and lungs;
- Heart;

- Abdomen;
- Musculoskeletal;
- Skin;
- Extremities;
- Lymph nodes;
- Neurological

Height and weight will be obtained at the at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up).

A brief physical examination will include at a minimum general appearance; head, eyes, ears, nose, mouth and throat; chest and lung; heart and extremities (including pulses).

7.8. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). Patients are to remain in a supine position for at least 5 minutes prior to measuring blood pressure and pulse. If possible, blood pressure measurements should be completed on the same arm at each visit. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2.

7.9. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up). ECGs should be performed in a supine position after 5 minutes rest.

All ECG results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit[s]) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

Where triplicate measurements are required (DoR), each ECG will be taken within 1 to 5 minutes of the previous one.

8. ASSESSMENT OF PHARMACOKINETICS, PHARMACOGENOMICS, IMMUNOGENICITY AND [redacted]

8.1. Pharmacokinetic Assessment

Blood samples will be collected via venipuncture at the time points detailed in Table 3 (treatment period), and Table 4 (follow-up) for measurements of serum concentration of TEV-48574.

Additionally, efforts should be made to determine serum concentration of TEV-48574 in cases of suspected severe, systemic hypersensitivity reaction or anaphylaxis; LoAC or CAE; serious adverse event; or immunogenicity-related adverse events.

The dates and times of IMP administration and the date and time point (24-hour clock time) of each pharmacokinetic sample will be recorded both on the source documentation and the CRF.

Samples will be analyzed for concentration of TEV-48574 using an appropriate validated method.

Incurred sample reanalysis may be performed. Blood samples from patients who received placebo will not be analyzed.

Blood volumes are provided in the ICF and Laboratory Manual. Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

8.2. Immunogenicity Testing

Blood samples for ADA testing will be collected via venipuncture at the time points detailed in Table 3 (treatment period), and Table 4 (follow-up). Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Additionally, efforts should be made to collect ADA samples in cases of suspected severe, systemic hypersensitivity reaction or anaphylaxis; LoAC or CAE; serious adverse event; or immunogenicity-related adverse events. In cases of suspected or confirmed anaphylaxis, efforts should be made to collect samples as close to the onset of the event as possible, at resolution, and 30 days after onset of the event. Antibodies to TEV-48574 will be evaluated in serum samples. All samples collected for detection of antibodies to TEV-48574 may also be evaluated for TEV-48574 serum concentration to facilitate interpretation of the antibody data. Confirmed ADA positive samples may be further evaluated for TEV-48574 neutralizing antibodies.

The dates and times of IMP administration and the date and time point of each immunogenicity sample will be recorded both on the source documentation and the CRF.

The detection and characterization of antibodies to TEV-48574 will be performed using validated assay methods. Blood samples from patients who received placebo will not be analyzed by the ADA assay.

A patient will be classified as having a treatment-emergent ADA response if either: 1) the patient had a positive sample at any of the time points after first dose of IMP, but not at the time point before first dose of IMP, or 2) the patient had positive samples before first dose of IMP and 1 or more time points after first dose of IMP, with at least a 4-fold increase in titers after first dose relative to the sample ADA titers before first dose.

Where possible, the impact of the presence of ADAs on pharmacokinetics and clinical safety will be evaluated.

Samples may be stored if permitted by the ICF and local regulations after the last patient's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to TEV-48574.

8.3. [redacted] (Exploratory)

[redacted]

8.4. Pharmacogenomics Assessment (Optional)

Pharmacogenomics is the study of how a person's genetic makeup influences how he or she responds to a drug. Pharmacogenomics testing can contribute to a better understanding of the variation of drug responses seen during development of an investigational drug. A separate ICF is required for pharmacogenomics testing. An optional blood sample for pharmacogenomics testing will be collected (following signing of the ICF) via venipuncture into a PaxGene DNA tube at the time point detailed in Table 3.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP). After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR. In case of discrepancy between the descriptions in the protocol and the SAP, the SAP will take precedence.

Exploratory analyses, [redacted] may be described in a separate analysis plan and may be reported separately from the CSR.

9.1. Sample Size and Power Considerations

The primary efficacy analysis for this study will be the comparison between treatment groups of the proportion of patients experiencing a LoAC event during the 16-week treatment period. The study will be considered positive if the primary efficacy test indicates a statistically significant treatment effect versus placebo at the predefined significance level.

Sample size calculations were performed based on the following considerations:

In the Phase 2a study results for dupilumab, the observed LoAC rate in the placebo group was 44% (Wenzel et al 2013). The patients in that study had elevated peripheral blood eosinophil counts (≥300 cells/μL). To estimate the LoAC rate that would have been observed in patients with peripheral blood eosinophil counts <300 cells/μL, the ratio of exacerbation rates observed between eosinophil count strata in the placebo groups of the dupilumab Phase 3 study were used (Castro et al 2018). This resulted in an estimated LoAC rate of 27% for the patients meeting the entrance criteria for the current study.

This study is designed to detect a 60% reduction in LoAC rate versus placebo; ie, a placebo group rate of 27% and a TEV-48574 group rate of 10.8%.

Based on the assumptions above, and assuming a 15% dropout rate during the study, 62 randomized patients per treatment group will provide 80% power to detect a treatment effect of 60% reduction in LoAC rate in the TEV-48574 group using a Chi-square test with one-sided alpha (Type I error rate) of 0.1.

An unblinded interim analysis is planned to re-assess the sample size and conduct a futility analysis as described in Section 9.13. If the sample size increases as a result of the interim analysis, the number of evaluable patients would be expected to increase proportionately.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients and will be used as the population for the primary efficacy analysis.

In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

Data collected from patients after treatment discontinuation will be included in the ITT analysis set.

9.2.2. Safety Analysis Set

The safety analysis set will include all randomized patients who receive at least 1 dose of IMP.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

9.2.3. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients that did not experience any important protocol deviation prior to LoAC (if any) or the end of the treatment period, whichever comes first. The SAP will present a list of important deviations prospectively identified as having the potential to influence and/or bias the primary efficacy results. A complete list of important deviations resulting in exclusion of patients from the PP analysis will be determined at the end of the study based on a team review of accumulated blinded study data.

9.2.4. Additional Analyses Sets

Population Pharmacokinetic Analysis Set

The population pharmacokinetic analysis set will include those patients in the safety analysis set who have at least 1 measurable concentration of TEV-48574.

Patients with important protocol deviations affecting pharmacokinetics may be excluded from the population pharmacokinetic analysis set at the discretion of the pharmacometrician. Important protocol deviations will be identified before database lock.

Analysis methods may be detailed in a separate population pharmacokinetic analysis plan. Pharmacokinetic data from the current study will be pooled with previous data, and a population-pharmacokinetic analysis and, if data allows, a population pharmacokinetic-pharmacodynamic analysis, will be completed and reported separately.

Immunogenicity Analysis Set

The immunogenicity analysis set will include all patients in the safety set who receive TEV-48574, who undergo immunogenicity testing, and who have at least 1 reportable immunogenicity result. Patients with important protocol deviations affecting immunogenicity analysis may be excluded from the analysis set at the discretion of the Sponsor's clinical study physician or delegate. Important protocol deviations will be identified before database lock.

9.3. Data Handling Conventions

9.3.1. Handling Withdrawals and Missing Data

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. Detailed data imputation rules will be described in the SAP.

9.4. Study Population

The ITT analysis set (Section 9.2) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

Data from patients screened, patients screened but not randomized, patients randomized to treatment in the study, patients randomized but not treated, patients in the safety analysis set, patients in the per-protocol analysis set, patients who completed the treatment period (week 16), patients who completed the study (see Section 3.1 for definition of study completion), and patients who did not complete treatment but were followed up until end of study will be summarized. Data from patients who withdrew from the study will also be summarized by reason for withdrawal using descriptive statistics, and the number of patients who discontinued treatment for reasons other than LoAC/CAE but continued to attend study visits will be tabulated.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including but not limited to medical history, prior medications and therapies, and ECG findings, will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.5. Endpoints

9.5.1. Primary Endpoint

The primary efficacy endpoint of this study is the proportion of patients who experience LoAC during the treatment period. For a definition of LoAC, see Section 6.1.1.

9.5.2. Secondary Endpoints

Key secondary efficacy endpoints:

- Time from randomization to LoAC during the treatment period
- Asthma Control Questionnaire 6-question version (ACQ-6) at EOT and throughout the study
- FEV_1 (% predicted, L) at end of treatment EOT and throughout the study
- Use of SABA quick relief medication at EOT and throughout the study

Other efficacy endpoints:

- Proportion of patients who have a CAE during the treatment period
- Time from randomization to first CAE during the treatment period
- Number of nighttime awakenings due to asthma during the treatment period
- Percent decrease in ICS dose during the treatment period
- Other lung function parameters as assessed by hand-held spirometry at EOT and throughout the study

- Fractional exhaled nitric oxide (FeNO) throughout the study

9.5.3. Other endpoints

Safety and tolerability endpoints:

- Frequency of adverse events
- Change from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study
- Change from baseline in vital signs throughout the study
- Change from baseline in 12-lead electrocardiogram (ECG) findings throughout the study
- Use of concomitant medication
- Local tolerability
- Number (%) of patients who did not complete the study due to adverse events

Device-Related Events

- All device-related adverse events, malfunctions etc. will be recorded and evaluated for their impact relative to the safety and efficacy of the investigational medicinal product.

Pharmacokinetic endpoints:

- Trough serum TEV-48574 concentrations throughout the study (sparse sampling)
- Population pharmacokinetic analysis of pharmacokinetic data

Immunogenicity endpoints:

- Assessment of treatment-emergent ADA responses: change from baseline and throughout the study
- Impact of the presence of ADAs on pharmacokinetics and clinical safety (if possible). Efforts will be made to collect ADA samples in cases of suspected severe, systemic hypersensitivity reaction or anaphylaxis; LoAC or CAE; serious adverse event; or immunogenicity-related adverse events.
- Assessment of neutralizing ADA in ADA positive patients throughout the study

9.5.4. Exploratory

9.6. Efficacy Analysis

9.6.1. Planned Method of Analysis

The ITT analysis set (Sections 9.2.1) will be used for all efficacy analyses unless otherwise noted. Summaries will be presented by treatment group. The per-protocol analysis set will be used as sensitivity analysis for the primary analysis.

The baseline for spirometry parameters and e-diary variables will be the average of the values over the 7 days preceding day of randomization. The baseline for clinic visit variables will be the last observed value before the first dose of study drug. The baseline for absolute eosinophil count will be the average of all values obtained prior to the administration of the first IMP.

9.6.1.1. Primary Efficacy Analysis

The primary analysis will compare rates of LoAC between treatment groups using logistic regression with fixed effect for treatment, baseline FEV_1, weight, age group (<65 years vs ≥65 years), and gender as covariates. The primary analysis will be performed on the ITT analysis set. Patients who withdraw from the study or discontinue treatment due to lack of efficacy or due to an asthma-related adverse event will be analyzed as having experienced LoAC. Patients who withdraw from the study for other reasons will be analyzed as not experiencing LoAC. The treatment effect will be tested at a one-sided alpha of 0.1.

Subgroup analyses may be performed. These will be described and detailed in the SAP.

9.6.1.2. Sensitivity Analysis

Sensitivity analyses will include repeating the primary analysis on the per-protocol analysis set.

Additional sensitivity analyses may be detailed in the SAP.

9.6.1.3. Secondary Efficacy Analysis

All efficacy variables will be summarized by treatment group. For continuous variables, the summary statistics will include n, mean, SD, standard error (SE), median, minimum, and maximum. For categorical variables, patient counts and percentages will be provided.

LoAC rates, 90% and 95% CIs for LoAC rates, estimated treatment effects (ie, the odds ratio of TEV-48574 versus placebo), and 90% and 95% CIs of the odds ratio will be provided.

The key secondary efficacy analysis of time to LoAC will use a one-sided log-rank test to compare the hazard rates between the TEV-48574 and placebo groups. The analysis will be performed on the ITT analysis set. Patients who withdraw from the study or discontinue treatment due to lack of efficacy or due to an asthma-related adverse event will be analyzed as having experienced LoAC at the time of the withdrawal or treatment discontinuation. Patients who withdraw from the study for other reasons will be analyzed as being right-censored at the time of withdrawal.

The Kaplan-Meier (KM) method will be used to estimate and compare the distributions of time to LoAC between treatment groups.

Analysis of ACQ-6 will use the mixed model repeated measures model with treatment group, weight, age group (<65 years vs ≥65 years), gender, visit, and treatment and visit interaction, as fixed effects and patient as a random effect.

The on-site morning trough FEV1 throughout study will be analyzed using similar MMRM method, as described for the analysis ACQ-6.

Use of SABA quick relief medication will be derived from the e-diary data in monthly analysis intervals and will be analyzed using a similar MMRM method.

The efficacy endpoints defined at end-of-treatment (EOT) will take the last available assessment value in the treatment period, and will be analyzed using appropriate analysis of covariance models.

Additional covariates or factors may be added to the statistical models. These will be detailed in the SAP.

9.6.1.4. Other Efficacy Analysis

Statistical modeling to be used for other efficacy endpoints will be described and detailed in the SAP.

9.7. Multiple Comparisons and Multiplicity

As there are only 2 treatment groups and one primary analysis test in this study, no multiplicity correction is necessary. Secondary endpoints will be considered as hypothesis-generating, and multiple testing adjustment will not be made.

9.8. Safety Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.2).

Safety assessments and time points are provided in Table 2, Table 3, and Table 4.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety.

Summaries will be presented for

- All treatment-emergent adverse events (overall and by severity) (as defined in Section 7.1.2 and Section 7.1.3)
- Adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity),
- Serious adverse events (Section 7.1.5.1)
- Protocol-defined adverse events of special interest (Section 7.1.6)
- Adverse events causing withdrawal from the study.

Summaries will be presented by treatment group and for all patients. Patient listings of all adverse events (from signature of the ICF), serious adverse events, and adverse events leading to withdrawal will be presented.

Values and change from baseline in laboratory, ECG, and vital signs measurements data (including the incidence of abnormalities) will be summarized descriptively.
Local tolerability: administration site findings (erythema, ecchymosis, induration, tenderness, warmth, and swelling) and administration site pain will be assessed as described in Section 7.6 and summarized descriptively.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

Physical examination data will be listed and may be summarized descriptively.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the CSR.

