Clinical Study Protocol

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Efficacy and Pharmacodynamics of TEV-53275 Administered Subcutaneously in Adult Patients with Persistent Eosinophilic Asthma

Study Number TV53275-AS-20033

NCT04847674

Protocol with Amendment 01 Approval Date: 18 November 2021

Clinical Study Protocol with Amendment 01

Study TV53275-AS-20033

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Efficacy and Pharmacodynamics of TEV-53275 Administered Subcutaneously in Adult Patients with Persistent Eosinophilic Asthma

Short title: **A Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of TEV-53275 in Adults with Persistent Eosinophilic Asthma**

Title of the protocol for lay people: **A Study to Test if TEV-53275 is Effective in Relieving Asthma**

Efficacy and Safety Study (Phase 2)

IND number: 138687 EudraCT number: 2021-001439-22

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Original Clinical Study Protocol Version Date: 22 December 2020

Protocol with Amendment 01 Version Date: 18 November 2021

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

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

COVID-19 pandemic-related operational updates are provided in Appendix N

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

DOCUMENT HISTORY

Amendment 01	18 November 2021 63 patients randomized/enrolled to date
Administrative Letter 01	23 March 2021
Original Protocol	22 December 2020

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.

SPONSOR PROTOCOL APPROVAL

Clinical Study Protocol with Amendment 01

Study TV53275-AS-20033

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Efficacy and Pharmacodynamics of TEV-53275 Administered Subcutaneously in Adult Patients with Persistent Eosinophilic Asthma

Original Version Date: 22 December 2020

Protocol with Amendment 01 Version Date: 18 November 2021

I have read the protocol with Amendment 01 and approve the design of this study.

Sponsor's Authorized Representative	**Signature**	**Date**
[redacted], Clinical Development		

Executed signature pages are maintained separately within the Trial Master File

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 01

Study TV53275-AS-20033

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Efficacy and Pharmacodynamics of TEV-53275 Administered Subcutaneously in Adult Patients with Persistent Eosinophilic Asthma

Original Version Date: 22 December 2020

Protocol with Amendment 01 Version Date: 18 November 2021

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 01 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, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local GCP regulations as well as all other national and international laws and regulations.

Principal Investigator	Signature	Date

Executed signature pages are maintained separately within the Trial Master File

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 01

Study: TV53275-AS-20033

Title of Study: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Efficacy and Pharmacodynamics of TEV-53275 Administered Subcutaneously in Adult Patients with Persistent Eosinophilic Asthma

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Investigational New Drug (IND) Number: 138687 **EudraCT number:** 2021-001439-22

EMA Decision number of Pediatric Investigation Plan: Article 45 or 46 of 1901/2006 does not apply

Name of Test Investigational Medicinal Product (IMP): TEV-53275

EudraVigilance (EV) code for the IMP, if applicable: Not applicable

Active Substance: Fully human IgG4 monoclonal antibody that blocks the biological function of Interleukin 5 (IL-5)

Type of Study: Safety and Efficacy

Phase of Clinical Development: 2

Indication: Maintenance treatment of asthma in adult patients with an eosinophilic phenotype

Is this study conducted to investigate the New Use of an approved, marketed product? No

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 80 investigational centers depending on feasibility.

Countries Planned: The study is planned to be conducted in the United States (US), Canada and elsewhere internationally, pending feasibility assessments.

Planned Study Period: The study is planned to begin in approximately Quarter (Q)2/2021 and complete in approximately Q4/2022 (end of the follow-up period).

Number of Patients Planned (total): Approximately 860 patients will be screened to achieve 300 randomized patients. The number of evaluable patients is planned to be approximately 255. Adjustments may be made following the interim analysis.

Study Population: Female or male patients ≥18 years of age with persistent asthma and an eosinophilic phenotype.

Study Objectives and Endpoints: The objectives of this study are to evaluate the safety and efficacy of TEV-53275 comparing 2 dose strengths to placebo in patients with persistent asthma and an eosinophilic phenotype. The primary and secondary study objectives and endpoints are presented below.

Study Objectives and Endpoints

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of TEV-53275 administered subcutaneously (sc) in adult patients with persistent asthma and an eosinophilic phenotype compared to placebo	The primary endpoint is the change from baseline in clinic-based standardized baseline-adjusted trough (pre-bronchodilator) morning forced expiratory volume in 1 second (FEV_1) at week 12
A **secondary objective** of the study is to evaluate the efficacy of TEV-53275 compared to placebo assessed by lung function, asthma symptoms, rescue medication use, and quality of life measures	The secondary efficacy endpoints are: • overall weekly well-controlled asthma status defined by the asthma control composite score and weekly asthma control status (Yes versus No) from week 1 through 12 and overall weekly well-controlled asthma status from week 1 through 16 • overall changes from baseline in the weekly average of daily morning trough (pre-rescue bronchodilator) FEV_1 as measured by a handheld device over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16 • overall changes from baseline in weekly average of rescue medication use over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16 • changes from baseline in percentage of asthma control days (no symptoms and no rescue medication use) over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16 • change from baseline in clinic-based standardized baseline-adjusted morning trough FEV_1 at week 16 • proportions of patients who achieve clinic-based FEV_1 ≥80% predicted at weeks 12, 16, and at endpoint • proportions of patients who achieve forced expiratory flow at 25% to 75% of forced vital capacity (FEF_{25-75}) ≥70% predicted at weeks 12, 16, and at endpoint • time to first clinical asthma exacerbation (CAE) throughout the study • changes from baseline in Asthma Control Questionnaire (ACQ-6) at weeks 12 and 16 • changes from baseline in Asthma Control Test (ACT) at weeks 12 and 16 • changes from baseline in Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) at weeks 12 and 16 • proportions of patients who achieve FEV_1:FVC (forced vital capacity) ratio ≥0.80 at weeks 12, 16, and at endpoint
A **secondary objective** of the study is to evaluate the safety and tolerability of TEV-53275 administered sc in adult patients with persistent asthma and an eosinophilic phenotype compared with placebo	The secondary safety and tolerability endpoints are: • frequency of adverse events • changes from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study • changes from baseline in vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) throughout the study • changes from baseline in 12-lead electrocardiogram (ECG)

Objectives	Endpoints
	findings throughout the study • use of concomitant medication • local tolerability • number (%) of patients who did not complete the study due to adverse events
A **secondary objective** of the study is to evaluate the immunogenicity of TEV-53275 administered sc in adult patients with persistent asthma and an eosinophilic phenotype	The immunogenicity will be assessed by measuring the development anti-drug antibodies (ADA), and the titer and neutralizing activity of the ADA at baseline and throughout the study
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

General Study Design: This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of TEV-53275 administered subcutaneously (sc) at doses of 600 mg and 1200 mg or placebo in adult patients with moderate to severe asthma with an eosinophilic phenotype.

Patients may be eligible to participate if they have a diagnosis of asthma for at least 6 months and their current asthma maintenance therapy has been stable for at least 1 month and includes 1 of the following:

- medium or high dose inhaled corticosteroid (ICS)±another controller
- any fixed dose combination ICS (low, medium or high) with a long-acting β-adrenergic agonist (LABA)±another controller

The patient will continue on this asthma maintenance therapy throughout the treatment period (visit [V9]). For patients taking once-daily inhaled treatment, it must be taken in the morning to enable trough lung function assessments. If a patient requires a change in the timing of dosing, it is allowable as long as the investigator believes there is no inherent harm in changing the timing of the dose and the patient agrees to such change.

The study will consist of 4 periods:

- screening period of up to approximately 2 weeks
- run-in period of approximately 14 days
- double-blind treatment period of 16 weeks
- follow-up period of approximately 14 weeks beginning at the end of the double-blind treatment period

After obtaining informed consent, a screening period of up to approximately 2 weeks is allowed. Patients may be evaluated for inclusion into the run-in period during the screening period. An absolute eosinophil count of ≥300 cells/μL is required to participate in the study. A complete blood count (CBC) will be obtained and may be repeated once during the screening period to demonstrate an absolute eosinophil count of ≥300 cells/μL (a total of 2 attempts during the screening period). Other laboratory testing, medical history assessments, blood collection for biomarkers, physical examination, and other assessments will be completed during the screening period and may be conducted at more than one visit.

Formal pulmonary function testing (spirometry and reversibility testing) will be conducted in the morning between 0530 and 1100 hours using the study-provided spirometry equipment. Testing will be performed in the clinic unless specified as by handheld device. Patients are required to withhold asthma maintenance medications prior to any formal pulmonary function testing. If the patient has taken asthma maintenance medication within 24±2 hours for medication dosed once daily (QD), or within 12±2 hours for medications dosed more frequently than once daily or has taken short-acting β_2-adrenergic agonist (SABA) rescue medication within 6 hours or inhaled corticosteroid in combination with long-acting β_2-adernergic agonist (ICS/LABA) used as rescue medication within 12 hours of the planned pulmonary function testing, the visit must be rescheduled. Patients who meet the pre-albuterol/salbutamol lung function requirements may undergo reversibility testing approximately 30 minutes after 4 inhalations of albuterol/salbutamol hydrofluroalkane (HFA) inhalation aerosol (90 μg ex-actuator or equivalent). Patients who demonstrate reversibility ≥12% and a ≥200 mL increase in forced expiratory volume in 1 second (FEV_1) from baseline may enter the run-in period if they meet other eligibility requirements as specified.

Patients who meet the criteria for inclusion and none of the exclusion criteria may enter into the run-in period at V2 and will continue the current asthma maintenance medication. The patient's current rescue medication will be discontinued and the patient will be provided with albuterol sulfate (117 µg per inhalation) electronic multidose dry powder inhaler (albuterol/salbutamol eMDPI) (ProAir® Digihaler™[1]) or equivalent albuterol/salbutamol (dry powder or aerosol formulations are acceptable) for use as needed as rescue medication to control asthma symptoms. Patients will be provided and trained on the use of an electronic diary and handheld device to measure daily FEV_1 and peak expiratory flow (PEF). During the run-in period, patients will measure FEV_1 and PEF each morning using the handheld device prior to the use of rescue medication (whenever possible) and prior to the morning dose of asthma maintenance medication(s). Patients will also record asthma (daytime or night-time) symptom score and rescue medication (number of puffs) twice daily whether used or not. Patients may be evaluated for randomization into the study after a minimum of 14±2 days after entering the run-in period.

The randomization visit (V3) will occur after a minimum of 14±2 days after entering the run-in period. At this visit the patient's diary data should be reviewed prior to formal lung function testing, laboratory testing and the various questionnaires to ensure compliance with diary entries and to determine if lung function, symptoms and rescue medication use meet the randomization criteria. If the patient fails to meet the diary requirements, the patient will be considered a randomization failure. Further procedures for V3 will only be conducted for patients who meet the diary requirements.