9.9. Population Pharmacokinetic, Pharmacodynamic, and Pharmacokinetic/Pharmacodynamic Analysis

A population pharmacokinetic analysis will be performed, and, if feasible, a pharmacokinetic/pharmacodynamic analysis of relevant pharmacodynamic variables may be performed and reported in a separate Pharmacometrics Analysis Report (PAR). This section describes the possible population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses foreseen at the time of the preparation of this protocol. Changes, additions, and further details about the analysis will be described in the Modeling Analysis Plan. After finalization of the Modeling Analysis Plan, any additional analyses or changes to the analyses that may be required will be described in the PAR**.**

9.9.1. Population Pharmacokinetics

All patients in the safety analysis set who have at least 1 measurable concentration of TEV-48574 will be included in the analysis of pharmacokinetic data. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. TEV-48574 concentration data will be summarized by visit and treatment group. In addition to mean, standard deviation, coefficient of variation, median and quartiles, the geometric mean and geometric coefficient of variation and n(log) will be presented. Pharmacokinetic data per TEV-48574 study treatment may be analyzed with a population-pharmacokinetic mixed effects model. The analysis will be based on a pooled data set, including pharmacokinetic data from previous studies and will be reported in the PAR.

9.9.2. Pharmacokinetics/Pharmacodynamics (PK/PD)

Based on graphical exploration of the observed data, an appropriate PK/PD modeling approach may be used to characterize the time course of efficacy response. Further details of the modeling approach, if performed, may be specified in a detailed Modeling Analysis Plan. The PK/PD analysis may be reported in the Pharmacometrics Analysis Report.

9.10. Immunogenicity Analysis

Immunogenicity analyses will be performed on the immunogenicity analysis set. Listing(s) of patients with positive ADA sample(s) will be provided. Summaries may be provided if appropriate.

Treatment-emergent ADA responses and the impact of the presence of ADAs on pharmacokinetics and clinical safety may be assessed. Confirmed ADA positive samples may be further characterized (eg, assessment of neutralizing ADA) as needed.

9.11. [redacted]

9.12. [redacted]

9.13. Planned Interim Analyses

An unblinded interim analysis is planned after the first 40 to 52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely. The main purposes of the interim analysis include sample size re-assessment and futility analysis, as described below.

The assumed LoAC event rate in the placebo group is 0.270. If the actual placebo event rate is lower than expected, the study will be underpowered to detect a 60% reduction in event rate. At the interim analysis, if the observed placebo event rate is lower than expected, and the observed treatment effect is at least a 40% reduction (event rate ratio ≤0.6), the sample size may

be increased by up to 50 additional randomized patients, from the initially planned 124 to up to 174. This procedure corresponds to a Promising Zone methodology and does not increase the Type I error rate (Mehta and Pocock, 2011).

The interim futility analysis comprises a statistical comparison between treatment group versus placebo in LoAC rate using logistic regression with fixed effect for treatment among the randomized patients who have completed the treatment period, experienced LoAC, or withdrawn from the study completely at the interim analysis. A p-value above 0.5 will be declared as treatment efficacy futility, which could potentially result in early termination of the trial. According to simulation analyses, this cutoff value yields correct early termination rates under the null hypothesis of 0.43 (40 patients) and 0.44 (52 patients) and controls incorrect early termination rate under the alternative hypothesis at approximately 0.06 (40 patients) and 0.04 (52 patients). More details will be provided in a separate Interim Statistical Analysis Plan that will be finalized prior to the interim analysis.

The interim analysis will be conducted by an independent, unblinded statistician who is not a part of the study team. A group of the sponsor's management team who are not a part of the study team may have access to the unblinded interim analysis results. A communication plan to ensure the maintenance of the study blind among the blinded personnel involved in the conduct of the study will be put in place prior to the interim analysis.

9.14. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the SAP, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix D for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Refer to Appendix G for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

Details are given in a Study Manual.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with competent authorities.

See Appendix E for the ethics expectations of informed consent or assent, competent authorities and independent ethics committee and institutional review board, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix H for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are eg, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Food and Drug Administration (FDA) 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

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15. SUMMARY OF CHANGES TO PROTOCOL

15.1. Amendment 02 Dated 28 April 2021

The primary reasons for this amendment are to make changes to the inclusion and exclusion criteria, as well as other changes in order to increase enrollment to the study. This includes changes that address enrollment of subjects with prior COVID-19 infection, as well as COVID-19 vaccination. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc.) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
1.2.2. First-in-Human Clinical Study		
No adverse events consistent with immunosuppression (including opportunistic or unusual infections or malignancies), cytopenias, cytokine release syndrome, or systemic reactions were reported and no safety signal was observed with treatment-emergent ADA responses.	No adverse events consistent with immunosuppression (including opportunistic or unusual infections or malignancies), cytopenias, cytokine release syndrome, or systemic reactions were reported and no safety signal was observed with treatment-emergent ADA responses.	Malignancies added to immunosuppression risk to align with ICF
1.3. Know and Potential Benefits and Risks of the Test Investigational Medicinal Product		
Given the targeted action of TEV-48574 on TL1A, and considering that the product is a mAb, immunosuppression (e.g. higher risk for infections and malignancies, incomplete response to vaccines, etc.), cytokine release syndrome, systemic hypersensitivity, and immunogenicity may be considered potential risks of TEV-48574.	Given the targeted action of TEV-48574 on TL1A, and considering that the product is a mAb, immunosuppression (e.g. higher risk for infections and malignancies, incomplete response to vaccines, etc.), cytokine release syndrome, systemic hypersensitivity, and immunogenicity may be considered potential risks of TEV-48574.	Added to immunosuppression risk to align with ICF
Management of study activities during coronavirus disease 2019 (COVID-19) outbreaks is detailed in Appendix J.	Management of study activities during coronavirus disease 2019 (COVID-19) outbreaks is detailed in Appendix J.	Added definition for the abbreviation COVID-19
2.1. Primary, Secondary, and Other Study Objectives and Endpoints		
• Forced expiratory volume in the first second of exhalation (FEV_1) (% predicted, L) at EOT and throughout the study	• Forced expiratory volume in the first second of exhalation (FEV_1) (% predicted, L) at EOT and throughout the study	Added to the definition of FEV_1
2.2.1. Exploratory [redacted] (Other sections affected by this change: 8.3, 9.5.4)		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
[redacted]		
3.1. General Study Design and Study Schematic Diagram (Other sections affected by these changes: 3.6.1.1., 3.6.1.2.9, 3.6.1.2.10)		
~~A subset of patients at selected sites will have sputum collected during screening and at EOT.~~	Not applicable	Sputum collection removed due to lack of experienced staff at sites in collecting sputum samples correctly
~~At selected sites, a subset of patients will undergo induced sputum collection during the screening period and at EOT. Patients who are scheduled to undergo sputum induction collection must be tested for active COVID-19 infection within no later than 5 business days from the planned date of the sputum induction prior to the sputum collection. Only patients who are confirmed to not have active COVID-19 will be deemed safe to undergo sputum induction. Patients who are considered to have a high probability of being exposed to COVID-19 infection during the study duration should not be included in the sputum collection cohort.~~	Not applicable	Sputum collection removed due to lack of experienced staff at sites in collecting sputum samples correctly
~~The subset of patients who had sputum collected during the screening period (approximately 40 patients in total) will have sputum collected again at EOT.~~	Not applicable	Sputum collection removed due to lack of experienced staff at sites in collecting sputum samples correctly
3.1. General Study Design and Study Schematic Diagram		
Eligibility requirements include: peripheral blood eosinophil counts of <250 cells/µL (at least 2 out of 3 measurements both <250 cells/µL separated by ~~3–4~~ 2 weeks ± 3 days); ~~FeNO <25 ppb;~~	Eligibility requirements include: peripheral blood eosinophil counts of <250 cells/µL (at least 2 out of 3 measurements both <250 cells/µL separated by 2 weeks ± 3 days)	Simplified and clarified eosinophil measurements during screening; eosinophil measurements now to be taken at Visit S1 and Visit S2 (14 days apart), and at Visit S3 (14 days from Visit S2) if needed. No guidelines exist establishing whether or not any particular level of FeNO truly characterizes T2-low/Non-T2 asthma. Thus, FeNo levels will be measured during the trial, but will no longer be used as an entrance criterion for the trial.

Original text with changes shown	New wording	Reason/Justification for change
3.1 General Study Design and Study Schematic Diagram		
…an ACQ-6 score ≥1.5 despite daily treatment with medium/high dose ICS+LABA for at least 3 months with a stable dose for at least 1 month prior to screening, with or without other asthma controller medications, and at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma, or a 2-fold or higher increase from the subject's usual maintenance ICS dose during the exacerbation period, documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit (Visit S1).	an ACQ-6 score ≥1.5 despite daily treatment with medium/high dose ICS+LABA for at least 3 months with a stable dose for at least 1 month prior to screening, with or without other asthma controller medications, and at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma, or a 2-fold or higher increase from the subject's usual maintenance ICS dose during the exacerbation period, documented in the patient's medical or pharmacy records 18 months prior to (but not within 30 days of) the initial screening visit (Visit S1).	Follows current standard of care regarding asthma exacerbations that now includes an increase in the subject's maintenance inhaled corticosteroids (with or without LABAs) by at least 2-fold, for at least 5 days or more until exacerbation symptoms begin to subside. The dose of the inhaled medication can then be tapered back to pre-exacerbation levels.
3.1 General Study Design and Study Schematic Diagram		
The study will consist of an approximate ~~5-week~~ 4- to 5-week screening/run-in period consisting of screening followed by a run-in, a 16 week treatment period, and an 8 week follow-up period.	The study will consist of an approximate 4- to 5-week screening/run-in period consisting of screening followed by a run-in, a 16 week treatment period, and an 8 week follow-up period.	Simplified text for screening period for clarity
All inclusion and exclusion criteria, with the exception of the second eosinophil count, should be assessed within the first 2 weeks of ~~the initial screening visit~~ S1.	All inclusion and exclusion criteria, with the exception of the second eosinophil count, should be assessed within the first 2 weeks of Visit S1.	Simplified text for screening period for clarity
See New wording column	If a patient contracted and recovered from COVID-19 more than 6 weeks prior to screening, and the patient was not admitted to a hospital's ICU during that COVID-19 infection, and if the patient's symptoms from COVID-19 completely resolved back to pre-COVID-19 status (no lingering anosmia, weakness, persistent dyslogia or feelings of dysphoria for many months after the infection resolved), then the patient may enroll in the trial. The principal investigator should determine whether or not the subject has truly recovered back to his/her usual pre-COVID-19 status and is eligible for enrollment in the study.	Text to clarify eligibility criteria for COVID-19 patients

Original text with changes shown	New wording	Reason/Justification for change
An e-diary will be dispensed ~~within the first week of the initial screening visit~~ at the second screening visit (Visit S2), 2 weeks (± 3 days) after the initial S1 screening visit.	An e-diary will be dispensed at the second screening visit (Visit S2), 2 weeks (± 3 days) after the initial S1 screening visit.	Simplified text for screening period for clarity
Patients who meet all inclusion criteria (except for eosinophil counts if assessment is incomplete) and none of the exclusion criteria are eligible to enter the run-in and have their ICS+LABA standardized with study-provided ICS+LABA (background asthma controller therapy) at the Visit S2.	Patients who meet all inclusion criteria (except for eosinophil counts if assessment is incomplete) and none of the exclusion criteria are eligible to enter the run-in and have their ICS+LABA standardized with study-provided ICS+LABA (background asthma controller therapy) at the Visit S2.	Simplified text for screening period for clarity
Figure 1, FeNO removed from figure	Figure 1, FeNO removed from figure	No guidelines exist establishing whether or not any particular level of FeNO truly characterizes T2-low/Non-T2 asthma. Thus, FeNo levels will be measured during the trial, but will no longer be used as an entrance criterion for the trial.
Screening and Run-in (5 weeks)		
An effort should be made to complete screening assessments and procedures in the first 2 weeks following Visit S1, with the exception of obtaining the samples for the second (and if applicable third) peripheral blood eosinophil counts.	An effort should be made to complete screening assessments and procedures in the first 2 weeks following Visit S1, with the exception of obtaining the samples for the second (and if applicable third) peripheral blood eosinophil counts.	Simplified text for screening period for clarity
Samples for peripheral blood eosinophil counts should be collected at 2 time points. The first time point should be at ~~the initial screening visit~~ S1, if possible, ~~and the second approximately 3-4 weeks after the first (ie, samples collected at least 21 days apart from each other)~~ and the second (Visit S2) 14 days (± 3 days) after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that the third time point is 14 days (± 3 days) after ~~the second time point~~ Visit S2. If the value at a third time point is	Samples for peripheral blood eosinophil counts should be collected at 2 time points. The first time point should be at Visit S1, if possible, and the second (Visit S2) 14 days (± 3 days) after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that the third time point is 14 days (± 3 days) after Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.	The major criterion for defining a subject as having T2-low/Non-T2 asthma is having eosinophil count of <250 cells/µL of blood. It is possible that this level may transiently increase to above 250 cells/µL. If one measurement exceeds 250 cells/µL, it is now felt that having 2 other measurements below 250 will satisfy the definition of T2-low/non-T2 asthma

Original text with changes shown	New wording	Reason/Justification for change
used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.		
Patients will receive a hand-held spirometer ~~at the initial screening visit~~ and an e-diary ~~within the first 2 weeks of the initial screening visit~~ at Visit S2 (14 ± 3 days) after the initial screening Visit S1, and will be trained on their use.	Patients will receive a hand-held spirometer and an e-diary at Visit S2 (14 ± 3 days) after the initial screening Visit S1, and will be trained on their use.	To align with the screening period of up to 2 weeks
~~At the initial screening visit,~~When the e-diary is dispensed….	When the e-diary is dispensed….	To align with the screening period of up to 2 weeks
~~Once all eligibility criteria (inclusion and exclusion) have been confirmed, with the exception of the second peripheral blood eosinophil count, eligible patients will have their ICS+LABA converted to study-provided ICS+LABA inhalers and commence run-in;~~	The subject's pre-study quick relief rescue medication will be converted to study-provided albuterol/salbutamol inhalers at Visit S1. At Visit S2, once all eligibility criteria (inclusion and exclusion) have been confirmed, with the exception of the second peripheral blood eosinophil count, eligible patients will have their ICS+LABA converted to study-provided ICS+LABA inhalers and commence run-in	Simplified text for screening period for clarity
Patients on additional asthma controller medication(s) except those excluded by the eligibility criteria (see Section 4.2) will continue those medications throughout the run-in period and will discontinue them at ~~randomization~~ 4 weeks after randomization (Visit 3).	Patients on additional asthma controller medication(s) except those excluded by the eligibility criteria (see Section 4.2) will continue those medications throughout the run-in period and will discontinue them at 4 weeks after randomization (Visit 3).	Original text incorrect
3.4. Stopping Rules for the Study		
• discontinuation of the development of TEV–48574 for the treatment of asthma	discontinuation of the development of TEV–48574 for the treatment of asthma	For clarification
3.5. Joint Safety Review Committee		
See New wording column	Joint Safety Review Committee changed to Joint Data Monitoring Committee (change made throughout document)	Correction
3.6. Schedule of Study procedures and Assessments		
Table 2. Study Procedures and Assessments: Screening and Run-In		
Samples for peripheral blood eosinophil counts will ~~should~~ be collected at a minimum of 2 time points. The first time point should be at the initial screening visit (Visit S1), if possible, and the	Samples for peripheral blood eosinophil counts will be collected at a minimum of 2 time points. The first time point should be at the initial screening visit (Visit S1), if possible, and the second (Visit S2) 14 days (± 3 days) after	The major criterion for defining a subject as having T2-low/Non-T2 asthma is having eosinophil count of <250 cells/µL of blood. It is possible that this level may

Original text with changes shown	New wording	Reason/Justification for change
second (Visit S2) 14 days (± 3 days) ~~approximately 3-4 weeks after the first with the samples collected at least 21 days apart from each other.after~~ after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that third time point is ~~at least~~ 14 days (± 3 days) after the ~~second time point~~ sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL ~~and the mean of the 3 values should also be <250 cells/µL~~.	the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that the third time point is 14 days (± 3 days) after the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.	transiently increase to above 250 cells/µL. If one measurement exceeds 250 cells/µL, it is now felt that having 2 other measurements below 250 will satisfy the definition of T2-low/non-T2 asthma.
Review e-diary for SABA/quick-relief medication usage, and nighttime awakenings/asthma symptoms, including ~~for~~ adherence	Review e-diary for SABA/quick-relief medication usage, and nighttime awakenings/asthma symptoms, including adherence	For clarification
See New wording column	X (S3)	Review of e-diary and spirometry now performed at S3 if applicable
Spirometry with reversibility testing[g]	Spirometry with reversibility testing[g]	To ensure spirometry is included as part of reversibility testing
See New wording column	TB test added to S2/S3 column (at S3 if needed)	Adds additional TB test to be done at S3 if needed
Distribute albuterol/~~SABA~~ quick-relief medication[j]	Distribute albuterol/quick-relief medication[j]	Albuterol is the SABA being used in the study; SABA redundant
[redacted] ~~(exploratory)~~ [redacted]	Not applicable	[redacted]
[a] ~~Screening and~~ R~~r~~un-in may be extended for up to 14 days if needed for the shipment of IMP to the investigational site or to complete assessment of eosinophil counts.	Run-in may be extended for up to 14 days if needed for the shipment of IMP to the investigational site or to complete assessment of eosinophil counts.	Simplified text for screening period for clarity
[b] Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or	[b] Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or during	Additional text added to ensure patients who were hospitalized in the intensive care unit are ineligible and not enrolled

Original text with changes shown	New wording	Reason/Justification for change
during screening/run-in, will be tested for active COVID-19 infection. Patients who were hospitalized in the intensive care unit for COVID-19 will be excluded.	screening/run-in, will be tested for active COVID-19 infection. Patients who were hospitalized in the intensive care unit for COVID-19 will be excluded.	
[f] FeNO should be completed before reversibility testing. ~~Patients can repeat the FeNO assessment once to meet inclusion criterion "d" at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.~~	[f] FeNO should be completed before reversibility testing.	FeNO no longer used as inclusion criteria
[g] The e-diary will be dispensed ~~within the first week of the initial screening visit~~ at Visit S2.	[i] The e-diary will be dispensed at Visit S2	To align with the new description of screening period
[l]~~Patients who are scheduled to undergo sputum induction collection must be tested for active COVID-19 infection within no later than 5 business days from the planned date of the sputum induction prior to the sputum collection. Only patients who are confirmed to not have active COVID-19 will be deemed safe to undergo sputum induction. Patients who are considered to have a high probability of being exposed to COVID-19 infection during the study duration should not be included in the sputum collection cohort.~~	Not applicable	Sputum collection removed due to lack of experienced staff at sites in collecting sputum samples correctly; OLINK platform not being used
Table 3: Study Procedures and Assessments: Treatment Period (Visits 1 – 10)		
See New wording column	Reversibility testing deleted, in-office spirometry (full flow-volume loop) added to V2, V4, V7, and V9.	To align with other asthma studies that evaluate the pre-BD PFTs as an objective sign of improvement during the study; pre-BD PFTs will be performed at each visit during the active treatment phase (visits 1- 10), done routinely at every 2 week interval throughout treatment.
~~Peripheral eosinophil count~~	Not applicable	Redundant with "CBC with differential count" since eosinophil count is included with CBC

Original text with changes shown	New wording	Reason/Justification for change
~~Reversibility testing should only be attempted after withholding short acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.~~	Not applicable	To align with other asthma studies that evaluate the pre-BD PFTs as an objective sign of improvement during the study; pre-BD PFTs will be performed at each visit during the active treatment phase (visits 1- 10), done routinely at every 2 week interval throughout treatment.
If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from IMP and will need to visit the clinical site again for an early termination visit. Remote assessment of safety via teleconference and/or videoconference, with videoconference being the preferred method, is recommended until the patient is able to visit the clinical site for the early termination visit.	If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from IMP and will need to visit the clinical site again for an early termination visit. Remote assessment of safety via teleconference and/or videoconference, with videoconference being the preferred method, is recommended until the patient is able to visit the clinical site for the early termination visit.	Additional text added ensuring patients who test positive for COVID-19 infection will be discontinued from IMP
[i] FeNo should be completed before ~~reversibility testing~~ in-office spirometry.	[i] FeNo should be completed before in-office spirometry.	Reversibility testing no longer included in Table 3
[redacted] (exploratory)	[redacted] (exploratory)[m]	[redacted]
See New wording column	Pharmacogenomics – Blood in PaxGene DNA tube (optional)[n]	Clarification that pharmacogenomics testing and the additional blood sample collected for this testing is optional.
See New wording column	[n] On the signing the appropriate ICF, an optional blood sample may be collected for pharmacogenomics analysis.	Clarification that pharmacogenomics testing and the additional blood sample collected for this testing is optional.
Table 4: Study Procedures and Assessments: Follow-up Period		
~~i FeNO should be completed before reversibility testing.~~	Requirement for reversibility testing removed	Not needed, requirement for reversibility testing removed
Reversibility testing	Not applicable	To align with other asthma studies that evaluate the pre-BD PFTs as an objective

Original text with changes shown	New wording	Reason/Justification for change
		sign of improvement during the study; pre-BD PFTs will be performed at each visit during the active treatment phase (visits 1- 10), done routinely at every 2 week interval throughout treatment.
~~Peripheral eosinophil count~~	Not applicable	Redundant since this is done with CBC differential.
[f]~~Reversibility testing should only be attempted after withholding short acting bronchodilators (ie, inhaled short acting beta adrenergic agonists and/or short acting anticholinergics) for at least 6 hours and long acting bronchodilators (ie, inhaled long acting beta adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.~~	Not applicable	To align with other asthma studies that evaluate the pre-BD PFTs as an objective sign of improvement during the study; pre-BD PFTs will be performed at each visit during the active treatment phase (visits 1- 10), done routinely at every 2 week interval throughout treatment.
3.6.1.1 Assessments and Procedures for Screening and Run-in		
Note: Screening will include at least 2 visits and may be completed over more than 2 visits. The screening assessments and procedures for the first screening visit may be completed over more than one visit: sites should make every effort to complete the screening assessments and procedures in the first 2 weeks following the initial screening visit, with the exception of the second eosinophil count.~~ If the screening assessments and procedures are divided over more than one visit, each additional screening visit should include the following: prior/concomitant medication inquiry; adverse event inquiry, LoAC/CAE inquiry, daily e-diary and handheld spirometry review including adherence, vital signs, and brief physical exam. Once all inclusion and exclusion criteria have been assessed, with the exception of the second eosinophil count, and it has been confirmed that patients meet all of the inclusion criteria and none of the exclusion criteria (with the exception of incomplete assessment of	Note: Screening will include at least 2 visits and may be completed over more than 2 visits. The screening assessments and procedures for the first screening visit may be completed over more than one visit: sites should make every effort to complete the screening assessments and procedures in the first 2 weeks following the initial screening visit, with the exception of the second eosinophil count. It is recommended that the site consider consenting the subject and completing the first peripheral eosinophil count at the initial S1 screening visit in order to determine if the subject meets the eosinophil criteria for enrollment. If the subject is eligible, the remaining S1 assessments and procedures may be performed within two weeks of the initial S1 screening visit. However, sites may elect to conduct the entire S1 screening assessments and procedures at one visit only.	Section is redundant with text that is before Table 2 and additional text added for clarification indicating S1 screening assessments may occur at one visit only

Original text with changes shown	New wording	Reason/Justification for change
~~eosinophil count), the run-in will commence with the provision of study-provided ICS+LABA.~~ It is recommended that the site consider consenting the subject and completing the first peripheral eosinophil count at the initial S1 screening visit in order to determine if the subject meets the eosinophil criteria for enrollment. If the subject is eligible, the remaining S1 assessments and procedures may be performed within two weeks of the initial S1 screening visit. However, sites may elect to conduct the entire S1 screening assessments and procedures at one visit only.		
~~If the aforementioned screening assessments and procedures are completed over more than one visit, each additional screening visit should include the followingthe following assessments should be completed at each additional visit:~~ • ~~Review inclusion/exclusion criteria.~~ • ~~Perform prior/concomitant medication inquiry.~~ • ~~Perform adverse event inquiry.~~ • ~~Perform COVID-19 symptoms inquiry.~~ • ~~Review daily e-diary for SABA/quick-relief medication usage and nighttime awakenings, including for adherence.~~ • ~~Review daily hand-held spirometry, including for adherence.~~ • ~~Perform LoAC and CAE inquiry.~~ • ~~Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).~~ • ~~Perform brief physical examination.~~	If the screening assessments and procedures are divided over more than one visit, each additional screening visit should include the following: review inclusion/exclusion criteria, prior/concomitant medication inquiry; adverse event inquiry, COVID-19 symptoms inquiry, LoAC/CAE inquiry, vital signs, and brief physical exam. Once all inclusion and exclusion criteria have been assessed, with the exception of the second eosinophil count, and it has been confirmed that patients meet all of the inclusion criteria and none of the exclusion criteria (with the exception of incomplete assessment of eosinophil count), the run-in will commence with the provision of study-provided ICS+LABA at Visit S2.	Bullets removed to simplify and review of e-diary and hand-held spirometry now to be done only at S3 if applicable and section added before Visit S1 section
~~Efforts to perform the following assessments and procedures in the order listed should be made and may be divided over more than one visit:~~	Not applicable	To streamline and simply section 3.6.1.1

Original text with changes shown	New wording	Reason/Justification for change
See New wording column	Subheadings 3.6.1.1.1 Visit S1, 3.6.1.1.2 Visit S2, and 3.6.1.1.3 Visit S3 added	Reorganized Section 3.6.1.1 to simply and match Table 2
• ~~Distribute e-diary and handheld spirometer within 1 week of the initial screening visit, instruct the patient on how to perform the respective assessments, and perform first assessments.~~	Not applicable	Now being done at Visit S2
• Distribute albuterol ~~SABA~~/quick-relief medication ~~when the e-diary is dispensed or when reversibility is performed (whichever comes first)~~ at Visit S1.	• Distribute albuterol/quick-relief medication at Visit S1.	To simplify screening procedures and assessments
~~Samples for peripheral blood eosinophil counts should be collected at 2 time points. The first time point should be at the initial screening visit, if possible, and the second approximately 3-4 weeks after the first with the samples collected at least 21 days apart from each other. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at a third time point provided that third time point is at least 14 days after the second time point. If the value at a third time point is used to meet the eligibility criteria, 2 of the 3 values should be <250 cells/µL and the mean of the 3 values should also be <250 cells/µL.~~	Not applicable	Deleted because text is redundant with test before Table 2
~~At Visit S2 (approximately 3-4 weeks after the first peripheral blood eosinophil sample, with the samples collected at least 21 days apart from each other), efforts should be made to perform the following assessments and procedures in the order listed:~~	Not applicable; new subheading for Visit S2 added	To be consistent with new screening timeframe
• ~~At selected sites, confirm that the screening sputum sample for [redacted] was obtained in a subset of patients. If not, obtain at this visit.~~	Not applicable	Sputum collection removed due to lack of experienced staff at sites in collecting sputum samples correctly

Original text with changes shown	New wording	Reason/Justification for change
~~The FeNO assessment can be repeated once to meet inclusion criterion "d" at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.~~	Not applicable	No guidelines exist establishing whether or not any particular level of FeNO truly characterizes T2-low/Non-T2 asthma. Thus, FeNo levels will be measured during the trial, but will no longer be used as an entrance criterion for the trial.
3.6.1.1 Assessments and Procedures for Screening and Run-in		
• Distribute e-diary and handheld spirometer within ~~1~~ 2 weeks of the initial screening visit, instruct the patient on how to perform the respective assessments, and perform first assessments.	• Distribute e-diary and handheld spirometer within 2 weeks of the initial screening visit, instruct the patient on how to perform the respective assessments, and perform first assessments.	To align with the screening period of up to 2 weeks
The first time point should be at ~~the initial screening visit~~ S1, if possible, and the second ~~approximately 3-4 weeks after the first with the samples collected at least 21 days apart from each other~~ at Visit S2 14 days (± 3 days) after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at ~~a third time point~~ Visit S3 provided that the third time point is ~~at least~~ 14 days (± 3 days) after ~~the second time point~~ the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL~~and the mean of the 3 values should also be <250 cells/µL.~~	The first time point should be at Visit S1, if possible, and the second at Visit S2 14 days (± 3 days) after the first sample collected at Visit S1. To meet eligibility criteria, the peripheral blood eosinophil counts from both time points should be <250 cells/µL. If one of the results is ≥250 cells/µL, samples may be collected at Visit S3 provided that the third time point is 14 days (± 3 days) after the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.	The major criterion for defining a subject as having T2-low/Non-T2 asthma is having eosinophil count of <250 cells/µL of blood. It is possible that this level may transiently increase to above 250 cells/µL. If one measurement exceeds 250 cells/µL, it is now felt that having 2 other measurements below 250 will satisfy the definition of T2-low/non-T2 asthma.
At Visit S2 (14 days [± 3 days] after the first peripheral blood eosinophil sample~~, with the samples collected at least 21 days apart from each other),…~~	At Visit S2 (14 days [± 3 days] after the first peripheral blood eosinophil sample,	Visit S2 now occurs 14 days [± 3 days] after Visit S1