Patients who meet all of the randomization criteria will be stratified based on maintenance therapy (ICS and low dose ICS/LABA will be stratified separately from the medium and high dose ICS/LABA [2 separate strata]), absolute eosinophil count determined at screening (300 to <400 or ≥400 cells/µL) into 1 of 2 treatment groups or placebo via an interactive response technology (IRT) system:

- TEV-53275 600 mg sc
- TEV-53275 1200 mg sc
- Placebo sc

Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients (may be adjusted based on the interim analysis) on medium or high dose ICS/LABA will be randomized and stratified across all treatment arms. Screening may be adjusted as needed to meet these criteria as much as possible.

Patients who meet the requirements for randomization, after the procedures for specimen collection and other testing have been completed, will be randomized via the IRT. Each patient will receive a total of 4 sc injections in the abdomen at V3, administered by a qualified health care provider (according to local regulations) who is prepared to manage anaphylaxis, as described in the study reference manual. The kit number and location will be recorded in the source documents and entered in the case report form (CRF) for each of the 4 injection site locations along with any injection site reaction for each site, evaluated at approximately 1 hour

[1] ProAir® Digihaler™ is a registered trademarks of Teva Pharmaceutical Industries Ltd.

after dosing. If the patient develops clinical symptoms, vital signs should be recorded and the patient should be assessed for anaphylaxis/hypersensitivity reactions. Patients will be observed for a minimum of 1 hour after dosing. Before leaving the clinic, patients will additionally be advised of symptoms/signs for which they should seek medical advice or medical treatment. At all other visits, patients will be free to leave the clinic when all procedures have been completed.

During the treatment period (baseline/day of randomization [DoR, V3] through week 16 [V9]), patients will perform morning lung function assessments (FEV_1 and PEF) by handheld device prior to morning asthma maintenance medication and prior to rescue medication use (whenever possible), assess and record daytime and night-time asthma symptom scores, record rescue medication use (number of puffs) twice daily and confirm (in the evening) that they have taken that day's asthma maintenance medication. During the treatment period visits, formal pulmonary function testing (as required) will be completed in the morning between 0530 and 1100±1 hour on the study-provided spirometry equipment. If a patient has taken rescue medication within 6 hours of the planned pulmonary function testing or has taken the morning dose of asthma maintenance medication, the testing should be cancelled, and the visit should be rescheduled. All formal pulmonary function testing should be conducted at approximately the same time of day ±1 hour of the time it was conducted at baseline/DoR (V3).

Patients who complete week 16 (end of treatment visit [EoTV; V9]) will enter the follow-up period. The handheld device and diary, along with study provided rescue medication will be collected. The investigator should determine and implement appropriate asthma therapy (including rescue treatment) to be used during the follow-up period. Medication started for the purpose of ongoing asthma treatment will not be considered a protocol violation, provided it is started after the final spirometry assessments are completed at week 16 (V9). Patients will be contacted approximately monthly by telephone to assess CAEs, adverse events, and concomitant medications. A final follow-up visit will occur at approximately week 30 for final assessments. A CAE is defined as worsening asthma requiring treatment with a systemic corticosteroid for ≥3 days, emergency room visit resulting in systemic corticosteroid treatment or hospitalization due to asthma. All instances of a CAE should be recorded in the CRF.

Alert criteria for individual patients who develop worsening asthma have been designed to ensure patient safety. If any of the criteria listed below are met, the investigator will determine whether the patient's overall clinical picture is consistent with worsening asthma and if the patient should be placed on additional asthma maintenance therapy in the interest of patient safety. Meeting 1 of these criteria does not automatically require a patient to be placed on alternative asthma therapy; rather it requires a clinical evaluation to determine if the patient's asthma can continue to be managed on the current regimen per the study or necessitates a change in asthma maintenance therapy:

- morning FEV_1 by handheld spirometer, as measured at home, falls below the FEV_1 stability limit (FEV_1 <80% of the screening visit FEV_1 measurement that was measured in the clinic during the screening period) for the run-in period and the baseline value (by handheld device) determined at the randomization visit (V3) for the treatment period on 4 or more days out of any 7-day period. These values are based on the handheld device.

- FEV_1, as measured at the study center, is below the FEV_1 stability limit value calculated at the randomization visit (V3) (<80% of baseline by clinic-based spirometry).
- based upon a review of patient diary data, the patient has experienced any of the following during any 7-day period (the days need not be consecutive and may overlap visits):
  - 3 or more days in which 12 or more inhalations/day of rescue medication (albuterol eMDPI or equivalent albuterol/salbutamol) were used
  - 3 or more days with a night-time asthma symptom score of 3 or higher.
- patients who, by the assessment of the investigator, are identified as having experienced a clinically meaningful worsening of their asthma warranting a change in their asthma treatment (based on the investigator's judgment) will start appropriate treatment. A patient may be deemed by the investigator as having a clinically meaningful worsening of their asthma even when they do not meet the alert criteria above.

Patients who require a change in background asthma maintenance treatment should complete assessments as outlined for V8 and continue to participate in all laboratory and safety assessments lung function, completion of questionnaires and daily diary assessments. (If a patient requires a change in medication between V8 and V9, the procedures for V9 should be completed. If a change of medication occurs within 2 weeks of the next planned visit, that visit may be skipped). Patients who withdraw consent or are withdrawn from participation in the study should complete the procedures for the Early Withdrawal Visit (EWV).

Method of Randomization and Blinding: This is a randomized, double-blind, placebo-controlled, parallel-group study. Patients will be randomly assigned to 1 of 2 treatment groups or placebo in a 1:1:1 ratio and will be stratified by prior asthma maintenance therapy (ICS and low dose ICS/LABA, or medium and high dose ICS/LABA) and absolute eosinophil count (300 to <400 cells/µL, ≥400 cells/µL). Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients (may be adjusted based on the interim analysis) on medium or high dose ICS/LABA will be included and screening will be adjusted as needed to meet these criteria.

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate: The sc route of administration was chosen because it is the intended human therapeutic route. The lowest proposed dose (600 mg) was chosen based on the sponsor's intention to explore potential efficacy of 2 doses of TEV-53275. A placebo control design is scientifically appropriate as placebo will be compared to TEV-53275 as add-on therapy in patients with moderate to severe eosinophilic asthma.

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	TEV-53275	TEV-53275 Placebo
Formulation	[redacted]	[redacted]
Unit dose strength(s)/Dosage level(s)	300 mg/vial	Vehicle buffer absent of protein
Route of administration	sc injection	sc injection
Dosing instructions/Dosing schedule/Titration periods/Treatment periods	As instructed in the clinical protocol and pharmacy manual	As instructed in the clinical protocol and pharmacy manual
Packaging	Type 1 glass vial with butyl rubber stopper and crimp seal with a plastic flip-off cap	Type 1 glass vial with butyl rubber stopper and crimp seal with a plastic flip-off cap
Manufacturer	Teva Branded Pharmaceutical Products R&D, Inc., West Chester, Pennsylvania, USA	Teva Branded Pharmaceutical Products R&D, Inc., West Chester, Pennsylvania, USA
Storage conditions	2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze	2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze

IMP=investigational medicinal product; INN=international nonproprietary name; sc=subcutaneous; USA=United States of America.

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be approximately 34 weeks including up to an approximate 2-week screening period, approximately a 2-week run-in period, a 16-week treatment period, and a follow-up visit 14 weeks after the final treatment visit.

Study Duration: Approximately 16 months, from Q2/2021 to Q4/2022.

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

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: No TEV-53275 treatment is planned after the end of the study.

Selection of Patients/Study Population

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

a. The patient is capable of giving signed informed consent.

b. The patient is an adult female or male ≥18 years of age. Note: Age requirements are as specified or allowed by local regulations.

c. [Revision 1] The patient has a diagnosis of asthma for at least 6 months as defined by the National Institutes of Health (NIH) and has been stable without exacerbation or change in medications for at least 1 month.

d. The patient has an absolute blood eosinophil count ≥300 cells/μL demonstrated during the screening period. **Note: Rounding of the value (count) is not permitted**.

e. Severity of Disease: The patient has persistent asthma, with a trough FEV_1 ≥40% and ≤85% of the value predicted as per the National Health and Nutrition Examination Survey (Hankinson et al 1999, NHANES III 1998) and adjusted for ethnicity (Hankinson et al 2010). **Note: Patients who do not qualify for the study due to failure to meet baseline spirometry or fail to achieve spirometry consistent with the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria (Miller et al 2005) will be permitted to perform repeat spirometry during the screening period on 1 occasion and if criteria are not met, will be considered to have failed screening.**

f. Reversibility of Disease: The patient has demonstrated reversibility of ≥12% (increase) of FEV_1 and a minimum 200 mL increase from pre-albuterol/salbutamol FEV_1 approximately 30 minutes after 4 inhalations of albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) (90 μg ex-actuator) or equivalent during the screening period.

g. [Revision 1] Current Asthma Therapy: The patient has been maintained for at least 1 month on stable doses of:

   – medium or high dose ICS±another controller.

   – any fixed dose combination ICS (low, medium, or high) with LABA±another controller.

h. 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-human chorionic gonadotropin (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) prior to IMP administration and 30 weeks after the dose of IMP. Highly effective contraception includes:

   – 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 14 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, except for hysteroscopic bi-tubal ligation for which a hysterosalpingogram (HSP) is required 3 months post procedure to assess surgical success
- 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.

i. 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 the follow-up procedures and assessments as specified, and be willing to return to the investigational center for further visits, as applicable.

j. The patient, as judged by the investigator, is able to continue their current asthma maintenance medications throughout the study.

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

a. Life threatening asthma, defined as a history of asthma episode(s) requiring intubation and/or associated hypercapnea, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).

b. The patient has 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 screening period. Note: Patients who develop an upper respiratory infection/lower respiratory infection (URI/LRI) during the run-in period may rescreen 2 weeks after symptoms resolve and undergo coronavirus disease 2019 (COVID-19) testing as outlined in exclusion criteria "d".

c. Patients with a confirmed infection with COVID-19 within 3 months prior to the screening visit.

d. 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 4 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.

e. The patient has an eosinophilic condition including hypereosinophilic syndrome, eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis (EGPA [Churg Strauss syndrome]), or allergic bronchopulmonary aspergillosis.

f. The patient has an active helminthic or parasitic infection currently or within the last 6 months.

g. The patient has a history of malignancy other than fully resected basal cell carcinoma of the skin.

h. The patient has any clinically significant, uncontrolled medical or psychiatric condition (treated or untreated) that would interfere with the study schedule or procedures, interpretation of efficacy results, or compromise the patient's safety.

(Note: Chronic obstructive pulmonary disease [emphysema], bronchiectasis requiring treatment, cystic fibrosis, chronic bronchitis, and other diseases of the lung that may complicate interpretation of the study results are prohibited).

i. The patient has known history of, or a positive test result for, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies (Ab), or human immunodeficiency virus (HIV) Types 1 or 2 Ab (according to 4th generation serology testing).

j. The patient is a pregnant or lactating woman, or plans to become pregnant during the study.

k. The patient has taken prohibited prior medications within the washout period. Prohibited medications are listed in the protocol with the appropriate washout periods (see Appendix G).

l. The patient has previously participated in a study with TEV-53275.

m. The patient has participated in another study of an IMP (or a medical device) within the previous 30 days or 5 half-lives of the IMP (whichever is longer) or is currently participating in another study of an IMP (or a medical device).

n. [Revision 1] The patient has been treated with a monoclonal antibody used to treat asthma or other inflammatory conditions within the washout period (5 half-lives), has demonstrated hypersensitivity or anaphylaxis to a monoclonal antibody (Appendix G), or is currently using or has used a systemic immunosuppressive medication within the last 6 months. NOTE: Prior depemokimab exposure is prohibited without exception.

o. The patient has a known hypersensitivity to any components of the IMP stated or study supplied rescue medication.

p. The patient has a history of chronic alcohol or drug abuse within the previous 2 years.

q. [Revision 1] The patient currently smokes or has a smoking history of 10 pack years or more (a pack year is defined as smoking 1 pack of cigarettes [20 cigarettes]/day for 1 year), OR the patient used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco), OR the patient has smoked marijuana within 1 month, OR the patient has a history of "vaping" tobacco, marijuana, or any other substance within 24 months.

r. Vulnerable patients (eg, people kept in detention).

Randomization Criteria:

The following criteria must be fulfilled at the randomization visit (day 0):

a. The patient continues to be in general good health, meeting the entry criteria.

b. The patient's average of 5 most recent **highest** daily trough values (from 3 attempts) for morning FEV_1 obtained at home (by handheld spirometry) over 7 days prior to V3 is within 40% to 80% predicted for age, height, sex, and race (Hankinson et al 1999, Hankinson et al 2010, NHANES III 1998). If rescue medication was taken within 4 hours of the FEV_1 assessment, or asthma maintenance medication was taken before

the measurement, the data from that day should be excluded and data from a previous day during the 7-day period should be included.

c. The patient has an FEV_1 as assessed by clinic-based pulmonary function testing that is within 40% to 85% or the value predicted for age, height, sex, and race (Hankinson et al 1999, Hankinson et al 2010, NHANES III 1998).

d. The patient has demonstrated FEV_1 reversibility as required during the screening period.

e. The patient's ACQ-6 score assessed on V3 day 0 is ≥1.5.

f. The patient has remained on background asthma maintenance medication without changes during the run-in period other than study rescue medication (albuterol eMDPI [ProAir Digihaler for use as needed or equivalent albuterol/salbutamol depending on availability]) and albuterol/salbutamol used for reversibility testing.

g. The patient has had no exacerbation of asthma during the run-in period, defined as any worsening of asthma requiring significant treatment other than rescue medication (albuterol eMDPI [ProAir Digihaler for use as needed or equivalent albuterol/salbutamol depending on availability]). Significant treatment includes any of the following: use of systemic corticosteroids or the addition of ICS-containing asthma medications, LABA, long-acting muscarinic antagonist (LAMA), biologic or other non-corticosteroid asthma medications, emergency room/urgent care visit, or hospitalization for asthma. **Note: A single dose of nebulized albuterol/salbutamol will not meet the criteria for an asthma exacerbation. Emergency room/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.**

h. The patient has complied with home spirometry and diary entry on at least 5 of the last 7 days prior to the visit including:

   – completion of daytime and night-time asthma symptom scores

   – completion of daytime and night-time rescue medication use, whether used or not

   – completion of the morning FEV_1 and PEF by handheld device

   – confirmed daily use of asthma maintenance medication as prescribed

i. The patient has not had an upper respiratory infection (URI) or lower respiratory infection (LRI) during the run-in period. Patients who develop a URI or LRI during the run-in period may be discontinued from the study and allowed to rescreen 2 weeks after resolution of symptoms. They must have a negative test for COVID-19 active infection.

j. The patient has used rescue medication or had a daytime or night-time asthma symptom score ≥1 on 3 or more days in the 7 days prior to the randomization visit as reported in the patient diary.

Statistical Considerations

Sample Size Rationale: The sample size is calibrated based on simulation studies to assess the operating characteristics of the following Bayesian success criterion for the final analysis of the primary efficacy endpoint: adjusted mean change from baseline at week 12 in trough FEV_1:

[redacted]

Analysis Sets

Intent-to-Treat Analysis Set: The intent-to-treat (ITT) analysis set will include all randomized patients.

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

Modified Intent-to-Treat Analysis Set: The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP.

The mITT analysis set will serve as the primary analysis set for efficacy analyses.

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, patients will be assigned to the treatment they actually received regardless of which treatment they were randomized, unless otherwise specified.

Per-Protocol Analysis Set: The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients without important protocol violations. Important protocol violations will be determined before unblinding and will include incorrect IMP received by a patient.

The PP analysis will serve as a supportive analysis for the primary efficacy analysis as well as the secondary efficacy analysis.

Pharmacokinetic Analysis Set: The pharmacokinetic analysis set will include those patients in the safety analysis set who have at least 1 available serum concentration value.

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[1] CINQAIR® is a registered to Teva Pharmaceutical Industries Ltd.

Anti-drug Antibody Analysis Set: The ADA analysis set (for anti-TEV-53275 antibodies) will include those patients treated with TEV-53275 in the safety analysis set.

Efficacy Analysis

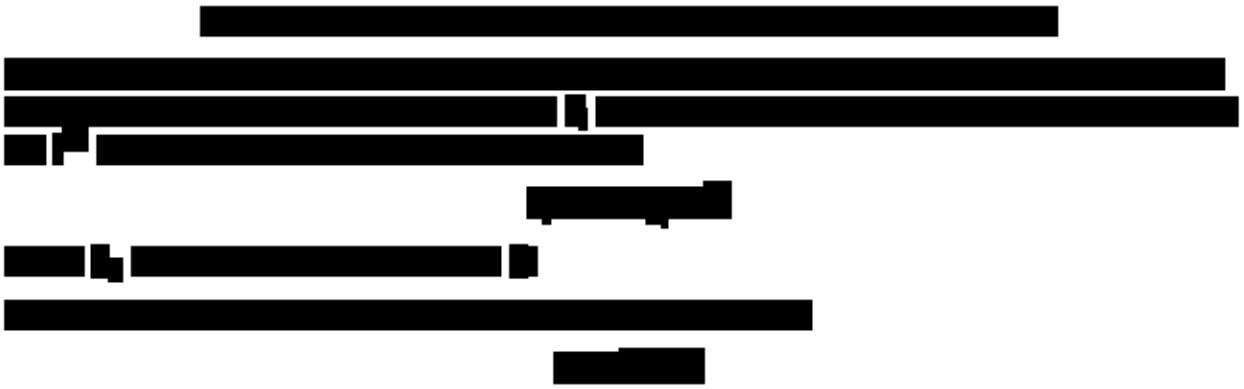
Primary Efficacy Analysis: An estimand, in general, includes 4 inter-related attributes – population of interest, variable (endpoint) of interest, inter-current events (ICE) along with the strategy for handling ICE, and population-level summary for the endpoint.

The estimand selected for the primary efficacy endpoint will assess the change from baseline in morning trough FEV_1 at week 12 due to the initially randomized treatment as actually taken (Mallinckrodt 2013) in the mITT population. This estimand assesses the treatment efficacy at week 12 attributable to the initially randomized medication.

Inter-current events (ICEs) that are expected to affect the efficacy endpoint will include:

1. Instances where a patient experiences worsening of asthma or an asthma exacerbation and the patient is placed on systemic corticosteroids, or additional asthma therapy treatment. In such cases, the investigators will be instructed to encourage the patient to continue in the study and return for planned visits until study completion in order to collect safety data after additional maintenance treatments are used. However, for these patients, improvement in FEV_1 would be expected as rapidly as 1 day after treatment with ICS (Kerwin et al 2019) and within 1 week after a patient receives the ICS/LABA treatment (Corren et al 2007, Pearlman et al 1999). The inclusion of data after a patient receives alternative medications would potentially bias the treatment response estimates due to initially randomized study medications. Therefore, for the primary analysis, the strategy to handle these ICEs will be to exclude observations after the use of asthma maintenance medications (regardless of availability of data obtained afterwards).
2. Confirmed COVID-19 infections: Since COVID-19 is a known respiratory disease which can adversely affect lung functions, as a result, the same strategy for handling such ICEs will be applied in the primary analysis. Observations that occurred after the diagnosis of COVID-19 infections will not be used in the primary analysis.

The population-level summaries would be the Bayesian estimates of (posterior) mean changes from baseline at week 12 for the treatment groups and corresponding 95% credible intervals, as well as posterior probability of treatment effect between each of the TEV-53275 treatment groups vs placebo being greater than 0, ie:



[redacted]

Table 1: Prior Parameters for the Longitudinal Model

	μ_α	σ_α	μ_β	σ_β	a_λ	b_λ
All visits	0	5	0	5	0.5	0.02

The priors for the strata parameters will be provided in the statistical analysis plan.

The posterior is evaluated using Monte Carlo Markov Chain (MCMC) with individual parameters updated by Metropolis Hastings (or Gibbs sampling where possible), using only the y_i and y_{it} data available at the time of the update.

Using the posterior for each treatment group, the Bayesian estimates of mean changes from baseline at week 12 for the treatment groups and corresponding 95% credible intervals can be derived. Furthermore, we calculate the following posterior probability for each TEV-53275 dose group:

Posterior probability (TEV-53275 treatment effect vs placebo >0)

Bayesian Final Analysis Success Rule: A TEV-53275 treatment group is considered to have promising efficacy if it meets the following criterion at the final analysis:

Posterior probability (TEV-53275 1200 mg treatment effect vs placebo >0 at final analysis) >0.85.

Supportive Analysis: The frequentist approach will be used for analyzing the primary efficacy endpoint as a supportive analysis. The same estimand with respect to study population, efficacy endpoint and ICEs along with the same handling strategies will be applied. The population-level summary statistics will be the least squares means in the treatment groups derived from the mixed-effects model for repeated measures (MMRM).

The MMRM model will include baseline morning trough FEV_1, the randomization stratification factor (prior therapy use), baseline eosinophil count visit (weeks 2, 4, 8, 12, and 16), treatment group, and visit-by-treatment group interactions. Contrasts for pairwise treatment comparisons of interest will be constructed. The unstructured covariance matrix will first be used; however, in case of convergence issues, the compound symmetry covariance matrix structure will be used instead.

Missing data are expected to occur due to early dropouts from study or "analysis dropouts" resulting from the use of additional or alternative medications and COVID-19 infections, as mentioned above. We plan to use the reference-based multiple imputations method (Mallinckrodt et al 2017) to handle the missing data problem. This approach imputes missing data based on regression models from the placebo-treated patient data, representing a missing not at random (MNAR) mechanism. It is expected to yield a conservative treatment effect estimate as compared to the estimate obtained from multiple imputations (MI) under a missing at random (MAR) mechanism. This approach has recently been successfully applied in a Phase 3 pediatric trial comparing fluticasone propionate multidose dry powder inhaler (MDPI) with fluticasone propionate/salmeterol MDPI (Study FSS-AS-30003). More details on implementing the reference-based MI will be provided in the protocol and statistical analysis plan.