Original text with changes shown	New wording	Reason/Justification for change
If required, to meet the eosinophil count inclusion criterion, at Visit S3 (14 days [± 3 days] after Visit S2) efforts should be made to perform the following assessments and procedures in the order listed	If required, to meet the eosinophil count inclusion criterion, at Visit S3 (14 days [± 3 days] after Visit S2) efforts should be made to perform the following assessments and procedures in the order listed	Visit S3 now occurs 14 days [± 3 days] after Visit S2
3.6.1.1 Assessments and Procedures for Screening and Run-in		
See New wording column	Collect optional blood sample for pharmacogenomics analysis	Clarification that pharmacogenomics testing and the blood sample collected for this testing is optional.
3.6.1.2.1 Assessments and Procedures for the Day of Randomization (Visit 1): Pre-Study Drug Administration; Randomization, and Administration of the Loading Dose (Other sections affected by this change: 3.6.1.2.10)		
• Perform ~~reversibility testing (includes~~ in office spirometry (full flow volume loop~~)~~	• Perform in-office spirometry (full flow-volume loop)	To align with other asthma studies that evaluate the pre-BD PFTs as an objective sign of improvement during the study; pre-BD PFTs will be performed at each visit during the active treatment phase (visits 1- 10), done routinely at every 2 week interval throughout treatment.
See New wording column	• Collect optional blood sample in PaxGene DNA tube for pharmacogenomics analysis.	Blood sample for pharmacogenomics being collected at Day of Randomization
3.6.1.2.2. Treatment Visit 2 (Week 2) (Other sections affected by this change: 3.6.1.2.3, 3.6.1.2.4, 3.6.1.2.8, 3.6.1.2.9)		
See New wording column	• Perform in-office spirometry (full flow-volume loop)	To align with other asthma studies that evaluate the pre-BD PFTs as an objective sign of improvement during the study; pre-BD PFTs will be performed at each visit during the active treatment phase (visits 1- 10), done routinely at every 2 week interval throughout treatment.
3.6.1.2.9. ET Visit		
• Perform ~~reversibility testing~~ in-office spirometry(full-volume loop)	• Perform in office spirometry (includes full-volume loop)	To align with rest of PFTs

Original text with changes shown	New wording	Reason/Justification for change
3.6.1.3.1 Assessments and Procedures at the End of Study Visit		
~~• Perform reversibility testing.~~	Not applicable	To align with other asthma studies that evaluate the pre-BD PFTs as an objective sign of improvement during the study; pre-BD PFTs will be performed at each visit during the active treatment phase (visits 1- 10), done routinely at every 2 week interval throughout treatment.
3.6.1.3.1 Assessments and Procedures at the End of Study Visit		
~~• At selected sites, in a subset of patients, obtain sputum sample for [redacted] in a subset of patients following procedures described in the Lab Manual.~~	Not applicable	Sputum collection removed due to lack of experienced staff at sites in collecting sputum samples correctly
4.1 Patient Inclusion Criteria		
c. The patient must have an absolute eosinophil count <250 cells/µL (at least 2 measurements both <250 cells/µL separated by ~~3-4 weeks~~ 14 days [± 3 days]). If one of the results is ≥250 cells/µL, samples may be collected at a third time point(Visit S3) provided that third time point is at least 14 days (± 3 days) after ~~the second time point~~ sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL ~~and the mean of the 3 values should also be <250 cells/µL~~.	c. The patient must have an absolute eosinophil count <250 cells/µL (at least 2 measurements both <250 cells/µL separated by 14 days [± 3 days]). If one of the results is ≥250 cells/µL, samples may be collected at a third time point (Visit S3) provided that third time point is at least 14 days (± 3 days) after the sample collected at Visit S2. If the value at a third time point is used to meet the eligibility criteria, 2 out of the 3 values should be <250 cells/µL.	Visit S2 now occurs 14 days [± 3 days] after Visit S1 and Visit S3 now occurs 14 days [± 3 days] after Visit S2
~~d. The patient has fractional exhaled nitric oxide (FeNO) level <25 ppb.~~	Not applicable	No guidelines exist establishing whether or not any particular level of FeNO truly characterizes T2-low/Non-T2 asthma. Thus, FeNo levels will be measured during the trial, but will no longer be used as an entrance criterion for the trial.
~~g.~~ f. The patient has asthma with a FEV_1 ≥~~40~~30% and <80% of the value predicted for age, height, sex, and race at screening. FEV_1 must be performed	f. The patient has asthma with a FEV_1 ≥30% and <80% of the value predicted for age, height, sex, and race at screening. FEV_1 must be performed using the office-based	The lower floor is being reduced to include eligible subjects who are at a lower threshold of pulmonary function,

Original text with changes shown	New wording	Reason/Justification for change
using the office-based spirometer provided for the study. One pulmonary function test during the screening visit(s) period (up to 2 weeks) is allowed to fulfill this criterion.	spirometer provided for the study. One pulmonary function test retest during the screening visit(s) period (up to 2 weeks) is allowed to fulfill this criterion.	but will be deemed safe for the study since their pulmonary function will be monitored on a daily basis with the peak flow meter.
~~h.~~g. The patient is able to perform technically acceptable and repeatable spirometry, including with a hand-held spirometer, after training (applicable to FEV1, not PEF).	g. The patient is able to perform technically acceptable and repeatable spirometry, including with a hand-held spirometer, after training (applicable to FEV1, not PEF).	Most asthma trials have FEV1 as the primary endpoint. In this trial, both FEV1 and PEF are measured, but it is not mandated that PEF be in a tight 40 liter/min range, as this parameter is usually more effort-dependent and more variable than FEV1. Thus, the reliance in this trial on FEV1 is consistent with most other asthma trials.
~~i.~~ h. The patient's background asthma therapy includes daily medium- or high-dose ICS plus LABA for at least 3 months prior to the initial screening visit with or without other asthma controller medications. The dose of ICS may vary during these 3 months, but must remain at a stable daily dose for at least 1 month prior to Visit S1.	h. The patient's background asthma therapy includes daily medium- or high-dose ICS plus LABA for at least 3 months prior to the initial screening visit with or without other asthma controller medications. The dose of ICS may vary during these 3 months, but must remain at a stable daily dose for at least 1 month prior to Visit S1.	The requirement for a stable dose of inhaled medication is now reduced to 30 days (i.e. the dosage may have changed in the 2 preceding months, but has to be steady for the last month before screening). This requirement is in concert with medication treatment requirement that is commonly used in other asthma trials.
i. The patient has had at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to ~~asthma treated with systemic corticosteroids~~, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit.	i. The patient has had at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit.	Follows current standard of care regarding asthma exacerbations that now includes an increase in the subject's maintenance inhaled corticosteroids (with or without LABAs) by at least 2-fold, for at least 5 days or more until exacerbation symptoms begin to subside. The dose of the inhaled medication can then be tapered back to pre-exacerbation levels.

Original text with changes shown	New wording	Reason/Justification for change
4.2. Patient Exclusion Criteria		
a. The patient has any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results. Examples include but are not limited to: chronic obstructive pulmonary disease, chronic bronchitis or any respiratory condition that requires any chronic antibiotic use (some antibiotics can be immunomodulatory such as macrolides [eg, erythromycin, azithromycin, and clarithromycin]), bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, and interstitial lung disease (including eosinophilic granulomatosis with polyangiitis [EGPA] which is expressly prohibited), obstructive sleep apnea (sometimes referred to as Pickwickian syndrome), and gastroesophageal reflux disease that is not treated with a proton pump inhibitor on a scheduled treatment regimen (not as needed).	a. The patient has any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results. Examples include but are not limited to: chronic obstructive pulmonary disease, chronic bronchitis or any respiratory condition that requires any chronic antibiotic use (some antibiotics can be immunomodulatory such as macrolides [eg, erythromycin, azithromycin, and clarithromycin]), bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, and interstitial lung disease (including eosinophilic granulomatosis with polyangiitis [EGPA] which is expressly prohibited), obstructive sleep apnea (sometimes referred to as Pickwickian syndrome), and gastroesophageal reflux disease that is not treated with a proton pump inhibitor on a scheduled treatment regimen (not as needed).	Clarification of Sponsor's intention to NOT include subjects into the trial who may have any pulmonary disease that may confound the integrity of the study data, or if their underlying condition would interfere with the interpretation and potential impact of the study investigational medicinal product on the subject's underlying asthma condition.
- Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening/run-in, will be tested for active COVID-19 infection and will only be included if they test negative for COVID-19. Patients who were admitted to an ICU during a prior COVID-19 infection; or patients who contracted or recovered from COVID-19 less than 6 weeks prior to screening, or patients with COVID-19 symptoms (lingering anosmia, weakness, persistent dyslogia or feelings of dysphoria for many months) from a pre-study COVID-19 infection that have not completely resolved back to their pre-COVID-19 infection health status are excluded from the study.	- Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening/run-in, will be tested for active COVID-19 infection and will only be included if they test negative for COVID-19. Patients who were admitted to an ICU during a prior COVID-19 infection; or patients who contracted or recovered from COVID-19 less than 6 weeks prior to screening, or patients with COVID-19 symptoms (lingering anosmia, weakness, persistent dyslogia or feelings of dysphoria for many months) from a pre-study COVID-19 infection that have not completely resolved back to their pre-COVID-19 infection health status are excluded from the study.	To specify criteria for patients with COVID-19 infections pre-study
~~m. The patient has received any live or attenuated vaccine within 15 days of the initial screening visit.~~	n. Live and attenuated vaccines should be excluded 14 days before IMP dosing and throughout the study.	Further clarification text added around vaccination with live or attenuated

Original text with changes shown	New wording	Reason/Justification for change
~~(Note: live and attenuated vaccines are also prohibited during the study [screening through EOS].)~~	Inactivated vaccines (including approved inactivated COVID 19 vaccines) should preferably be completed 14 days before first IMP dosing. If administered during the study it is recommended to be at least 3 days before and after IMP administration, or as required by local country regulations.	vaccines and COVID-19 vaccine; vaccinations now allowed
n. The patient has a positive urine drug test during screening for compounds of abuse, or for cotinine, the relevant metabolite of tobacco abuse, the use of which would make the patient ineligible. Repeat testing will not be permitted. A positive urine test for tetrahydrocannabinol, the psychoactive ingredient in marijuana, is permitted during the trial.	n. The patient has a positive urine drug test during screening for compounds of abuse, or for cotinine, the relevant metabolite of tobacco abuse, the use of which would make the patient ineligible. Repeat testing will not be permitted. A positive urine test for tetrahydrocannabinol, the psychoactive ingredient in marijuana, is permitted during the trial.	Positive urine test for THC now permitted
4.3. Randomization Criteria		
b. The patient has not had a clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but within 30 days of) the initial screening visit, or other need for systemic corticosteroids during the screening period.	b. The patient has not had a clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma, or a 2-fold or greater increase from the subject's usual maintenance ICS dose during the exacerbation period documented in the patient's medical or pharmacy records in the 18 months prior to (but within 30 days of) the initial screening visit, or other need for systemic corticosteroids during the screening period.	Follows current standard of care regarding asthma exacerbations that now includes an increase in the subject's maintenance inhaled corticosteroids (with or without LABAs) by at least 2-fold, for at least 5 days or more until exacerbation symptoms begin to subside. The dose of the inhaled medication can then be tapered back to pre-exacerbation levels.
a. The patient has at least 57% adherence (complete and acceptable data for 4 out of the 7 days prior to randomization) to hand-held spirometry and e-diary assessments.	a. The patient has at least 57% adherence (complete and acceptable data for 4 out of the 7 days prior to randomization) to hand-held spirometry and e-diary assessments.	Added definition for 57% adherence
4.6. Rescreening		
~~Specific rescreening criteria for reversibility, FeNO, and peripheral blood eosinophil count are described~~	A subject may be rescreened up to 2 times in the study. Rescreening for urine test found positive for illicit drugs or cotinine, or failure to meet inclusion criterion "e" (ACQ-6	Establishes more clearly rescreening criteria and removes FeNO which is no longer being used as a screening criteria.

Original text with changes shown	New wording	Reason/Justification for change
~~in Section 3.6.1.1.~~ A subject may be rescreened up to 2 times in the study. Rescreening for urine test found positive for illicit drugs or cotinine, or failure to meet inclusion criterion "e" (ACQ-6 score ≥1.5, Section 4.1) will not be allowed. ~~A patient who screen fails for reasons other than the 3 aforementioned reasons may be permitted to rescreen once if there is a reasonable expectation that this patient will become eligible for the study. The sponsor may grant permission to rescreen more than once under extenuating circumstances and only with the approval of the sponsor's.~~ A subject may be rescreened for all other inclusion and exclusion criteria that are not fulfilled.	score ≥1.5, Section 4.1) will not be allowed. A subject may be rescreened for all other inclusion and exclusion criteria that are not fulfilled.	
4.7. Screen Failure		
See New wording column	Patients will be allowed to screen fail twice before no longer being considered for enrollment in the clinical study.	Now allows subjects 2 screen failures; subjects who previously failed to randomize with the Protocol Amendment 1 version may be eligible with the new inclusion/exclusion criteria
5.8.2. Tobacco and Illicit Drugs		
Smoking or use of tobacco products (eg, cigarettes, e-cigarettes, cigars, chewing tobacco, pipe tobacco), ~~or smoking or use of inhaled marijuana products,~~ and use of illicit drugs is strictly forbidden in this study, and objective tests that indicate the use of and/or exposure to these drugs will be administered at the screening visit. Positive tests will result in an irrevocable screen failure of the subject, and retesting is not permitted. In addition, these drugs may not be used or taken at any time during the trial (from Screening Visit S1 through EOS visit). ~~will not be allowed from screening until the EOS visit~~. A positive urine test for tetrahydrocannabinol, the psychoactive ingredient in marijuana, is however, permitted during the trial.	Smoking or use of tobacco products (eg, cigarettes, e-cigarettes, cigars, chewing tobacco, pipe tobacco), and use of illicit drugs is strictly forbidden in this study, and objective tests that indicate the use of and/or exposure to these drugs will be administered at the screening visit. Positive tests will result in an irrevocable screen failure of the subject, and retesting is not permitted. In addition, these drugs may not be used or taken at any time during the trial (from Screening Visit S1 through EOS visit). A positive urine test for tetrahydrocannabinol, the psychoactive ingredient in marijuana, is however, permitted during the trial.	Since there are now many states in the US that have legalized use of marijuana in several forms, the presence of tetrahydrocannabinol in urine is no longer included as an exclusion criteria.