The Rubin's method will be used to combine estimates from multiply-imputed datasets. The final estimated treatment differences will be presented together with the 2-sided 90% confidence intervals (CI) and p-values.

Sensitivity Analyses: The primary efficacy analysis and supportive analysis will be repeated using the PP population.

Other sensitivity analyses will be conducted by evaluating the impact of missing data on the supportive MMRM analysis using a 2-dimensional "tipping-point", multiple-imputation approach under the MNAR assumption. Shifts to the distributions of missing observations in both the placebo and active treatment arms will be applied to represent different degrees of effect losses. More details will be provided in the statistical analysis plan.

Sensitivity analysis using all data, including retrieved observations following alternative medication use will be run to assess the robustness of study results to a different estimand.

Secondary Efficacy Analysis: For the overall weekly asthma control status from week 1 through 12, the weekly binary endpoints from week 1 through 12 will be analyzed using the repeated measures logistic regression with treatment group, baseline status, prior therapy use, week, and week-by-treatment group interactions in the model and with an unstructured covariance matrix. In the case of convergence issues with the unstructured covariance form, the exchangeable covariance matrix will be used. The overall probability estimate of weekly asthma control over 12 weeks in each treatment group, as well as the overall estimate of odds ratio of weekly asthma control over 12 weeks, comparing each TEV-53275 treatment group versus placebo with corresponding 95% CI and p-value will be derived.

Using the mITT analysis set, each of the following secondary efficacy endpoints will be summarized descriptively and analyzed using a MMRM including baseline value, randomization stratification factors, visit/week, treatment group, and visit/week -by-treatment group interactions in the model with an unstructured covariance matrix:

- overall changes from baseline in weekly average of daily morning trough (pre-rescue bronchodilator) FEV_1 as measured by handheld device over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16
- overall changes from baseline in weekly average of rescue medication use over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16
- changes from baseline in clinic-based standardized baseline-adjusted morning trough FEV_1 at week 16
- changes from baseline in ACQ-6 at weeks 12 and 16
- changes from baseline in ACT at weeks 12 and 16
- changes from baseline in AQLQ(S) at weeks 12 and 16

For weekly binary endpoints, such as the following:

- proportions of patients who achieve clinic-based FEV_1 ≥80% predicted at weeks 12, 16, and at endpoint
- proportions of patients who achieve forced expiratory flow at 25% to 75% of forced vital capacity (FVC) (FEF_{25-75}) ≥70% predicted at weeks 12, 16, and at endpoint
- proportions of patients who achieve FEV_1:FVC ratio ≥0.80 at weeks 12, 16, and at endpoint

The repeated measures logistic regression model with treatment group, corresponding baseline parameter value, prior therapy use, week, and week-by-treatment group interactions in the model and with an unstructured covariance matrix will be used. In the case of convergence issues with the unstructured covariance form, the exchangeable covariance matrix will be used. The weekly probability estimates of achieving the improvement criterion in each treatment group, as well as the estimates of weekly odds ratios comparing each TEV-53275 treatment group versus placebo with corresponding 95% CI and p-values will be derived.

All repeated measures model will be run including measurements at all visits/weeks through week 16.

For changes from baseline in weekly average of rescue medication use over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16, and changes from baseline in percentage of asthma control days (no symptoms and no rescue medication use) over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16, Wilcoxon rank-sum test will be used stratified on randomization stratification factors.

The frequency of CAEs will be analyzed using a negative binomial regression method including randomization stratification factors and treatment group in the model and the logarithm of follow-up time as an offset variable. The ratio of CAE rate between the treatment groups and its 95% CI will be estimated from the negative binomial regression model. Treatment effects will be tested using the likelihood-based Chi-square test.

The Kaplan-Meier method will be used to estimate and compare the distributions of time to the first CAE between treatment groups. Distribution difference will be compared by a log rank test adjusting for the randomization stratification factors.

[redacted]

Multiple Comparisons and Multiplicity: No adjustments will be made for the preplanned multiple comparisons/endpoints.

Safety Analyses: The safety of TEV-53275 will be assessed throughout the study by evaluating adverse events, clinical laboratory test results, vital signs measurements, electrocardiogram (ECG) findings, physical examination results, local tolerability and pain, and concomitant medication usage. Protocol-defined adverse events of special interest (PDAESI) include systemic severe reactions (including anaphylaxis), injection site findings, opportunistic infections, helminth infections, and malignancies.

Safety analyses will be performed on the safety analysis set.

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), adverse events determined by the investigator to be related to test IMP/non-IMP (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of all adverse events, serious adverse events and adverse events leading to withdrawal will be presented.

Values and changes from baseline in clinical laboratory, ECG, and vital signs measurement data (including the incidence of abnormalities) will be summarized descriptively.

Local tolerability at the injection site (erythema, ecchymosis, induration, tenderness, warmth, and swelling, and pain) will be assessed using standardized scales and summarized descriptively.

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

For continuous variables, descriptive statistics (n, mean, standard deviation [SD], standard error, 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.

Pharmacokinetic Analysis: Summaries of TEV-53275 serum concentrations will be presented by nominal time point and dose. Plots of individual TEV-53275 serum concentrations will be presented by actual day (linear and log scales). Plots of mean or median TEV-53275 serum concentrations will be presented by nominal day (linear and log scales).

Pharmacodynamic/Biomarker Analysis: Blood eosinophil count and serum IL-5 (free and total) levels will be summarized by treatment and time point using descriptive statistics. Individual data will be listed.

[redacted]

Immunogenicity Analysis: Anti-TEV-53275 antibody information, number and percent of patients positive for ADA and their antibody titers, and the number of ADA positive patients who are positive for neutralizing antibody, will be described. The impact of the presence of ADA on pharmacokinetics, efficacy, and clinical safety will be evaluated, if appropriate, and results will be provided in the clinical study report.

Ancillary Studies Analysis: During the run-in and treatment periods of this study, patients will be supplied with ProAir Digihaler. Data from these inhalers will be collected centrally. [redacted]

Planned Interim Analysis: The final primary efficacy analyses will be performed when all patients have completed V9 (week 16) or withdrawn from the study. An unblinded interim analysis is planned, when approximately 120 patients (40 patients per arm) have completed the week 8 visit or withdrawn from the study, to assess the early efficacy data. The objectives of the unblinded interim analysis are 1) to detect an early efficacy success signal; 2) to conduct a formal futility analysis, and; 3) to evaluate early stopping criteria.

It is of note that meeting the interim efficacy success criterion will not result in terminating the study early. The early efficacy success result, combined with satisfactory safety data, may assist with preparation / initiation of further safety and efficacy studies, and enable communications with regulatory agencies regarding further clinical development. However, meeting the study futility criterion may result in early termination of the study due to futility.

At the time of the interim analysis, a blinded safety analysis will be conducted. If there is any safety signal of concern at the time of the interim analysis, unblinded safety analyses may be warranted. [redacted]

[redacted]

Further, due to challenges in patient enrollment in the face of the COVID-19 pandemic, the feasibility of an early stopping of the trial with smaller sample sizes may also be evaluated during the interim analysis. The feasibility analysis will be described in the statistical analysis plan.

For the early efficacy success and futility analysis, the week 8 efficacy endpoint, ie, change from baseline at week 8 in morning trough FEV1, will be analyzed. The same Bayesian analysis for the final primary efficacy analysis will be applied, and both the early success and futility criteria will be based on the derived posterior probability of the TEV-53275 dose group performing better than the placebo in improving the week 8 endpoint.

[redacted]

[redacted]

The execution of the unblinded interim analysis

The unblinded interim analysis will be conducted by independent, unblinded statistician(s) and programmer(s) who are not part of the study team, following the pre-specified algorithms and rules. An independent unblinded data review committee will be set up to review the unblinded interim efficacy analysis results. 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. In order to maintain the study blind and the study conduct integrity, a data review charter will be finalized prior to the interim analysis, which specifies the processes for securely unblinding the interim analysis results. The processes will be followed to ensure that the study blind will be maintained in the blinded study personnel who are involved in managing the study activities until the study is unblinded at the final analysis. This charter will also detail the blinded safety review.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
β-HCG	beta human chorionic gonadotropin
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADA	anti-drug antibody/antibodies
AESI	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AQLQ(S)	Standardized Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
AUC_{0-28d}	area under the concentration-time curve from time 0 to 28 days
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of the last measurable concentration
AUC_{τ}	area under the concentration-time curve during a dosing interval
BP	blood pressure
CAE	clinical asthma exacerbation
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent clearance
C_{max}	maximum observed drug concentration
CMV	change of medication visit
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRF	case report form
CRO	Clinical Research Organization
CRSwNP	chronic rhinosinusitis with nasal polyposis

Abbreviation	Term
CSR	clinical study report
D	day
$DNAUC_{0-t}$	dose normalized area under the concentration-time curve from time 0 to the time of the last measurable concentration
$DNAUC_{0-\infty}$	dose normalized area under the concentration-time curve from time 0 to infinity
DNC_{max}	dose normalized maximum observed drug concentration
DoR	day of randomization
DRF	dose-range finding
ECG	electrocardiography, electrocardiogram
EDN	eosinophil-derived neurotoxin
EGPA	eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
eMDPI	electronic multidose dry powder inhaler
EoTV	end of treatment visit
EQ-5D-5L	European Quality of Life 5-dimension health state utility index (5-level version)
ERS	European Respiratory Society
ET	early termination visit
EU	European Union
EV	EudraVigilance
Fc	crystallizable fragment
FDA	Food and Drug Administration (US)
FEF_{25-75}	forced expiratory flow at 25% to 75% of FVC
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
GPSP	Global Patient Safety and Pharmacovigilance
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HFA	hydrofluoroalkane
HIV	human immunodeficiency virus

Abbreviation	Term
HSP	hysterosalpyngogram
IB	Investigator's Brochure
IC_{50}	concentration resulting in 50% reduction of maximal inhibitory effect
IC_{90}	concentration resulting in 90% reduction of maximal inhibitory effect
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL-5	interleukin 5
IL-5Rα	interleukin 5 receptor subunit α
ILC2	group 2 innate lymphoid cells
IMP	investigational medicinal product
IND	Investigational New Drug
INN	international nonproprietary name
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
iv	intravenous
K_D	equilibrium dissociation constant
LABA	long-acting β_2 agonist
LAMA	long-acting muscarinic antagonist
LRI	lower respiratory infection
LSO	local safety officer
mAb	monoclonal antibody
MAD	multiple ascending dose
MAR	missing at random
MDI	metered-dose inhaler
MDPI	multidose dry powder inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputations
MID	minimal important difference

Abbreviation	Term
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MNAR	missing not at random mechanism
N/n	number of patients
NIAID/FAAN	Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NRS-11	11-point pain intensity numerical response scale
PDAESI	protocol defined adverse event(s) of special interest
PEF	peak expiratory flow
PI	Prescribing Information
PP	per protocol
Q	Quarter
Q12W	every 12 weeks
RSI	reference safety information
RT-PCR	reverse transcription polymerase chain reaction
RTSM	Randomization and Trial Supply Management
SABA	short-acting β_2 agonist
SAD	single ascending dose
SAE/PDAESI	serious and protocol defined adverse event of special interest
SAP	statistical analysis plan
sc	subcutaneous/subcutaneously
SEM	standard error of the mean
[redacted]	[redacted]
SMP	serious adverse event management plan
[redacted]	[redacted]
SOC	system organ class
SOP	standard operating procedure
SPR	surface plasmon resonance
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TCR	tissue cross reactivity
t_{max}	time to maximum observed drug concentration

Abbreviation	Term
ULN	upper limit of the normal range
URI	upper respiratory infection
US(A)	United States (of America)
V	visit
VC	videoconference
V_z/F	apparent volume of distribution
W	week
WHO	World Health Organization
WOCBP	women of childbearing potential
XML	Extensible Markup Language

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Interleukin 5

Interleukin 5 (IL-5) is a homodimeric cytokine produced primarily by T helper 2 T cells, group 2 innate lymphoid cells (ILC2), mast cells, natural killer T cells, and eosinophils (reviewed in Bagnasco et al 2017). It signals via a heterodimeric receptor consisting of an alpha subunit, IL-5Rα (CD125), unique to IL-5 and a beta subunit, βc (CD131), shared with IL-3 and granulocyte macrophage colony-stimulating factor (GM-CSF). In humans, the IL-5 receptor is primarily expressed on eosinophils and basophils. IL-5 signaling induces proliferation, differentiation, and activation of eosinophils (Fulkerson and Rothenberg 2013), and differentiation and priming of basophils (Steiner et al 2016).

1.1.2. TEV-53275

TEV-53275, a fully-human immunoglobulin (Ig)G4 monoclonal antibody (mAb), is a new biological entity being developed by Teva for the treatment of asthma patients with an eosinophilic phenotype. TEV-53275 is a neutralizing anti-human IL-5 mAb specifically engineered to enhance its serum half-life ($t_{½}$) and, as such, may allow for less frequent dosing and a significantly lower treatment burden over existing biologic therapies for the maintenance treatment of asthma. It is a hinge-stabilized crystallizable fragment (Fc) modified IgG4 (lambda) antibody that blocks the biological function of IL-5 which is responsible for the maturation, recruitment, and activation of eosinophils from marrow to end-organ tissue, thereby reducing circulating and tissue eosinophils.

1.1.3. TEV-53275 and Asthma

Approximately half of patients with asthma can be classified as eosinophilic based on airway or peripheral blood cellular profiles (Carr et al 2018). Airway eosinophilia has been associated with a reduction in lung function and risk for developing exacerbations in asthma patients (Green et al 2002, Jatakanon et al 2000, Leuppi et al 2001, Louis et al 2000, Miranda et al 2004, ten Brinke et al 2001). Blood eosinophil levels are accepted as a more practical biomarker (compared to sputum eosinophil levels) for identifying patients with active airway eosinophilia who could benefit from anti-IL-5 therapy. Patients with asthma and elevated eosinophils have a higher risk of exacerbation in the next 12 months compared to those with lower eosinophils (Tran et al 2014, Zeiger et al 2014) and patients with peripheral eosinophil counts ≥400 cells/μL tend to be less well-controlled and have more frequent and severe exacerbations. Higher peripheral blood eosinophils have been associated with higher rates of exacerbation (Price et al 2015).

Treatment of severe eosinophilic asthma with anti-IL-5 mAbs (ie, mepolizumab and reslizumab) results in reductions in eosinophil levels, as well as in clinically significant reductions in asthma exacerbations, improved lung function and improved quality of life measures (Castro et al 2015, Pavord et al 2012, Ortega et al 2014). Treatment with a mAb targeting the IL-5Rα (anti-IL-5Rα directed cytolytic mAb, ie, benralizumab) results in a near complete elimination of eosinophils and basophils, a reduction in exacerbations, and improvement in lung function and quality of life

measures (FitzGerald et al 2016, FitzGerald et al, 2018). Each of these agents is indicated for the add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype.

1.1.4. Purpose of the Study

The purpose of this study is to evaluate the safety and efficacy of 2 dose levels of TEV-53275 in patients with persistent eosinophilic asthma defined as asthma in patients with a baseline absolute eosinophil count of ≥300 cells/μL. Treatment with TEV-53275 will be assessed as "add-on treatment" in patients who have been maintained on medium or high dose inhaled corticosteroid (ICS) medications or any dose of ICS in combination with a long-acting β_2 agonist (LABA).

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetic, toxicology, and clinical studies are provided in the following sections. More detailed information is provided in the current version of the Investigator's Brochure (IB).

1.2.1. Nonclinical Studies

1.2.1.1. Pharmacology

[redacted]

1.2.1.2. Pharmacokinetics

[redacted]

[redacted]

[redacted]

1.2.1.3. Nonclinical Safety

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2.2. Clinical Studies

1.2.2.1. Study TV53275-PK-10152

TV53275-PK-10152 is an ongoing Phase 1 study with a randomized, double-blind, placebo-controlled, single ascending dose (SAD) part (Part A) and an open-label, non-randomized, multiple ascending dose part (Part B) to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of TEV-53275 administered sc in adult healthy volunteers. As of the date of this protocol, the SAD part (Part A) of the study had successfully dosed 59 healthy subjects with single doses of TEV-53275 at 50, 150, 450, 900, or 1800 mg, and 10 subjects received placebo. The final data analysis is ongoing. In the multiple ascending dose (MAD) part (Part B) of the study, TEV-53275 was administered sc every 28 days 3 times at dose levels of 450 or 900 mg. Part B of the study is complete and the analysis is ongoing.

1.2.2.1.1. Single Ascending Dose Pharmacokinetics

TEV-53275 concentrations increased with increased dose across all 5 SAD cohorts (50, 150, 450, 900, and 1800 mg). Median t_{max} values ranged from [redacted]. The C_{max} and total

exposure (AUC_{0-t}, area under the concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$]) values increased with each dose level after administration of TEV-53275. The mean $t_{½}$ values ranged from [redacted] across all treatment cohorts. TEV-53275 concentrations appeared to decrease in a bi-exponential fashion following sc administration of TEV-53275. The rate of elimination appeared similar across dose levels. Dose normalized exposure parameters (dose normalized maximum observed drug concentration [DNC_{max}], dose normalized area under the concentration-time curve from time 0 to the time of the last measurable concentration [$DNAUC_{0-t}$], dose normalized area under the concentration-time curve from time 0 to infinity [$DNAUC_{0-\infty}$]), apparent clearance (CL/F), and apparent volume of distribution (V_z/F) were similar across the doses studied in the SAD part of the study (Part A).

Dose proportionality of TEV-53275 was evaluated over the dose range of 50 to 1800 mg using a power model. Across tested exposure parameters (C_{max} and $AUC_{0-\infty}$), the estimated slope was close to 1 and the 90% confidence interval (CI) for the slope contained 1, indicating that the increase in TEV-53275 exposure is dose proportional.

1.2.2.1.2. Single Ascending Dose Pharmacodynamics

Reduction in blood eosinophils was dose and time dependent and observed as early as 2 days after dosing in all active treatment cohorts. Eosinophil counts decreased from baseline values to a maximum effect value within approximately 1 week from dosing after administration of 50, 150, 450, 900, and 1800 mg TEV-53275. Mean eosinophils began to return to baseline values from around 85 days (50 mg cohort), 113 days (150 mg cohort), 141 days (450 mg cohort), and 169 days (900 mg cohort) after administration of TEV-53275. At the highest dose level (1800 mg), mean eosinophil counts began to slowly return to baseline values from 225 days after administration of TEV-53275, although remained markedly lower than baseline, and lower than that for the other cohorts, at last sampling (267 days).

1.2.2.1.3. Single Ascending Dose Safety

As of the date of this protocol, no deaths, serious adverse events, or withdrawals due to adverse events have been reported. Sixteen (27%) of the 59 subjects receiving TEV-53275 and 3 (30%) of the 10 subjects receiving placebo in the SAD part (Part A) of the study experienced treatment-emergent adverse events.

All adverse events, with the exception of 2 headaches (mild and moderate in intensity), were considered by the investigator as not related to study drug. The most common adverse event reported (7 subjects receiving TEV-53275 and 1 subject receiving placebo) was asymptomatic transient blood creatine phosphokinase (CPK) increased (preferred term).

One adverse event of special interest (AESI) of diarrhea was reported in cohort 2 (150 mg TEV-53275). Injection site findings were mainly mild transient erythema. There were no AESIs of opportunistic infections, helminth infections, systemic severe reactions, malignancy, or severe hypersensitivity reactions.

Four pregnancies were reported during the SAD part (Part A) of the study: 3 in subjects receiving TEV-53275 and 1 in a subject receiving placebo. One case was a biochemical pregnancy and in the other 3 pregnancies, all subjects elected to undergo early termination and were discontinued.

No anti-TEV-53275 antibodies have been detected in any of the 59 subjects receiving TEV-53275 in the SAD part of the study (Part A). No clinical signs suggesting immunogenic properties were identified in the subjects dosed with TEV-53275.

The MAD part of the study (Part B) is ongoing and no multiple dose immunogenicity data are available.

Overall, the safety profile of the study drug has indicated a high level of tolerability in terms of any adverse events and no safety signals have been identified.

1.3. Known and Potential Benefits and Risks to Patients

1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

Overall, based on the results from the Phase 1 study (TV53275-PK-10152) and other anti-IL-5 compounds, there are no expected unmanageable risks for the study population.

Given the targeted action of TEV-53275 on IL-5, and considering that the product is a mAb, immunosuppression, hypersensitivity, and immunogenicity may be considered potential class effect risks of TEV-53275; however, this human antibody is expected to have a reduced tendency to elicit an unwanted immune response clinically. Currently, there have been no systemic hypersensitivity reactions or immunogenicity associated with the administration of TEV-53275.

Based on its molecular structure (recombinant mAb), TEV-53275 is not expected to be mutagenic. Furthermore, the currently available scientific literature on the role of IL-5 and eosinophils in tumor development or anti-tumor immunity (Leung et al 2017, Roufosse 2018, Zaynagetdinov et al 2015), along with nonclinical and clinical data from 3 approved mAbs targeting inhibition of IL-5 or IL-5 receptors, does not indicate an increased risk for malignancies following IL-5 pathway blockade. In patients with severe asthma receiving anti-IL-5 mAb treatment, cancers occurred in similar numbers amongst anti-IL-5 treated patients compared with placebo controls, and the types of cancers were similar to those occurring generally in people no matter what medicines they take. There are also recently described immunomodulatory roles of eosinophils in tumor surveillance that have benefited from anti-IL-5 mAb therapy (Zaynagetdinov et al 2015).