Original text with changes shown	New wording	Reason/Justification for change
5.10 Prior and Concomitant Medication or Therapy		
See New wording column	• Live and attenuated vaccines	Live and attenuated vaccines should be excluded 14 days before IMP and are now not allowed during the study.
Note: - Stable maintenance allergen immunotherapy will be allowed. Starting or build-up phase allergen immunotherapy will not be allowed. - Completion of inactivate vaccination (including available inactivated COVID-19 vaccinations) is preferable at least 14 days before the first IMP dose, if possible. Inactivated vaccination during the study is recommended to be at least 3 days before and after IMP administration, if possible, or as required by local country regulations.	Note: - Stable maintenance allergen immunotherapy will be allowed. Starting or build-up phase allergen immunotherapy will not be allowed. - Completion of inactivate vaccination (including available inactivated COVID-19 vaccinations) is preferable at least 14 days before the first IMP dose, if possible. Inactivated vaccination during the study is recommended to be at least 3 days before and after IMP administration, if possible, or as required by local country regulations.	Further clarification text added around vaccination with live or attenuated vaccines and COVID-19 vaccine; vaccinations now allowed
5.13.2. Blinding and Unblinding		
See New wording column	In addition, unblinding may occur if a review of data of COVID-19 patients per the JDMC or medical monitor is required.	To allow for review of safety data of COVID-19 patients if needed
6.1.2. Clinical Asthma Exacerbation		
~~For this study,~~ asthma exacerbation during the study is defined as a worsening of asthma symptoms (examples are described below) resulting in any of the following:	Asthma exacerbation during the study is defined as a worsening of asthma symptoms (examples are described below) resulting in any of the following:	Simplified text for clarity
6.1.3 e-Diary		
See New wording column	New Section 6.1.3 added: Patients will be trained in using the e-diary to ensure proper use and to ensure rigorous data is collected throughout the study.	To ensure proper training of patients on use of the e-diary and compliance with e-diary standards
7.1 Adverse Events		
7.1 Adverse Events and Adverse Device Effects	Adverse Events and Adverse Device Effects	To make consistent with section since section now contains device text

Original text with changes shown	New wording	Reason/Justification for change
drug or drug/device or device/device interactions	drug or drug/device or device/device interactions	To make more inclusive to include drug/device or device/device interactions
Section 8. ASSESSMENT OF PHARMACOKINETICS, PHARMACOGENOMICS, IMMUNOGENICITY AND [redacted]		
Section 8. ASSESSMENT OF PHARMACOKINETICS, PHARMACOGENOMICS, IMMUNOGENICITY AND [redacted]	**Section 8. ASSESSMENT OF PHARMACOKINETICS, PHARMACOGENOMICS, IMMUNOGENICITY AND** [redacted]	To align with new pharmacogenomics sections added in previous sections
If pharmacokinetic, pharmacogenomics, immunogenicity, and/or [redacted] cannot be collected due to limitations in ability to carry out the procedure or limitations in storage and shipments, the samples will not be collected for those respective visits.	If pharmacokinetic, pharmacogenomics, immunogenicity, and/or [redacted] cannot be collected due to limitations in ability to carry out the procedure or limitations in storage and shipments, the samples will not be collected for those respective visits.	To align with new pharmacogenomics sections added in previous sections
8.3 [redacted] **(Exploratory)**		
[redacted]	[redacted]	[redacted] ing
8.4 Pharmacogenomics Assessment (Optional) (New section)		
See New wording column	Pharmacogenomics is the study of how a person's genetic makeup influences how he or she responds to a drug. Pharmacogenomics testing can contribute to a better understanding of the variation of drug responses seen during development of an investigational drug. A separate ICF is required for pharmacogenomics testing. An optional blood sample for pharmacogenomics testing will be collected (following signing of the ICF) via venipuncture into a PaxGene DNA tube at the time point detailed in Table 3.	Clarification that pharmacogenomics testing and the blood sample collected for this testing is optional.

Original text with changes shown	New wording	Reason/Justification for change
9.6.1. Planned Method of Analysis		
The baseline for absolute eosinophil count will be the average of all ~~the~~ values obtained prior to the administration of the first IMP ~~in screening~~.	The baseline for absolute eosinophil count will be the average of all values obtained prior to the administration of the first IMP.	For clarification that all values will be used for the average
9.6.1.1. Primary Efficacy Analysis		
The primary analysis will compare rates of LoAC between treatment groups using logistic regression with fixed effect for treatment, baseline FEV_1, weight, age group (<65 years vs ≥65 years), and gender as covariates.	The primary analysis will compare rates of LoAC between treatment groups using logistic regression with fixed effect for treatment, baseline FEV_1, weight, age group (<65 years vs ≥65 years), and gender as covariates.	More detail added for the primary efficacy analysis
9.6.1.3. Secondary Efficacy Analysis		
Analysis of ACQ-6 will use the mixed model repeated measures model with treatment group, weight, age group (<65 years vs ≥65 years), gender, visit, and treatment and visit interaction, ~~and baseline value~~ as fixed effects and patient as a random effect.	Analysis of ACQ-6 will use the mixed model repeated measures model with treatment group, weight, age group (<65 years vs ≥65 years), gender, visit, and treatment and visit interaction, as fixed effects and patient as a random effect.	More detail added for the secondary efficacy analysis
See New wording column	The on-site morning trough FEV1 throughout study will be analyzed using similar MMRM method, as described for the analysis ACQ-6. Use of SABA quick relief medication will be derived from the e-diary data in monthly analysis intervals and will be analyzed using a similar MMRM method. The efficacy endpoints defined at end-of-treatment (EOT) will take the last available assessment value in the treatment period, and will be analyzed using appropriate analysis of covariance models.	More detail added for the secondary efficacy analysis
9.7. Multiple Comparisons and Multiplicity		
As there are only 2 treatment groups and one primary analysis test in this study, no multiplicity correction is necessary. Secondary endpoints will be considered as hypothesis-generating, and multiple testing adjustment will not be made.	As there are only 2 treatment groups and one primary analysis test in this study, no multiplicity correction is necessary. Secondary endpoints will be considered as hypothesis-generating, and multiple testing adjustment will not be made.	For clarification that multiple testing adjustment will not be done

Original text with changes shown	New wording	Reason/Justification for change
9. Statistics		
See New wording column	Section 9.11 changed to Section 9.10 and Section 9.10 changed to Section 9.11	To align with order in Section 8
9.12. [redacted] (New section)		
See New wording column	[redacted]	[redacted]
9.13. Planned Interim Analyses (Changed from Section 9.12)		
An unblinded interim analysis is planned after the first 40 to 52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely.	An unblinded interim analysis is planned after the first 40 to 52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely.	Relaxes the timing of the interim analysis to after 40 to 52 patients have completed the treatment period, experienced LoAC, or withdrawn from the study
The interim futility analysis comprises a statistical comparison between treatment group versus placebo in LoAC rate using logistic regression with fixed effect for treatment among the ~~52~~ randomized patients who have completed the treatment period, experienced LoAC, or withdrawn from the study completely at the interim analysis.	The interim futility analysis comprises a statistical comparison between treatment group versus placebo in LoAC rate using logistic regression with fixed effect for treatment among the randomized patients who have completed the treatment period, experienced LoAC, or withdrawn from the study completely at the interim analysis.	Text updated for consistency with first paragraph of section
According to simulation analyses, this cutoff value yields ~~a~~ correct early termination rates under the null hypothesis of 0.43 (40 patients) and 0.44 (~~under the null hypothesis~~ 52 patients) and controls incorrect early termination rate under the alternative hypothesis at approximately 0.06 (40 patients) and 0.04 (~~under the alternative hypothesis of true risk ratio 0.4~~ 52 patients).	According to simulation analyses, this cutoff value yields correct early termination rates under the null hypothesis of 0.43 (40 patients) and 0.44 (52 patients) and controls incorrect early termination rates under the alternative hypothesis at approximately 0.06 (40 patients) and 0.04 (52 patients).	Text updated to provide more detail of the interim futility analyses

Original text with changes shown	New wording	Reason/Justification for change
14. REFERENCES		
See New wording column	New reference: Graham B, Steenbruggen I, Miller M, Barjaktarevic I, Cooper B, Hall G, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Amer J Respir and Crit Care Med 2019; 200(8):e70-e88.	Added as cross-reference to Section 6.1.4
See New wording column	New reference: GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC Version 4, 04/02/2021. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-	Added as cross-reference to Appendix J
APPENDIX A. STUDY REPRESENTATIVES, CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
~~Sputum Supernatant and Sputum Cell Pellet~~ ~~Biomarker & Metabolism Analyties~~ ~~Teva Branded Pharmaceutical Products R&D, Inc.~~ ~~145 Brandywine Parkway~~ ~~West Chester, Pennsylvania 19380-4245~~	Not applicable	Sputum collection removed in Protocol Amendment #2
APPENDIX J. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19 OUTBREAKS		
Section 1.3. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product		
It should be noted that patients diagnosed with <u>active or residual</u> COVID-19 <u>or were hospitalized in ICU during COVID-19 infection</u>, would not be included in the study as they would meet exclusion criterion “a” and “c” ~~which exclude patients with “any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results” and “a suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not~~	It should be noted that patients diagnosed with active or residual COVID-19 or were hospitalized in ICU during COVID-19 infection, would not be included in the study as they would meet exclusion criterion “a” and “c”.	To shorten text and to add clarification; additional text not needed.

Original text with changes shown	New wording	Reason/Justification for change
~~resolved at least 2 weeks before the initial screening visit." Furthermore, exclusion criterion "e" stipulates that:~~		
~~Patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening/run-in, will be tested for active COVID-19 infection and will only be included if they test negative for COVID-19.~~	Not applicable	To shorten text; additional text not needed
~~Patients who are scheduled to undergo sputum induction collection must be tested for active COVID-19 infection within no later than 5 business days from the planned date of the sputum induction prior to the sputum collection. Only patients who are confirmed to not have active COVID-19 will be deemed safe to undergo sputum induction. Patients who are considered to have a high probability of being exposed to COVID-19 infection during the study duration should not be included in the sputum collection cohort.~~		Sputum collection removed in Protocol Amendment #2
See New wording column	The effect of TEV 48574 on the response to vaccines in general and specifically to COVID-19 vaccines is unknown. All live/attenuated vaccines are disallowed 14 days prior to IMP administration and throughout the study. The completion of planned inactivated vaccinations (including approved COVID-19 inactivated vaccinations) is preferable at least 14 days before first IMP dose, if possible. Inactivated vaccination during the study is recommended to be at least 3 days before and after IMP administration, if possible.	To add additional text around timing of COVID-19 vaccination relative to IMP administration.

Original text with changes shown	New wording	Reason/Justification for change
Section 4.2. Patient Exclusion Criteria; Section 5.10. Prior and Concomitant Medication or Therapy		
See New wording column	The eligibility criteria and list of prohibited medications can be updated to reflect new data on COVID-19 therapies or vaccines If a patient receives new COVID-19 therapies or vaccines not in compliance with the eligibility criteria and list of prohibited medications at the time of the patient's participation in the study, the investigator and sponsor will discuss how to proceed on a case-by-case basis.	Updated text added for future data and/or vaccinations for COVID-19
Study Monitoring		
See New wording column	(GUIDANCE 2021)	Provide reference for most recent guidance on monitoring during COVID-19 pandemic
Appendix K. Rules for Pulmonary Function Testing		
See New wording column	**Appendix K. Rules for Pulmonary Function Testing**	Appendix K added to provide clarification on pulmonary function testing

15.2. Administrative Letter Dated 02 December 2020

ADMINISTRATIVE LETTER 02

Study number: TV48574-AS-20031

Clinical Study Protocol with Amendment 01

A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma, version dated 09 November 2020

IND number: 133677; EudraCT number: 2020-001927-15

02 December 2020

Dear Investigator:

The purpose of this letter is to provide additional clarification related to exclusion criteria "a" (Section 4.2 of the protocol). Although the exclusion criteria itself remains the same (ie, the patient has any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results), additional examples are provided in the subsequent statement to provide further context for the investigators. Changes are noted below using track changes.

From:

a. The patient has any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results. Examples include but are not limited to: chronic obstructive pulmonary disease, chronic bronchitis, bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, and interstitial lung disease (including eosinophilic granulomatosis with polyangiitis [EGPA] which is expressly prohibited).

To:

b. The patient has any other pulmonary diagnosis that in the opinion of the investigator and/or the clinical study physician could adversely affect patient safety or interpretation of study results. Examples include but are not limited to: chronic obstructive pulmonary disease, chronic bronchitis or any respiratory condition requiring chronic antibiotic use (antibiotics can be immunomodulatory such as macrolides [eg, erythromycin, azithromycin, and clarithromycin]), bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, ~~and~~ interstitial lung disease (including eosinophilic granulomatosis with polyangiitis [EGPA] which is expressly prohibited), obstructive sleep apnea, sleep apnea, Pickwickian syndrome, and gastroesophageal

reflux disease that is not treated with a proton pump inhibitor on a scheduled treatment regimen (not PRN).