Clinical trials with TEV-53275 and other anti-IL-5 mAbs did not demonstrate an increased risk for helminth and or opportunistic infections in patients treated with anti-IL-5 mAbs compared to placebo. However, in view of the possibility of an immunomodulatory role of decreased eosinophils in infections, and specifically in helminth infections, these are considered potential risks for anti-IL-5 treatment.

In the current study, TEV-53275 will be administered via the sc route and nonserious injection site reactions may be seen. In the SAD part (Part A) of Study TV53275-PK-10152 injection site findings were all mild except for 1 subject in the 1800-mg dose group who experienced moderate injection site erythema and induration which resolved over 4 hours. The most common injection site finding was mild erythema seen at 20 minutes after injection.

Older adults and people of any age who have serious underlying medical conditions, including moderate to severe asthma, may be at higher risk for a more severe coronavirus disease 2019

(COVID-19) course when infected (Centers for Disease Control and Prevention [CDC] Coronavirus [COVID-19]). Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center SOPs. The testing may be conducted by the central laboratory or locally depending on feasibility. Those patients at risk for COVID-19 infection should be evaluated with testing and by the investigator to establish whether the patient should participate in the study. Other measures are outlined in Appendix N.

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

1.3.2. Overall Benefit and Risk Assessment for This Study

In this study patients will maintain their asthma maintenance therapy and will receive one of 2 doses of IMP (600 mg or 1200 mg) or placebo for IMP. The current study is designed to monitor safety during the run-in period, at the time of IMP administration (including the monitoring of injection site reactions), and throughout the study, including close daily remote monitoring of each patient's safety electronically with predefined alert criteria to capture patients with worsening asthma by daily lung function measurements, rescue medication use, and asthma symptoms allowing for early recognition of asthma worsening and intervention.

Treatment of asthmatics and exposure to healthy volunteers has demonstrated the safety of the anti-IL-5 mAb class (CINQAIR [reslizumab] Prescribing Information [PI] 02/2020, NUCALA [mepolizumab] PI 09/2019, CINQAIR [reslizumab] Product Monograph, 03/2017; Tsukamoto et al 2016) with adverse reactions generally similar between treated and untreated subjects. Both anti-IL-5 mAbs are approved in USA, Europe and Canada, and are being used to safely treat patients with severe asthma and other conditions. Mepolizumab recently gained approval in children with safety similar to that seen in the adult program (NUCALA [mepolizumab] PI 09/2019). The safety profile of TEV-53275 thus far demonstrated in Study TV53275-PK-10152 is consistent with the overall profile of both reslizumab and mepolizumab. In addition, no ADA has been detected in the SAD part (Part A) of the study. Taken together, the safety profile of the class and the demonstrated safety of TEV-53275 in line with the approved molecules suggest a positive benefit-risk assessment for this study.

The results of this study may facilitate the development of TEV-53275, with potential benefits for patients with moderate to severe eosinophilic asthma as an add-on therapy in patients with severe exacerbation-prone eosinophilic asthma.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of TEV-53275 administered subcutaneously (sc) in adult patients with persistent asthma and an eosinophilic phenotype compared to placebo	The primary endpoint is the change from baseline in clinic-based standardized baseline-adjusted trough (pre-bronchodilator) morning forced expiratory volume in 1 second (FEV_1) at week 12
A **secondary objective** of the study is to evaluate the efficacy of TEV-53275 compared to placebo assessed by lung function, asthma symptoms, rescue medication use, and quality of life measures	The secondary efficacy endpoints are: • overall weekly well-controlled asthma status defined by the asthma control composite score and weekly asthma control status (Yes versus No) from week 1 through 12 and overall weekly well-controlled asthma status from week 1 through 16 • overall changes from baseline in the weekly average of daily morning trough (pre-rescue bronchodilator) FEV_1 as measured by a handheld device over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16 • overall changes from baseline in weekly average of rescue medication use over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16 • changes from baseline in percentage of asthma control days (no symptoms and no rescue medication use) over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16 • change from baseline in clinic-based standardized baseline-adjusted morning trough FEV_1 at week 16 • proportions of patients who achieve clinic-based FEV_1 ≥80% predicted at weeks 12, 16, and at endpoint • proportions of patients who achieve forced expiratory flow at 25% to 75% of FVC (FEF_{25-75}) ≥70% predicted at weeks 12, 16, and at endpoint • time to first clinical asthma exacerbation (CAE) throughout the study • changes from baseline in Asthma Control Questionnaire (ACQ-6) at weeks 12 and 16 • changes from baseline in Asthma Control Test (ACT) at weeks 12 and 16 • changes from baseline in Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) at weeks 12 and 16 • proportions of patients who achieve FEV_1:FVC (forced vital capacity) ratio ≥0.80 at weeks 12, 16, and at endpoint

Objectives	Endpoints
A **secondary objective** of the study is to evaluate the safety and tolerability of TEV-53275 administered sc in adult patients with persistent asthma and an eosinophilic phenotype compared with placebo	The secondary safety and tolerability endpoints are: • frequency of adverse events • changes from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study • changes from baseline in vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) throughout the study • changes 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
A **secondary objective** of the study is to evaluate the immunogenicity of TEV-53275 administered sc in adult patients with persistent asthma and an eosinophilic phenotype	The immunogenicity will be assessed by measuring the development anti-drug antibodies (ADA), and the titer and neutralizing activity of the ADA at baseline and throughout the study

2.1.1. Justification of Primary Endpoint

Change from baseline in clinic-based standardized baseline-adjusted forced expiratory volume in 1 second (FEV_1) is a well-established endpoint used to assess the efficacy of asthma therapies. Additionally, 12-week duration clinical trials with FEV_1 as primary efficacy endpoint have been accepted by FDA as the pivotal design in programs evaluating asthma.

2.2. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Objectives	Endpoints
[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 study to evaluate the safety and efficacy of TEV-53275 administered subcutaneously (sc) at doses of 600 mg and 1200 mg or placebo in adult patients with moderate to severe asthma with an eosinophilic phenotype.

Patients may be eligible to participate if they have a diagnosis of asthma for at least 6 months and their current asthma maintenance therapy has been stable for at least 1 month and includes 1 of the following (see Appendix F):

- medium or high dose inhaled corticosteroid (ICS)±another controller
- any fixed dose combination ICS (low, medium or high) with a long-acting β-adrenergic agonist (LABA)±another controller

The patient will continue on this asthma maintenance therapy throughout the treatment period (V9). For patients taking once-daily inhaled treatment, it must be taken in the morning to enable trough lung function assessments. If a patient requires a change in the timing of dosing, it is allowable as long as the investigator believes there is no inherent harm in changing the timing of the dose and the patient agrees to such change.

The study will consist of 4 periods:

- screening period of up to approximately 2 weeks
- run-in period of approximately 14 days
- double-blind treatment period of 16 weeks
- follow-up period of approximately 14 weeks beginning at the end of the double-blind treatment period

After obtaining informed consent, a screening period of up to approximately 2 weeks is allowed. Patients may be evaluated for inclusion into the run-in period during the screening period. An absolute eosinophil count of ≥300 cells/μL is required to participate in the study. A complete blood count (CBC) will be obtained and may be repeated once during the screening period to demonstrate an absolute eosinophil count of ≥300 cells/μL (a total of 2 attempts during the screening period). Other laboratory testing, medical and asthma history assessments, physical examination and any other assessments as noted in Table 2 will be completed during the screening period and may be conducted at more than one visit.

Formal pulmonary function testing (spirometry and reversibility testing) will be conducted in the morning between 0530 and 1100 hours using the study-provided spirometry equipment. Testing will be performed in the clinic unless specified as by handheld device. Patients are required to withhold asthma maintenance medications prior to any formal pulmonary function testing. If the patient has taken asthma maintenance medication within 24±2 hours for medication dosed once daily (QD), or within 12±2 hours for medications dosed more frequently than once daily or has

taken short-acting β_2-adrenergic agonist (SABA) rescue medication within 6 hours or inhaled corticosteroid in combination with long-acting β_2-adernergic agonist (ICS/LABA) used as rescue medication within 12 hours of the planned pulmonary function testing, the visit must be rescheduled. Patients who meet the pre-albuterol/salbutamol lung function requirements may undergo reversibility testing approximately 30 minutes after 4 inhalations of albuterol/salbutamol hydrofluroalkane (HFA) inhalation aerosol (90 µg ex-actuator or equivalent). Patients who demonstrate reversibility ≥12% and a ≥200 mL increase in forced expiratory volume in 1 second (FEV_1) from baseline may enter the run-in period if they meet other eligibility requirements as specified.

Patients who meet the criteria for inclusion and none of the exclusion criteria may enter into the run-in period at (visit [V] 2) and will continue the current asthma maintenance medication. The patient's current rescue medication will be discontinued and the patient will be provided with albuterol sulfate (117 µg per inhalation) electronic multidose dry powder inhaler (albuterol/salbutamol eMDPI) (ProAir® Digihaler™[1]) or equivalent albuterol/salbutamol (dry powder or aerosol formulations are acceptable) for use as needed as rescue medication to control asthma symptoms. Patients will be provided and trained on the use of an electronic diary and handheld device to measure daily FEV_1 and peak expiratory flow (PEF). During the run-in period, patients will measure FEV_1 and PEF each morning using the handheld device prior to the use of rescue medication (whenever possible) and prior to the morning dose of asthma maintenance medication(s). Patients will also record asthma (daytime or night-time) symptom score and rescue medication (number of puffs) twice daily whether used or not. Patients may be evaluated for randomization into the study after a minimum of 14±2 days after entering the run-in period.

The randomization visit (V3) will occur after a minimum of 14±2 days after entering the run-in period. At this visit the patient's diary data should be reviewed prior to formal lung function testing, laboratory testing and the various questionnaires to ensure compliance with diary entries and to determine if lung function, symptoms and rescue medication use meet the randomization criteria. If the patient fails to meet the diary requirements, the patient will be considered a randomization failure. Further procedures for V3 will only be conducted for patients who meet the diary requirements.

Patients who meet all of the randomization criteria will be stratified based on maintenance therapy (ICS and low dose ICS/LABA will be stratified separately from the medium and high dose ICS/LABA [2 separate strata]) and absolute eosinophil count determined at screening (300 to <400 or ≥400 cells/µL) into 1 of 2 treatment groups or placebo via an interactive response technology (IRT) system:

- TEV-53275 600 mg sc
- TEV-53275 1200 mg sc
- Placebo sc

[1] ProAir® Digihaler™ is a registered trademarks of Teva Pharmaceutical Industries Ltd.

Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients (may be adjusted based on the interim analysis) on medium or high dose ICS/LABA will be randomized and stratified across all treatment arms. Screening may be adjusted as needed to meet these criteria as much as possible.

Patients who meet the requirements for randomization, after the procedures for specimen collection and other testing as described in Appendix B, will be randomized via the IRT. Each patient will receive a total of 4 sc injections in the abdomen at V3, administered by a qualified health care provider (according to local regulations) who is prepared to manage anaphylaxis, as described in the study reference manual. The kit number and location will be recorded in the source documents and entered in the case report form (CRF) for each of the 4 injection site locations along with any injection site reaction for each site, evaluated at approximately 1 hour after dosing. If the patient develops clinical symptoms, vital signs should be recorded and the patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Appendix H. Patients will be observed for a minimum of 1 hour after dosing. Before leaving the clinic, patients will additionally be advised of symptoms/signs for which they should seek medical advice or medical treatment. At all other visits, patients will be free to leave the clinic when all procedures have been completed.

During the treatment period (baseline/day of randomization [DoR, V3] through week 16 [V9]), patients will perform morning lung function assessments (FEV_1 and PEF) by handheld device prior to morning asthma maintenance medication and prior to rescue medication use (whenever possible), assess and record daytime and night-time asthma symptom scores, record rescue medication use (number of puffs) twice daily and confirm (in the evening) that they have taken that day's asthma maintenance medication. During the treatment period visits, formal pulmonary function testing (as required) will be completed in the morning between 0530 and 1100±1 hour on the study-provided spirometry equipment. If a patient has taken rescue medication within 6 hours of the planned pulmonary function testing or has taken the morning dose of asthma maintenance medication, the testing should be cancelled, and the visit should be rescheduled. All formal pulmonary function testing should be conducted at approximately the same time of day ±1 hour of the time it was conducted at baseline/DoR (V3). Other procedures for each visit are outlined in Table 2.

Patients who complete week 16 (end of treatment visit [EoTV; V9]) will enter the follow-up period. The handheld device and diary, along with study provided rescue medication will be collected. The investigator should determine and implement appropriate asthma therapy (including rescue treatment) to be used during the follow-up period. Medication started for the purpose of ongoing asthma treatment will not be considered a protocol violation, provided it is started after the final spirometry assessments are completed at week 16 (V9). Patients will be contacted approximately monthly by telephone to assess CAEs, adverse events, and concomitant medications. A final follow-up visit will occur at approximately week 30 for final assessments. A CAE is defined as worsening asthma requiring treatment with a systemic corticosteroid for ≥3 days, emergency room visit resulting in systemic corticosteroid treatment or hospitalization due to asthma. All instances of a CAE should be recorded in the CRF.

Alert criteria for individual patients who develop worsening asthma have been designed to ensure patient safety. If any of the criteria listed below are met, the investigator will determine whether the patient's overall clinical picture is consistent with worsening asthma and if the

patient should be placed on additional asthma maintenance therapy in the interest of patient safety. Meeting 1 of these criteria does not automatically require a patient to be placed on alternative asthma therapy; rather it requires a clinical evaluation to determine if the patient's asthma can continue to be managed on the current regimen per the study or necessitates a change in asthma maintenance therapy:

- morning FEV_1 by handheld spirometer, as measured at home, falls below the FEV_1 stability limit (FEV_1 <80% of the screening visit FEV_1 measurement that was measured in the clinic during the screening period) for the run-in period and the baseline value (by handheld device) determined at the randomization visit (V3) for the treatment period on 4 or more days out of any 7-day period. These values are based on the handheld device.
- FEV_1, as measured at the study center, is below the FEV_1 stability limit value calculated at the randomization visit (V3) (<80% of baseline by clinic-based spirometry).
- based upon a review of patient diary data, the patient has experienced any of the following during any 7-day period (the days need not be consecutive and may overlap visits):
  - 3 or more days in which 12 or more inhalations/day of rescue medication (albuterol eMDPI or equivalent albuterol/salbutamol) were used
  - 3 or more days with a night-time asthma symptom score of 3 or higher.
- patients who, by the assessment of the investigator, are identified as having experienced a clinically meaningful worsening of their asthma warranting a change in their asthma treatment (based on the investigator's judgment) will start appropriate treatment. A patient may be deemed by the investigator as having a clinically meaningful worsening of their asthma even when they do not meet the alert criteria above.

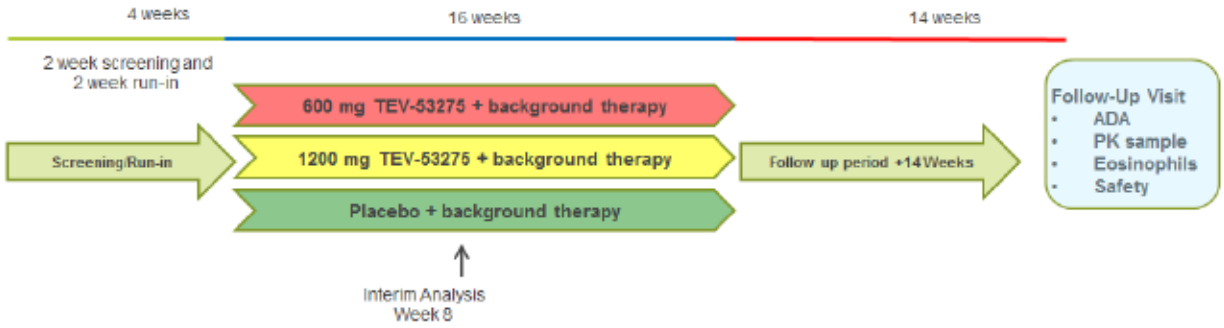
Patients who require a change in background asthma maintenance treatment should complete assessments as outlined for V8 and continue to participate in all laboratory and safety assessments lung function, completion of questionnaires and daily diary assessments. (If a patient requires a change in medication between V8 and V9, the procedures for V9 should be completed. If a change of medication occurs within 2 weeks of the next planned visit, that visit may be skipped). Patients who withdraw consent or are withdrawn from participation in the study should complete the procedures for the Early Withdrawal Visit (EWV).

The end of study is defined as the last visit of the last patient at the follow-up visit.

The assessments and procedures performed during each study visit are detailed in Table 2 and Appendix B.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



ADA=anti-drug antibody; PK=pharmacokinetics.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

3.2. Planned Number of Patients and Countries

Approximately 860 patients will be screened to achieve approximately 300 randomized patients, which may be adjusted based on an interim analysis. Details on the definition of evaluable patients and sample size are given in Section 9.

The study is planned to be conducted in the US, Canada and elsewhere internationally, pending feasibility assessments, in approximately 80 investigational centers. The study is expected to start in approximately Q2 2021 and last until approximately Q4 2022 (end of follow-up period).

3.3. Justification for Study Design and Selection of Population

This is a study to evaluate the safety, efficacy and pharmacodynamics of TEV-53275 when administered to patients with uncontrolled asthma as "add-on treatment" to the patient's current asthma maintenance regimen.

The criteria for inclusion and exclusion along with the randomization criteria allow for selection of a patient population with persistent asthma that is uncontrolled. The criteria also allow for selection of patients who have asthma with an eosinophilic phenotype as defined by elevated peripheral blood eosinophils. Patients with asthma and elevated blood eosinophils are more likely to be uncontrolled and suffer exacerbation of asthma. The study population includes patients who have moderate to severe asthma based on current asthma treatment and fall into Global Initiative for Asthma (GINA) steps 3, 4, and 5 (GINA 2020), but do not meet the criteria of severe difficult-to-treat asthma based on multiple exacerbations in the previous 12 months, need for systemic corticosteroids, or have required biologicals to control asthma (GINA 2020, Chung 2018). Patients with other lung conditions including smoking-related disease, other eosinophilic conditions, malignancy, and recent parasitic infection are excluded. It is anticipated that the patient population selected is well-suited for targeted monotherapy with anti-IL-5 mAb-directed therapy to control underlying eosinophilic inflammation.

Safety will be monitored during the run-in period, at the time of IMP administration (including the monitoring of injection site reactions), and throughout the study. There will be close assessment of vital signs for any adverse event occurring within 1 hour of dosing as well as inspection of the injection site to detect signs of injection site reaction. In addition to the on-site

scheduled evaluations, close daily remote monitoring of each patient's safety will be performed electronically with predefined alert criteria to capture patients with worsening asthma by daily lung function measurements, rescue medication use, and asthma symptoms allowing for early recognition of asthma worsening and intervention. The study will also employ standard safety monitoring including adverse event reporting, physical examinations, clinical laboratory testing, vital signs assessments, concomitant medication monitoring, and immunogenicity assessments, at predefined scheduled visits. Additionally, protocol-defined adverse events of special interest will include systemic severe reactions (including anaphylaxis), injection site findings, opportunistic infections, helminth infections, and malignancies. The safety follow-up visit is anticipated to allow for ADA detection when TEV-53275 is low or non-detectable by the current assay based on the Phase 1 program and to assess for any adverse event that may develop over time.

The duration of this placebo-controlled study is not unlike many other studies conducted successfully without this level of monitoring (Lötvall et al 2014, Busse et al 2014, Amar et al 2016, Sher et al 2017, Bernstein et al 2017, Raphael et al 2018). The overall design of the study is well accepted and Teva has significant expertise and experience in placebo-controlled asthma studies of similar duration (Amar et al 2016, Sher et al 2017, Raphael et al 2018).

The sc route of administration was chosen because it is the intended human therapeutic route. The lowest proposed dose (600 mg) was chosen based on the sponsor's intention to explore potential efficacy of lower doses of TEV-53275.

The primary efficacy endpoint (standardized baseline-adjusted trough [pre-bronchodilator] morning FEV_1 at week 12) is a well-established, clinically relevant endpoint and is standard in most asthma studies. The 12-week endpoint was selected based on the pharmacodynamic effects demonstrated in the SAD part (Part A) of Study TV53275-PK-10152 in which the pharmacodynamic effect was evaluated based on the change in absolute eosinophil counts. A secondary endpoint is included to assess the pharmacodynamic effect at week 16 given the pharmacodynamic effect was prolonged when increasing doses were given to healthy volunteers.

Formal pulmonary function testing at weeks 2, 4, 8, 12, and 16, and daily FEV_1 testing, will allow full characterization of the response to TEV-53275 across the various doses and time points. The sponsor believes that longer duration of the study is unwarranted as the FEV_1 response, as well as improvements in other clinically relevant endpoints, is observed and achieves its maximum effects within weeks of the first drug administration, as has been demonstrated for this mechanism of action and all mAbs that belong to this class of drugs (Castro et al 2015, Ortega et al 2014). Finally, 12-week duration clinical trials with FEV_1 as primary efficacy endpoint have been accepted by FDA as the pivotal design in programs evaluating asthma therapies and therefore meet the rigor generally required of to Phase 3 clinical programs. Further continuation of the efficacy assessments in the study beyond 16 weeks will not add further to the pharmacodynamics assessment in this population.