This change will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your Institutional Review Board/Independent Ethics Committee for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

_____

[redacted]
Clinical Development
Teva Pharmaceuticals

15.3. Amendment 01 Dated 09 November 2020

The primary reasons for this amendment are the addition of a JSRC to monitor safety of the patients and the addition of a planned futility analysis. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc.) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
1.3. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product		
None of these risks were observed in ~~either portion of~~ the [redacted] study, except for immunogenicity, predominantly in the low-dose level cohorts up to and including [redacted] in single and repeat dose settings.	None of these risks were observed in the [redacted] study, except for immunogenicity, predominantly in the low-dose level cohorts up to and including [redacted] mg in single and repeat dose settings.	Minor editorial clarification
See New wording column	Management of the patients' safety during the study, including their asthma control, is detailed in Section 3 (study design), Section 7 (assessment of safety), and Appendix B (joint safety review committee [JSRC]).	Addition of JSRC
2.2. Exploratory [redacted]		
See New wording column	Section 2.2.1.1 changed to Section 2.2.1 and Section 2.2.1.2 changed to Section 2.2.2	Correction for previously skipped heading level
2.2.1. Exploratory [redacted] **(Other sections affected by this change: 8.3)**		
[redacted]	[redacted]	[redacted]
3.1. General Study Design and Study Schematic Diagram		
Eligibility requirements include: peripheral blood eosinophil counts of <250 cells/μL (at least 2 measurements both <250 cells/μL separated by 3-4 weeks); FeNO <25 ppb; an ACQ-6 score ≥1.5 despite daily treatment with medium/high dose ICS+LABA for at least 3 months with or without other asthma controller medications, and at least one ~~documented~~ clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma) documented in the 18 months prior to (but not within 30 days of) the initial screening visit.	Eligibility requirements include: peripheral blood eosinophil counts of <250 cells/μL (at least 2 measurements both <250 cells/μL separated by 3-4 weeks); FeNO <25 ppb; an ACQ-6 score ≥1.5 despite daily treatment with medium/high dose ICS+LABA for at least 3 months with or without other asthma controller medications, and at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma) documented in the 18 months prior to (but not within 30 days of) the initial screening visit.	Clarification regarding background asthma therapy

Original text with changes shown	New wording	Reason/Justification for change
The study will consist of an approximate 5-week period consisting of screening followed by a run-in, a 16 week treatment period, and an 8 week follow-up period.	The study will consist of an approximate 5-week period consisting of screening followed by a run-in, a 16 week treatment period, and an 8 week follow-up period.	Clarification added since the window of for the screening and run-in period could also be 4 weeks
Screening and Run-in (5 weeks)		
The duration of the screening and run-in period will be approximately 5 weeks and may be extended by up to 14 days to allow for IMP shipping and to complete assessments of peripheral blood eosinophil count.	The duration of the screening and run-in period will be approximately 5 weeks and may be extended by up to 14 days to allow for IMP shipping and to complete assessments of peripheral blood eosinophil count.	Clarification added since the window of for the screening and run-in period could also be 4 weeks
The FeNO assessment can be repeated once to meet inclusion criterion “d” at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.	The FeNO assessment can be repeated once to meet inclusion criterion “d” at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.	Clarification regarding timing of FeNO assessments
Treatment Period (16 weeks)		
The subset of patients who had sputum collected during the screening period (~~up to~~ approximately 40 patients in total) will have sputum collected again at EOT.	The subset of patients who had sputum collected during the screening period (approximately 40 patients in total) will have sputum collected again at EOT.	Clarification that there is no cap to be placed on the subset of patients who have sputum collected
3.2. Planned Number of Patients and Countries		
An unblinded interim analysis (described in Section 9.12) ~~may be performed~~ is planned, which could result in a sample size increase, from the initially planned 124 to up to 174 total randomized patients (87 per arm), which would require up to 435 patients screened.	An unblinded interim analysis (described in Section 9.12) is planned, which could result in a sample size increase, from the initially planned 124 to up to 174 total randomized patients (87 per arm), which would require up to 435 patients screened.	Addition of futility analysis
3.5. Joint Safety Review Committee (New section)		
See New wording column	There will be a JSRC in this study. The data will be reviewed in a blinded fashion. The JSRC will recommend whether to continue the study as designed, conduct protocol/informed consent form (ICF) modifications, temporarily suspend enrollment and/or study intervention until some uncertainty is resolved, or discontinue the study. Details for the JSRC are given in Appendix B.	Addition of JSRC

Original text with changes shown	New wording	Reason/Justification for change
3.6. Schedule of Study Procedures and Assessments		
Table 2: Study Procedures and Assessments: Screening and Run-In		
See New wording column	Footnote "m" added to the table cell for FeNO (row) and S2/3 (column)	Clarification that FeNO assessment at this time point is not required
[f] FeNO should be completed before reversibility testing. Patients can repeat the FeNO assessment once to meet inclusion criterion "d" at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.	[f] FeNO should be completed before reversibility testing. Patients can repeat the FeNO assessment once to meet inclusion criterion "d" at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.	Clarification regarding timing of FeNO assessments
[h] Patients need to have signed the ICF before being asked to hold medications for reversibility testing. Therefore, initial reversibility testing may take place at a visit after the initial screening visit (see Section 3.6.1.1 for additional details). Reversibility testing should only be attempted after withholding short acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Patients who do not meet reversibility criteria (≥12% and ≥200 mL), may be re-tested once during the initial 2 weeks (±3 days) of the screening period.	[h] Patients need to have signed the ICF before being asked to hold medications for reversibility testing. Therefore, initial reversibility testing may take place at a visit after the initial screening visit (see Section 3.6.1.1 for additional details). Reversibility testing should only be attempted after withholding short acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Patients who do not meet reversibility criteria (≥12% and ≥200 mL), may be re-tested once during the initial 2 weeks (±3 days) of the screening period.	Revised reversibility criteria
[k] QuantiFERON® TB Gold Test (If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, additional samples will be tested to confirm diagnosis; see Section 7.5.2 for details.)	[k] QuantiFERON® TB Gold Test (If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, additional samples will be tested to confirm diagnosis; see Section 7.5.2 for details.)	Additional procedures to confirm TB diagnosis, if the QuantiFERON® TB Gold Test is suspected to be a false positive at screening

Original text with changes shown	New wording	Reason/Justification for change
3.6.1.1. Assessments and Procedures for Screening and Run-in		
• Measure FeNO. The FeNO assessment can be repeated once to meet inclusion criterion "d" at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.	• Measure FeNO. The FeNO assessment can be repeated once to meet inclusion criterion "d" at a second time point during screening (within approximately 2 weeks of the initial screening visit), if the first assessment is not <25 ppb.	Clarification regarding timing of FeNO assessments
4.1. Patient Inclusion Criteria		
f. The patient has demonstrated ≥12% and ≥200 mL response to a bronchodilator from baseline FEV1 within 30 minutes after 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent (eg, Ventolin) at screening.	f. The patient has demonstrated ≥12% and ≥200 mL response to a bronchodilator from baseline FEV1 within 30 minutes after 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent (eg, Ventolin) at screening.	Revised reversibility criteria
g. The patient has asthma with a FEV_1 ≥40% and <80% of the value predicted for age, height, sex, and race at screening. FEV_1 must be performed using the office-based spirometer provided for the study.	g. The patient has asthma with a FEV_1 ≥40% and <80% of the value predicted for age, height, sex, and race at screening. FEV_1 must be performed using the office-based spirometer provided for the study.	Clarification that handheld spirometers should not be used for FEV_1 testing at screening
i. The patient's background asthma therapy includes daily medium- or high-dose ICS plus LABA for at least 3 months prior to the initial screening visit with or without other asthma controller medications. Medium- and high-dose ICS classification will be based on the GINA Global Strategy for Asthma Management and Prevention (2019 update, Appendix C). Patients with asthma controller medications (excluding systemic corticosteroids and systemic immunomodulatory therapies) in addition to ICS+LABA may be eligible provided all eligibility criteria are met.	i. The patient's background asthma therapy includes daily medium- or high-dose ICS plus LABA for at least 3 months prior to the initial screening visit with or without other asthma controller medications. Medium- and high-dose ICS classification will be based on the GINA Global Strategy for Asthma Management and Prevention (2019 update, Appendix C). Patients with asthma controller medications (excluding systemic corticosteroids and systemic immunomodulatory therapies) in addition to ICS+LABA may be eligible provided all eligibility criteria are met.	Clarification regarding background asthma therapy
j. The patient has had at least one ~~documented~~ clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma) documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit. Only	j. The patient has had at least one clinical asthma exacerbation (worsening of asthma requiring systemic corticosteroids [oral or injected], or an emergency department visit due to asthma treated with systemic corticosteroids, or an inpatient hospitalization due to asthma) documented in the patient's medical or pharmacy records in the 18 months prior to (but not within 30 days of) the initial screening visit. Only	Clarification that retrospective documentation of the patient's medical or pharmacy records is not acceptable

Original text with changes shown	New wording	Reason/Justification for change
clinical asthma exacerbations with historical documentation in the patient's medical or pharmacy records may count towards this criterion.	clinical asthma exacerbations with historical documentation in the patient's medical or pharmacy records may count towards this criterion.	
l. The patient is a non-smoker for ≥6 months with lifetime history ≤10 pack-years, with no current e-cigarette or marijuana use. The patient must have a negative urine cotinine test at the screening visit.	l. The patient is a non-smoker for ≥6 months with lifetime history ≤10 pack-years, with no current e-cigarette or marijuana use. The patient must have a negative urine cotinine test at the screening visit.	Clarification added to confirm patient is a non-smoker, with no current e-cigarette or marijuana use
p. ...Women of childbearing potential must have a negative β-HCG test result and practice a highly effective method of birth control (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, see Section 5.9) prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer. Male patients (including vasectomized) with WOCBP partners (whether pregnant or not) must use condoms prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer.	p. ...Women of childbearing potential must have a negative β-HCG test result and practice a highly effective method of birth control (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, see Section 5.9) prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer. Male patients (including vasectomized) with WOCBP partners (whether pregnant or not) must use condoms prior to IMP administration and until the EOS visit or 10 weeks after last IMP dose, whichever is longer.	Minor editorial clarification
4.2. Patient Exclusion Criteria		
c. The patient has any of the following medical conditions:		
Tested positive for tuberculosis (TB) at screening by the QuantiFERON® TB Gold Test, or had a history of untreated latent or active TB. If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, a repeat specimen shall be submitted; if the second test is also positive, the patient screen fails; if the second test is negative, a third test shall be submitted; if the third test agrees with the first test, the patient screen fails; if the third test agrees with second test, the patient is considered to be negative for TB; see Section 7.5.2 for details.	Tested positive for tuberculosis (TB) at screening by the QuantiFERON® TB Gold Test, or had a history of untreated latent or active TB. If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, a repeat specimen shall be submitted; if the second test is also positive, the patient screen fails; if the second test is negative, a third test shall be submitted; if the third test agrees with the first test, the patient screen fails; if the third test agrees with second test, the patient is considered to be negative for TB; see Section 7.5.2 for details.	Additional procedures to confirm TB diagnosis, if the QuantiFERON® TB Gold Test is suspected to be a false positive at screening

Original text with changes shown	New wording	Reason/Justification for change
5.6. Other Medicinal Products		
5.6. Other Medicinal Products~~/Non-Investigational Medicinal Products~~	5.6. Other Medicinal Products	All references to non-IMP were removed (deemed unnecessary for the study-provided inhalers)
Note that other medicinal product is mandated for use in this study; however, for the purposes of this study it is not considered an IMP ~~but is termed "non-IMP"~~.	Note that other medicinal product is mandated for use in this study; however, for the purposes of this study it is not considered an IMP.	All references to non-IMP were removed (deemed unnecessary for the study-provided inhalers)
5.9. Effective Methods of Birth Control		
Bilateral tubal occlusion/ligation	Bilateral tubal occlusion/ligation	Bilateral tubal ligation added to list of effective birth control methods
5.10. Prior and Concomitant Medication or Therapy		
See New wording column	Reslizumab	Reslizumab added to list of examples of systemic immunosuppressive or immunomodulatory agents
5.13.2. Blinding and Unblinding		
See New wording column	Pharmacokinetic sample analysis by the bioanalytical laboratory and pharmacokinetic parameter calculations by pharmacokineticists will be performed during the course of the study. The population pharmacokinetic model for TEV-48574 may be updated with new pharmacokinetic data emerging from the ongoing study. The process to ensure study integrity, maintenance of the double blind, and the responsibilities of the relevant study personnel will be described in a pharmacokinetic analysis plan that will be approved prior to any data transfer, per the sponsor's relevant SOP(s) (eg, GBP-RD-502 [Performing Pharmacokinetic Analyses While Maintaining the Blind]). A similar process could be implemented for the pharmacokinetic/pharmacodynamic model with updated pharmacokinetic and pharmacodynamic data, based on availability of the appropriate SOP.	Clarification that the population pharmacokinetic model (and potentially the pharmacokinetic/pharmacodynamic model, if appropriate) will be updated with emerging data during the study

Original text with changes shown	New wording	Reason/Justification for change
See New wording column	The JSRC will review data in a blinded fashion, as outlined in Appendix B. An interim analysis (Section 9.12) will be conducted by an independent, unblinded statistician who is not a part of the study team. A group of the sponsor's management team who are not a part of the study team may have access to the unblinded interim analysis results. A communication plan to ensure the maintenance of the study blind among the blinded personnel involved in the conduct of the study will be put in place prior to the interim analysis.	Addition of JSRC and interim analysis
7. ASSESSMENT OF SAFETY		
Refer to Table 2 (screening and run-in), Table 3 (treatment period), ~~and~~ Table 4 (follow-up) for the timing of assessments and procedures, and Appendix B (JSRC).	Refer to Table 2 (screening and run-in), Table 3 (treatment period), Table 4 (follow-up) for the timing of assessments and procedures, and Appendix B (JSRC).	Addition of JSRC
7.1.2. Recording and Reporting of Adverse Events		
The relationship of each adverse event to the IMP and ~~non-IMP~~ to the device, as well as the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.	The relationship of each adverse event to the IMP and to the device, as well as the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.	All references to non-IMP were removed (deemed unnecessary for the study-provided inhalers)
7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product		
The relationship of adverse events will be captured separately for the relationship to the IMP and/or ~~the relationship~~ to the ~~non-IMP and/or~~ device. The relationship of an adverse event to the IMP and/or ~~non-IMP and/or~~ to the device will be determined according to the criteria in Table 6.	The relationship of adverse events will be captured separately for the relationship to the IMP and/or to the device. The relationship of an adverse event to the IMP and/or to the device will be determined according to the criteria in Table 6.	All references to non-IMP were removed (deemed unnecessary for the study-provided inhalers)

Original text with changes shown	New wording	Reason/Justification for change
Table 6: The Relationship of an Adverse Event to the IMP and/or Device Suspects		
See New wording column	Table 6 has been revised as described below: • Table title updated from "The Relationship of an Adverse Event to the IMP and non-IMP Device suspects" to 'The Relationship of an Adverse Event to the IMP and/or Device Suspects" • All references to "IMP/non-IMP/device" have been replaced with "IMP/device"	All references to non-IMP were removed (deemed unnecessary for the study-provided inhalers)
7.1.5.3.1. Investigator Responsibility		
The following information should be provided on the SAE/PDAESI form: • ~~additional suspects that are not considered IMP (as applicable), including: dose and unit, frequency, route and form, start and stop date, indication and investigator's assessment of the relationship of the adverse event to the suspect drug~~ • concomitant medication (including study-provided inhalers, doses, routes of administration, dates, and regimens) ~~and~~ • treatment ~~of~~ for the event~~.~~	The following information should be provided on the SAE/PDAESI form: • concomitant medication (including study-provided inhalers, doses, routes of administration, dates, and regimens) • treatment for the event	Clarification for concomitant medications including study-provided inhalers
Each report of a serious adverse event will be reviewed and evaluated by both the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP ~~and to underlying disease~~. In addition, the investigator will assess whether the etiology of the event is associated with the patient's primary condition, concomitant medications (including study-provided inhalers), or any other condition.	Each report of a serious adverse event will be reviewed and evaluated by both the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP. In addition, the investigator will assess whether the etiology of the event is associated with the patient's primary condition, concomitant medications (including study-provided inhalers), or any other condition.	Clarification for concomitant medications including study-provided inhalers
7.2. Adverse Device Effects (New section)		
See New wording column	An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for	Text updated for consistency with the protocol template.

Original text with changes shown	New wording	Reason/Justification for change
	use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device.	
7.2.1. Adverse Device Effect Reporting (New section)		
See New wording column	Adverse device effects (Figure 2) must be recorded on both the source documentation and the CRF. All adverse device effects shall be reviewed by the investigator, the medical monitor, and the sponsor. The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and device deficiency and will categorize each as guided in Section 7.2. The investigator should make an initial determination whether the adverse event may be related to a device deficiency (Section 7.1.4). Adverse device effects and device deficiencies will be listed in the clinical study report (CSR).	Text updated for consistency with the protocol template.
7.2.2. Serious Adverse Device Effects (New section)		
See New wording column	A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.5.1).	Text updated for consistency with the protocol template.
7.2.2.1. Serious Adverse Device Effect Reporting (New section)		
See New wording column	The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours); this information shall be promptly followed by detailed written reports as described below. The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.5.3. Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the	Text updated for consistency with the protocol template.

Original text with changes shown	New wording	Reason/Justification for change
	sponsor using the appropriate form according to national and local regulations. The investigator should make an initial determination whether the serious adverse event may be related to a device deficiency.	
See New wording column	New Figure 2 (Decision Tree for Adverse Events and Adverse Device Effects Classification) was added	Text updated for consistency with the protocol template.
7.5.2. Other Clinical Laboratory Tests		
See New wording column	If the QuantiFERON® TB Gold Test is negative at screening, then the patient may proceed in the screening period. However, if the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive at screening, then a second sample should be drawn and the following steps taken: • If the second QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure. • If the second QuantiFERON® TB Gold Test is negative (ie, results do not match the first test), then a third sample should be drawn. – If the third QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure. – If the third QuantiFERON® TB Gold Test is negative (ie, results match the second test), then the patient may proceed in the screening period. • Note that sites may choose to split the second and third samples and send one to the central laboratory and one to a local laboratory.	Additional procedures to confirm TB diagnosis, if the QuantiFERON® TB Gold Test is suspected to be a false positive at screening

Original text with changes shown	New wording	Reason/Justification for change
	However, the local lab result may not be used for decision making.	
9.1. Sample Size and Power Considerations		
Based on the assumptions above, and assuming a 15% dropout rate during the study, 62 randomized patients per treatment group will provide 80% power to detect a treatment effect of 60% reduction in LoAC rate in the TEV-48574 group using a Chi-square test with one-sided alpha (Type I error rate) of 0.1.	Based on the assumptions above, and assuming a 15% dropout rate during the study, 62 randomized patients per treatment group will provide 80% power to detect a treatment effect of 60% reduction in LoAC rate in the TEV-48574 group using a Chi-square test with one-sided alpha (Type I error rate) of 0.1.	Type of statistical test used in the sample size calculation was added
An unblinded interim analysis ~~may be performed~~ is planned to re-assess the sample size and conduct a futility analysis as described in Section 9.13.	An unblinded interim analysis is planned to re-assess the sample size and conduct a futility analysis as described in Section 9.13.	Addition of futility analysis
9.12. Planned Interim Analyses		
An unblinded interim analysis is planned after the first 52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely~~, an interim analysis may be performed on the unblinded data~~. The main purposes of the interim analysis include sample size re-assessment and futility analysis, as described below. The assumed LoAC event rate in the placebo group is 0.270. If the actual placebo event rate is lower than expected, the study will be underpowered to detect a 60% reduction in event rate. At the interim analysis, if the observed-placebo event rate is lower than expected, and the observed treatment effect is at least a 40% reduction (event rate ratio ≤0.6), the sample size may be increased by up to 50 additional randomized patients, from the initially planned 124 to up to 174. This procedure corresponds to a Promising Zone methodology and does not increase the Type I error rate (Mehta and Pocock 2011). ~~Details will be provided in a separate Interim Analysis Statistical Analysis Plan.~~ The interim futility analysis comprises a statistical comparison between treatment group versus placebo in	An unblinded interim analysis is planned after the first 52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely. The main purposes of the interim analysis include sample size re-assessment and futility analysis, as described below. The assumed LoAC event rate in the placebo group is 0.270. If the actual placebo event rate is lower than expected, the study will be underpowered to detect a 60% reduction in event rate. At the interim analysis, if the observed placebo event rate is lower than expected, and the observed treatment effect is at least a 40% reduction (event rate ratio ≤0.6), the sample size may be increased by up to 50 additional randomized patients, from the initially planned 124 to up to 174. This procedure corresponds to a Promising Zone methodology and does not increase the Type I error rate (Mehta and Pocock 2011). The interim futility analysis comprises a statistical comparison between treatment group versus placebo in LoAC rate using logistic regression with fixed effect for treatment among the 52 randomized patients who have	Addition of futility analysis

Original text with changes shown	New wording	Reason/Justification for change
LoAC rate using logistic regression with fixed effect for treatment among the 52 randomized patients who have completed the treatment period, experienced LoAC, or withdrawn from the study completely. A p-value above 0.5 will be declared as treatment efficacy futility, which could potentially result in early termination of the trial. According to simulation analyses, this cutoff value yields a correct early termination rate of 0.44 (under the null hypothesis) and controls incorrect early termination rate at approximately 0.04 (under the alternative hypothesis of true risk ratio=0.4). More details will be provided in a separate Interim ~~Analysis~~ Statistical Analysis Plan that will be finalized prior to the interim analysis. ~~If performed,~~ The interim analysis will be conducted by an independent, unblinded statistician who is not a part of the study team~~, and the final sample size will be reported~~. A group of the sponsor's management team who are not a part of the study team may have access to the unblinded interim analysis results. A communication plan to ensure the maintenance of the study blind among the blinded personnel involved in the conduct of the study will be put in place prior to the interim analysis.	completed the treatment period, experienced LoAC, or withdrawn from the study completely. A p-value above 0.5 will be declared as treatment efficacy futility, which could potentially result in early termination of the trial. According to simulation analyses, this cutoff value yields a correct early termination rate of 0.44 (under the null hypothesis) and controls incorrect early termination rate at approximately 0.04 (under the alternative hypothesis of true risk ratio=0.4). More details will be provided in a separate Interim Statistical Analysis Plan that will be finalized prior to the interim analysis. The interim analysis will be conducted by an independent, unblinded statistician who is not a part of the study team. A group of the sponsor's management team who are not a part of the study team may have access to the unblinded interim analysis results. A communication plan to ensure the maintenance of the study blind among the blinded personnel involved in the conduct of the study will be put in place prior to the interim analysis.	
14. REFERENCES		
See New wording column	Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med 2011;30(28):3267-84.	Reference added
APPENDIX A. STUDY REPRESENTATIVES, CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
[redacted]	[redacted]	Updated the Legal Representative of the Sponsor in the EU

Original text with changes shown	New wording	Reason/Justification for change
Teva Specialty R&D [redacted] Phone: [redacted] Email: [redacted]	Teva Specialty R&D [redacted] Phone: [redacted] Email: [redacted]	
[redacted] ~~Phone:~~ [redacted] ~~Cell:~~ [redacted] ~~Email:~~ [redacted] [redacted] Clinical Development, Teva Pharmaceuticals Cell: [redacted] Email: [redacted]	[redacted] Clinical Development, Teva Pharmaceuticals Cell: [redacted] Email: [redacted]	Updated the Sponsor's Medical Expert

Original text with changes shown	New wording	Reason/Justification for change
APPENDIX B. JOINT SAFETY REVIEW COMMITTEE (New appendix)		
See New wording column	During the conduct of this study, a JSRC will review accumulating safety data in a blinded manner at 2 scheduled time points, as described below, to ensure the continuing safety of the study patients and to monitor study conduct issues. The JSRC will be composed (at a minimum) of ≥1 of the study principal investigators, the study medical monitor or designee, the sponsor's clinical lead, and the sponsor's responsible pharmacovigilance physician. External consultants with relevant expertise may also be engaged as part of the JSRC, as applicable. The JSRC will convene and review all available safety data after 20 patients (approximately 10 patients on IMP and 10 patients on placebo) have completed 8 weeks of treatment. A subsequent review will be convened after 50% of randomized patients (approximately 31 patients on IMP and 31 patients on placebo) have completed 8 weeks of treatment. A summary of the data will be reviewed in a blinded fashion. The JSRC will recommend whether to continue the study as designed, conduct protocol/ICF modifications, temporarily suspend enrollment and/or study intervention until some uncertainty is resolved, or discontinue the study. The JSRC may also convene at any time during the study at the discretion of any of the JSRC members if new and pertinent safety issues arise. The JSRC will document its recommendations with rationale and inform the study team as appropriate. Additional details on the conduct of the JSRC sessions are outlined in the JSRC charter.	Addition of JSRC
APPENDIX G. PRODUCT COMPLAINTS		
I. Clinical Product Complaints/Device Deficiency	I. Clinical Product Complaints/Device Deficiency	Text updated for consistency with the protocol template.

Original text with changes shown	New wording	Reason/Justification for change
For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent back to the sponsor for investigative testing whenever possible.	For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent back to the sponsor for investigative testing whenever possible.	Text updated for consistency with the protocol template.
Handling of Investigational Medicinal Product(s) and Devices at the Investigational Center(s)	Handling of Investigational Medicinal Product(s) and Devices at the Investigational Center(s)	Text updated for consistency with the protocol template.
If it is determined that the investigational center must return all IMP or devices, the sponsor will provide the information needed to handle the return.	If it is determined that the investigational center must return all IMP or devices, the sponsor will provide the information needed to handle the return.	Text updated for consistency with the protocol template.
A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient, if applicable.	A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient, if applicable.	Text updated for consistency with the protocol template.
The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), and any actions taken to resolve the complaint and to preserve the safety of the patient.	The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), and any actions taken to resolve the complaint and to preserve the safety of the patient.	Text updated for consistency with the protocol template.

Original text with changes shown	New wording	Reason/Justification for change
See New wording column	II. Assessment of Device Performance Device performance will be assessed by device deficiencies and product complaints. A device deficiency is defined as any inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety, or performance (Appendix Figure 1). This definition includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect expiry date), and product complaints that are related to the device. The investigator should make an initial determination whether the device deficiency could have led to a serious adverse event and notify the sponsor by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com. Device deficiencies with potential serious adverse device effect are defined as deficiencies that might have led to a serious adverse device effect if (Appendix Figure 1): • suitable action had not been taken (or) • intervention had not been made (or) • circumstances had been less fortunate	Text updated for consistency with the protocol template.
See New wording column	New Appendix Figure 1 (Decision Tree for Device Deficiencies) was added	Text updated for consistency with the protocol template.

15.4. Administrative Letter 01 Dated 13 October 2020

ADMINISTRATIVE LETTER 01

Study number: TV48574-AS-20031

Clinical Study Protocol

A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma, version dated 28 May 2020

IND number: 133677; EudraCT number: 2020-001927-15

13 October 2020

Dear Investigator:

The purpose of this letter is to clarify the procedures for the QuantiFERON® tuberculosis (TB) testing at screening. As per patient exclusion criteria (c), described in Section 4.2 of the protocol, a patient would be excluded if they tested positive for TB at screening by the QuantiFERON® TB Gold Test or had a history of latent or active TB. In order to protect against false positives, the steps outlined below should be followed when the QuantiFERON® TB Gold Test is drawn at screening and sent to the central laboratory:

- If the first QuantiFERON® TB Gold Test is negative, then the patient may proceed in the screening period.
- If the first QuantiFERON® TB Gold Test is positive, then a second sample should be drawn and sent to the central laboratory.
  - If the second QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure.
  - If the second QuantiFERON® TB Gold Test is negative (ie, results do not match the first test), then a third sample should be drawn and sent to the central laboratory.
    - If the third QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure.
    - If the third QuantiFERON® TB Gold Test is negative (ie, results match the second test), then the patient may proceed in the screening period.
  - Note that sites may choose to split the second and third samples and send one to the central laboratory and one to a local laboratory. However, the local laboratory result may not be used for decision making.

This change will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your Institutional Review Board/Independent Ethics Committee for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

_____

[redacted]
Clinical Development
Teva Pharmaceuticals

APPENDIX A. STUDY REPRESENTATIVES, CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] [redacted] Teva Pharmaceuticals [redacted]
Legal Representative of the Sponsor in the EU	[redacted] Teva Specialty R&D [redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study For **serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, an email address will be provided in the SAE management plan.	[redacted] [redacted] Clinical Development, Teva Pharmaceuticals [redacted]
Contract Research Organization	ICON Clinical Research South County Business Park Leopardstown Dublin 18, Ireland Phone: +353 (1) 291 2000
Electronic Data Capture	Medidata Solutions, Inc. 350 Hudson Street 9th Floor New York, New York 10014 USA

	212-918-1800 www.mdsol.com
Central Clinical Laboratory	ICON PLC South County Business Park Leopardstown Dublin 18, Ireland Phone: +353 (1) 291 2000
Spirometry Evaluation	Vitalograph Ltd Vitalograph Business Park Maids Moreton Buckingham MK18 1SW England Phone: +44(0) 1280 827110
Central Electrocardiogram Evaluation	Vitalograph Ltd Vitalograph Business Park Maids Moreton Buckingham MK18 1SW England Phone: +44(0) 1280 827110
E-Diary	Vitalograph Ltd Vitalograph Business Park Maids Moreton Buckingham MK18 1SW England Phone: +44(0) 1280 827110
Bioanalytical Pharmacokinetics Evaluation	[redacted]
Bioanalytical Immunogenicity Evaluation	[redacted]

Pharmacogenomics Evaluation	[redacted]
Serum TL1a Samples	[redacted]
[redacted]	[redacted]
Randomization and Trial Supply Management (RTSM) vendor	Parexel International Corporation

APPENDIX B. JOINT DATA MONITORING COMMITTEE

During the conduct of this study, a JDMC will review accumulating safety data in a blinded manner at 2 scheduled time points, as described below, to ensure the continuing safety of the study patients and to monitor study conduct issues.

The JDMC will be composed (at a minimum) of ≥1 of the study principal investigators, the study medical monitor or designee, the sponsor's clinical lead, and the sponsor's responsible pharmacovigilance physician. External consultants with relevant expertise may also be engaged as part of the JDMC, as applicable.

The JDMC will convene and review all available safety data after 20 patients (approximately 10 patients on IMP and 10 patients on placebo) have completed 8 weeks of treatment. A subsequent review will be convened after 50% of randomized patients (approximately 31 patients on IMP and 31 patients on placebo) have completed 8 weeks of treatment. A summary of the data will be reviewed in a blinded fashion. The JDMC will recommend whether to continue the study as designed, conduct protocol/ICF modifications, temporarily suspend enrollment and/or study intervention until some uncertainty is resolved, or discontinue the study.

The JDMC may also convene at any time during the study at the discretion of any of the JDMC members if new and pertinent safety issues arise.

The JDMC will document its recommendations with rationale and inform the study team as appropriate.

Additional details on the conduct of the JDMC sessions are outlined in the JDMC charter.

APPENDIX C. CLASSIFICATION OF INHALED CORTICOSTEROIDS

Classification of ICS into low-, medium- and high-dose will be performed using the classification provided in GINA Global Strategy for Asthma Management and Prevention (2019 update), summarized in the following table.

Table 9: Classification of ICS into low/medium/high dose

Drug	Daily dose (µg)		
	Low	Medium	High
Beclomethasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclomethasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	Not applicable	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

CFC=chlorofluorocarbon propellant; DPI=dry powder inhaler; HFA=hydrofluoroalkane propellant
*Beclometasone dipropionate CFC is included for comparison with older literature

APPENDIX D. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

Important Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to IMP administration; use of prohibited medications. Important protocol deviations will be identified and recorded in the patient's source. All-important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the ICF and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor(s) are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the ICF are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

APPENDIX E. ETHICS

Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the ICF, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original ICFs, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

A separate informed consent will be obtained for pharmacogenomic testing.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start <at a given investigational center> before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance (GCA), or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

APPENDIX F. ASTHMA CONTROL QUESTIONNAIRE

(Sample provided in this appendix is provided as an example only.)

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

(QUESTIONS 1 – 6 ONLY: QUESTION 7 (FEV1) OMITTED)

For further information:

[redacted]
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
[redacted]
Web: http://www.qoltech.co.uk

DECEMBER 2002

Revised September 2010 ACQ-SA North American English Version
ACQ 6 – North American English September 2017

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
ACQ 6 – North American English September 2017

ASTHMA CONTROL QUESTIONNAIRE©

PATIENT ID: _____

DATE: _____

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

Revised September 2010 ACQ-SA North American English Version
ACQ 6 – North American English September 2017

APPENDIX G. PRODUCT COMPLAINTS

I. Clinical Product Complaints/Device Deficiency

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.

For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return: Yes/No
- product was taken or used according to protocol: Yes/No

- description or nature of complaint
- associated serious adverse event: Yes/No
- clinical supplies unblinded (for blinded studies): Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

Handling of Investigational Medicinal Product(s) and Devices at the Investigational Center(s)

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP or devices, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient, if applicable.

Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

II. Assessment of Device Performance

Device performance will be assessed by device deficiencies and product complaints.

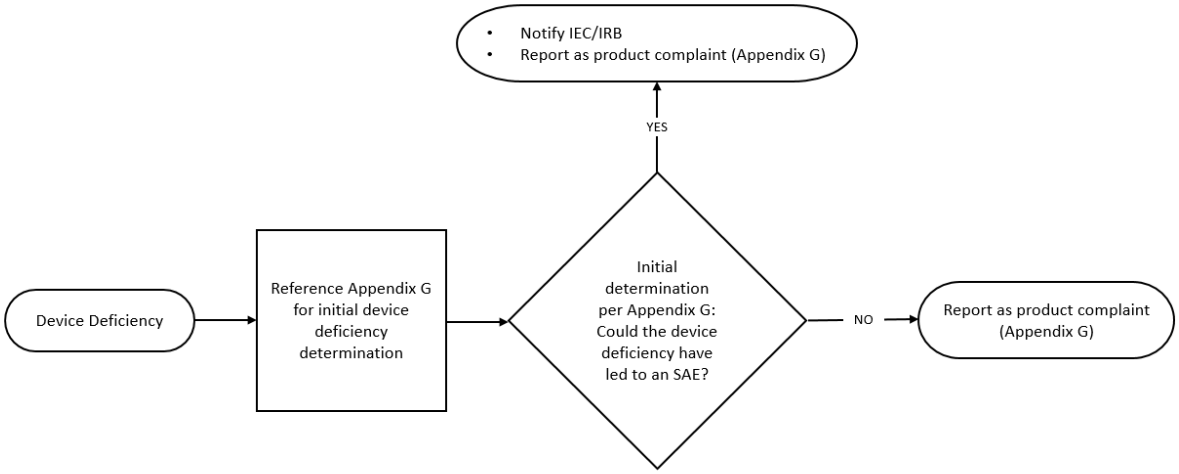
A device deficiency is defined as any inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety, or performance (Appendix Figure 1). This definition includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect expiry date), and product complaints that are related to the device.

The investigator should make an initial determination whether the device deficiency could have led to a serious adverse event and notify the sponsor by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com.

Device deficiencies with potential serious adverse device effect are defined as deficiencies that might have led to a serious adverse device effect if (Appendix Figure 1):

- suitable action had not been taken (or)
- intervention had not been made (or)
- circumstances had been less fortunate

Appendix Figure 1: Decision Tree for Device Deficiencies



IEC=Independent Ethics Committee; IRB=Institutional Review Board; SAE=serious adverse event.

APPENDIX H. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, IEC/IRB, and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, electronic patient-reported outcome [ePRO] tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's SOPs for clinical studies. Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source, and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed ICFs
- patient identification lists
- case report forms for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

Appendix I. LIST OF EXAMPLES OF OPPORTUNISTIC INFECTIONS

- Bacterial enteric infections
- Bartonellosis
- Candidiasis (excluding vulvovaginal candidiasis)
- Chagas disease
- Coccidioidomycosis
- Cryptococcosis
- Cryptosporidiosis
- Cystoisosporiasis (Formerly Isosporiasis)
- Cytomegalovirus Disease
- Hepatitis B Virus Infection
- Hepatitis C Virus Infection
- Herpes Simplex Virus
- Histoplasmosis
- Human Herpesvirus-8
- Human Papillomavirus
- Leishmaniasis
- Malaria
- Microsporidiosis
- Mycobacterium avium
- Mycobacterium tuberculosis
- Pneumocystis Pneumonia
- Progressive Multifocal Leukoencephalopathy/JC Virus Infection
- Syphilis
- Talaromycosis (Formerly Penicilliosis)
- *Toxoplasma gondii*
- Varicella-Zoster Virus

Any suspected opportunistic infections (ie, infections that occur more frequently and are more severe than expected) are to be reported.

Further details are available in “Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents”. Available at:

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0). Accessed 20-May-2020. Community-acquired pneumonia and vulvovaginal candidiasis were removed from the list above as they may be expected in the study patient population.

Appendix J. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19 OUTBREAKS

This appendix is to address the modifications set-up in study conduct during coronavirus disease 2019 (COVID-19) outbreaks.

The changes will be effective for the period of the COVID-19 outbreaks and will be implemented exclusively at the sites impacted by COVID-19. When the situation at specific sites/countries allows the return to regular study activities, the full protocol will govern the study for all sites including those impacted by COVID-19.

The following sections of the protocol are affected:

Section 1.3. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product

In the event of an emergency situation (eg, COVID-19 outbreaks), the sponsor, in close collaboration with the investigators, will determine if the benefit-risk assessment remains positive as a whole, and will assess any additional risks on a patient-by-patient basis. The measures outlined in this appendix are aimed at further mitigating the additional risks in an emergency situation.

It should be noted that patients diagnosed with active or residual COVID-19 or were hospitalized in ICU during COVID 19 infection would not be included in the study as they would meet exclusion criterion “a” and “c”.

The effect of TEV 48574 on the response to vaccines in general and specifically to COVID-19 vaccines is unknown. All live/attenuated vaccines are disallowed 14 days prior to IMP administration and throughout the study. The completion of planned inactivated vaccinations (including approved COVID-19 inactivated vaccinations) is preferable at least 14 days before first IMP dose, if possible. Inactivated vaccination during the study is recommended to be at least 3 days before and after IMP administration, if possible.

If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from IMP and will attend for an ET visit. Remote assessment of safety via teleconference (TC) and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends for the ET visit.

Section 3.1. General Study Design and Study Schematic Diagram; Section 3.6. Schedule of Study Procedures and Assessments

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), the patient will be discontinued from IMP, will continue with daily hand-held spirometry and e-diary completion, scheduled adverse event and concomitant medication monitoring will be continued, and the patient will attend for an ET visit when that becomes possible. Remote assessment of safety via teleconference (TC) and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends for the ET visit. All other tests (including safety labs, pharmacokinetics, ADA, and

[redacted] [if applicable and only in patients who do not have active COVID-19 infection]) are to be conducted once the patient can return to the study center for the ET visit.

In the event that a patient completes the run-in but cannot come to the site for the DoR visit for randomization (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), it may be possible to extend the duration of run-in on a case-by-case basis, following discussion between the investigator and the sponsor study physician. Re-screening of the patient will also be allowed.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 4.2 Patient Exclusion Criteria; Section 5.10. Prior and Concomitant Medication or Therapy

The eligibility criteria and list of prohibited medications can be updated to reflect new data on COVID-19 therapies or vaccines. If a patient receives new COVID-19 therapies or vaccines not in compliance with the eligibility criteria and list of prohibited medications at the time of the patient's participation in the study, the investigator and sponsor will discuss how to proceed on a case-by-case basis.

Section 4.5 Replacement of Patients

In the event of an emergency situation (eg, COVID-19 outbreaks), in case the proportion of patients who terminate the study early due to reasons other than loss of asthma control exceeds the anticipated 15%, the number of patients to be randomized may be increased to ensure the targeted number of completers per arm.

Section 5.13. Maintenance of Randomization and Blinding

Unblinded data review of COVID-19 patients by the JDMC may be conducted upon JDMC recommendations and Teva's discretion.

Section 6. Assessment of Efficacy

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), the patient will be discontinued from IMP, will continue with daily hand-held spirometry and e-diary completion, remote monitoring for asthma-specific alerts will continue, and the patient will attend for an ET visit when that becomes possible.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 7. Assessment of Safety

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), remote assessment of safety (ie, inquiries regarding adverse events and use of concomitant medication) via TC and/or VC, with VC being

the preferred method, may be allowed. The results will be directly entered into the eCRF per the usual process.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 7.4. Clinical Laboratory Tests

For ET patients (patients who cannot be administered the IMP), all required samples scheduled for ET will be collected once the patient can return to the study center.

Section 8. ASSESSMENT OF PHARMACOKINETICS, PHARMACOGENOMICS, IMMUNOGENICITY AND [redacted]

If pharmacokinetic, pharmacogenomics, immunogenicity, and/or [redacted] samples cannot be collected due to limitations in ability to carry out the procedure or limitations in storage and shipments, the samples will not be collected for those respective visits. Study samples collected from confirmed COVID-19 positive patients during the study, with confirmation either before or after the sample collection, will be kept at the central lab and will not be shipped to Teva bioanalytical laboratories nor analyzed. Teva bioanalytical laboratories will be informed within a week of any COVID-19 positive patients confirmed after samples being collected.

Section 9.6.1.2. Sensitivity Analysis

Sensitivity and supplementary analyses will be conducted to evaluate the impact of the change to remote monitoring (TC/VC visits) and the impact of COVID-19 on LoAC rates. The analysis will include subgroup analysis (eg, pre, during, and post-COVID-19 outbreak, where each patient will be classified into one of the levels), a multivariate model (eg, Cox regression with time dependent covariates for COVID-19 and/or use of remote monitoring), and/or imputation methodology for patients' attrition due to the COVID-19, as appropriate and if data permit. Details of the supplementary and sensitivity analyses will be presented in the statistical analysis plan or addendum thereof, following a blinded review meeting prior to database lock.

Section 10. Quality Control and Quality Assurance

Deviations from the study conduct due to emergency situations (eg, COVID-19 outbreaks), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with investigational medicinal product and/or study, alternative procedures used to collect critical safety and/or efficacy data, etc), will be described in the appropriate sections of the Clinical Study Report (CSR), as applicable.

Appendix D. Quality Control and Quality Assurance

Important Protocol Deviations

Deviations from the study conduct due to emergency situations (eg, COVID-19 outbreaks), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with investigational medicinal product and/or study, alternative procedures used to collect critical safety and/or efficacy data, etc), will be described in the appropriate sections of the CSR as applicable.

Study Monitoring

In case of an emergency situation (eg, COVID-19 outbreaks), monitors may not be able to access the investigational centers for on-site visits in a timely manner. A remote monitoring risk mitigation plan will be utilized for sites where on-site monitoring visits are not permitted due to an increased public health risk, in accordance with IRB/EC approval and current guidance (GUIDANCE, 2021). Details are provided in the monitoring plan.

Appendix K. Rules for Pulmonary Function Testing

PFTs – When should you continue to test your subjects?

The protocol and pulmonary function testing equipment indicates when it is okay to continue testing your subjects for the TEV-48574 trial. Here are some guidelines for you to follow with your subjects:

1. **Pulmonary function testing MUST follow ATS (American Thoracic Society) Standards (**Graham 2019)

   This means:

   a) At least 3 good quality spirometry efforts must be done for every spirometry session.

   b) You can do up to 8 efforts to achieve this 3 good quality effort requirement

   c) The values from the top 2 spirometry efforts MUST BE WITHIN 150 mLs of each other. This applies to both FEV1 and FVC.

   d) When you are done with the Pre-BD spirometry, the Spirotrac will give you an alert **IF** the Pre-BD efforts did NOT meet the ATS standards. **STOP TESTING**. You should not perform post-BD spirometry

2. Protocol Criteria

   a) The best FEV1 obtained at the screening visit, and at the Day of Randomization visit, MUST BE WITHIN 30% and 80%. Values outside of this range means the subject should stop testing.

   b) If this out of range PFT testing occurs at screening, the PFT testing must stop, and the subject can return within 2 weeks to try again to meet the spirometry entrance criteria.

   c) If this excursion of PFTs occurs on the Day of Randomization, the subject is a Randomization Failure, but may come back once again to rescreen for the study.

3. Retesting for Reversibility

   a) **If** the subject has done acceptable and repeatable spirometry for the Pre-BD testing at visit S1, and the subject **cannot reverse** at least 12% after bronchodilator administration at this S1 visit, then the subject is allowed to return to the office within two weeks after initial Screening visit, to try again to meet the spirometry criteria.

   b) Again, spirometry must also meet the ATS standards and the Protocol standards identified above.