The secondary efficacy measures are designed to support the primary outcome measure to evaluate TEV-53275 and confirm the effects on asthma control and lung function over 12 and 16 weeks, including weekly well-controlled asthma status, daily assessment of FEV_1, assessing asthma control by daily symptom scores and rescue medication use, time to clinical asthma exacerbation (CAE), and standardized questionnaires that assess asthma control and quality of

life. In addition, formal pulmonary function testing will be conducted at week 16 to evaluate for efficacy beyond 12 weeks.

Blood eosinophil levels are accepted as a more practical biomarker (compared to sputum eosinophil levels) for identifying patients with active airway eosinophilia who could benefit from anti-IL-5 therapy. Patients with asthma and elevated eosinophils have a higher risk of exacerbation in the next 12 months compared to those with lower eosinophils (Tran et al 2014, Zeiger et al 2014) and patients with peripheral eosinophil counts ≥400 cell/μL tend to be less well-controlled and have more frequent exacerbations, and exacerbations increased as the peripheral blood eosinophil counts increase (Price et al 2015).

3.4. Stopping Rules for the Study

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should 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 the IMP

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

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 2. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetics, immunogenicity, biomarkers, and pharmacogenetics). Study procedures and assessments by visit are listed in Appendix B. For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

Table 2: Study Procedures and Assessments

Study period	Pretreatment		Double-blind treatment period								Follow-up period			Follow-up[a]
Visit number	V1[b]	V2[c]	V3[d]	V4	V5	V6	V7	V8	V9[e] (EoTV)	EWV[f]	Telephone[g]			V10
Day and allowed time windows	Up to 2 weeks	14±2 days	Day 0	Day 3±2	Day 14±2	Day 28±2	Day 56±2	Day 84±2	Day 112±2	NA	Day 140±2	Day 168±2	Day 196±2	Day 210±5
Procedures and assessments	Screening	Run-in	Baseline/ DoR	W1	W2	W4	W8	W12	W16	NA	W20	W24	W28	W30
Informed consent[h]	X													
Demographics	X													
Inclusion and exclusion criteria	X	X	X											
Randomization criteria			X											
Perform randomization and treatment assignment in IRT[i]			X											
Medical history	X													
Asthma history[j]	X													
Current asthma medication assessment[k]	X													
Prior medication and treatment history[l]	X													
Full physical examination[m]			X						X	X				
Brief physical examination[n]	X				X	X	X	X						X
Height (cm)	X													
Weight (kg)	X								X	X				
Pulmonary function testing with reversibility[o]	X													
Pulmonary function testing[p]			X	X	X	X	X	X	X	X				
Hematology (CBC with differential[q])	X		X											

Study period	Pretreatment		Double-blind treatment period								Follow-up period			Follow-up[a]
Visit number	V1[b]	V2[c]	V3[d]	V4	V5	V6	V7	V8	V9[e] (EoTV)	EWV[f]	Telephone[g]			V10
Day and allowed time windows	Up to 2 weeks	14±2 days	Day 0	Day 3±2	Day 14±2	Day 28±2	Day 56±2	Day 84±2	Day 112±2	NA	Day 140±2	Day 168±2	Day 196±2	Day 210±5
Procedures and assessments	Screening	Run-in	Baseline/ DoR	W1	W2	W4	W8	W12	W16	NA	W20	W24	W28	W30
Hematology (blinded CBC with differential[r])				X	X	X	X	X	X	X				X
Serum chemistry[s]	X		X[t]			X	X	X	X[t]	X				X
Optional blood sample for biomarker banking[t]	X													
Blood sample for Hepatitis B, Hepatitis C and HIV testing[u]	X													
Blood sample for Phadiatop allergy test and total IgE			X											
Blood sample for pharmacogenetic testing[v, w]			X											
Blood sample for serum concentration of IMP[w]			X	X	X	X	X	X	X	X				X
Blood sample for ADA[w]			X						X	X				X
Blood sample for serum biomarker (IL-5) analysis[w]			X	X	X	X	X	X	X	X				X
Urinalysis	X		X						X	X				
Urine pregnancy test for WOCBP (β-HCG)	X		X			X	X	X	X	X				X
FSH[x]	X													
12-lead ECG[y]			X[z]						X	X				
Vital signs measurement[aa]	X	X	X		X	X	X	X	X	X				X
[redacted]			X					X		X				

Study period	Pretreatment		Double-blind treatment period								Follow-up period			Follow-up[a]
Visit number	V1[b]	V2[c]	V3[d]	V4	V5	V6	V7	V8	V9[e] (EoTV)	EWV[f]	Telephone[g]			V10
Day and allowed time windows	Up to 2 weeks	14±2 days	Day 0	Day 3±2	Day 14±2	Day 28±2	Day 56±2	Day 84±2	Day 112±2	NA	Day 140±2	Day 168±2	Day 196±2	Day 210±5
Procedures and assessments	Screening	Run-in	Baseline/ DoR	W1	W2	W4	W8	W12	W16	NA	W20	W24	W28	W30
ACQ-6[cc]		X	X		X	X	X	X	X	X				
ACT			X			X	X	X	X	X				
AQLQ(S)[cc]			X					X	X	X				
[redacted]			X					X		X				
Dispense handheld device and diary		X												
Conduct training for handheld device and diary use[dd]		X	X											
Review compliance with diary and handheld device[ee]			X		X	X	X	X						
Collect handheld device and diary									X	X				
IMP dosing[ff]			X											
Injection site evaluation[gg]			X											
Dispense rescue medication[hh]		X	X	X	X	X	X	X						
Collect rescue medication[hh]			X	X	X	X	X	X	X	X				
CAE inquiry[ii]		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X
Perform COVID-19 symptoms inquiry[jj]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] The study is completed when the last patient completes the follow-up visit.

[b] The screening visit will take place not more than approximately 4 weeks before the baseline/DoR visit (V3) and is limited to approximately 14 days duration. It is understood that not all procedures can be completed on the same day. In particular, the patient may need to return for repeat CBC testing as needed or to satisfy the medication wash out for pulmonary function testing or to undergo repeat pulmonary function testing.

[c] V2 is the beginning of the run-in period. The run-in period should be approximately 14±2 days in duration with allowances made for scheduling. Patients will be trained on proper use of the handheld device and electronic diary with emphasis on proper use and compliance with procedures.

[d] V3 should be held after the patient has completed 12 days at minimum in the run-in period. Assessment of randomization criteria should be completed prior to taking blood samples or administering IMP to ensure that the patient qualifies to enter the treatment period. Daily lung function and diary compliance will be calculated electronically and should be assessed for compliance. At this visit the patient's diary data should be reviewed prior to formal lung function testing, laboratory testing and the various questionnaires to ensure compliance with diary entries and to determine if lung function, symptoms and rescue medication use meet the randomization criteria or if the patient should be considered to have failed randomization. Once all of the randomization criteria are met, the blood samples will be collected prior to randomization in the IRT system and IMP dosing.

[e] V9 is the last visit during the double-blind treatment period. Patients who complete this visit should be advised regarding ongoing asthma maintenance treatment. Study provided rescue medication should be collected (albuterol/salbutamol). Patients who require a change in medication due to a CAE or to maintain asthma control (see alert criteria for worsening asthma) should complete V8 procedures prior to the change in medication whenever possible and these patients should continue participation for collection of lung function testing, questionnaires, blood samples and safety monitoring until the end of the study. If a change occurs after V8, the V9 procedures should be completed and the patient should enter the follow-up period.

[f] Patients who withdraw consent or cannot participate in the remaining study assessments.

[g] Results from the telephone follow-up calls should be recorded on the CRF and noted within the patients' source documents.

[h] Informed consent should be obtained prior to any other study procedures.

[i] Randomization via the IRT system should not be done until all lung function, questionnaires and clinical assessments have been completed to ensure that patients meet the study requirements and are appropriate for dosing.

[j] The patient's history of asthma should be evaluated including duration, current medication, and history of exacerbations in the last year.

[k] The patients asthma maintenance medication should be evaluated based on ICS dose. Medium or high dose ICS (without LABA) and low dose ICS/LABA together and medium or high dose ICS/LABA combination will be grouped together and entered into the IRT system at V2.

[l] Any prior or concomitant therapy, medication, or procedure a patient has had up to 30 days before screening will be recorded in the source documentation and in the CRF.

[m] The full physical examination will include HEENT, chest, cardiovascular, abdominal, skin, extremity and neurological examinations.

[n] The brief physical examination will include, at minimum, chest, cardiovascular, abdominal, and skin examinations.

[o] Pulmonary function testing (spirometry) and reversibility testing will be conducted in the morning between 0530 and 1100 hours using the study-provided spirometry equipment. Patients are required to withhold asthma maintenance medications for approximately 24 hours prior to lung function testing for once daily medications, 12 hours for twice daily or more frequently dosed medication. If the patient has taken asthma maintenance medication within 24±2 (daily dosed) or 12±2 hours (dosed twice daily or more frequently) or SABA rescue medication within 6 hours of the planned pulmonary function testing or ICS/LABA used as rescue medication within 12 hours of the planned pulmonary function testing, the visit must be rescheduled. Patients who meet the pre-albuterol/salbutamol lung function requirements and demonstrate reversibility ≥12% and a 200 mL increase from pre-albuterol/salbutamol FEV_1 approximately 30 minutes after 4 inhalations of albuterol/salbutamol HFA MDI (90 µg ex-actuator) or equivalent may enter the run-in period if they meet other eligibility requirements as specified. Patients may repeat pulmonary function testing (spirometry) and reversibility testing once during the screening period as needed to qualify.

[p] Pulmonary function testing (spirometry) will occur in the morning between the hours of 0530 to 1100 at V3. For subsequent visits, testing should be within approximately 1 hour of the time the testing occurred at baseline/DoR (V3), ie 0530-1100±1 hour. The patient should withhold asthma maintenance medication for 24±2 (daily dosed) or 12±2 hours (dosed twice daily or more frequently) or SABA rescue medication within 6 hours of the planned pulmonary function testing.

[q] CBC with differential including an eosinophil count during screening to establish safety and minimum eosinophil count. To be included in the study, the eosinophil count must be ≥300 cells/μL. Testing may be repeated once during screening. No rounding of the result is permitted.

[r] Blinded CBC with differential count will be drawn at visits after V3 onward to maintain study blinding. The eosinophil and monocyte counts will not be reported to the study personnel.

[s] Serum chemistry assessments should be drawn with the patient fasting for at least 8 hours prior to testing at V3 and V9.

[t] A blood sample for biomarker banking should be drawn from all subjects at screening who have provided informed consent for the storage and potential future testing of samples in this or other asthma programs, or other diseases that may be explored by the sponsor.

[u] Testing for Hepatitis B surface antigen, Hepatitis C and HIV are required to participate in the study. Patients must provide consent and reporting will follow local regulations.

[v] Blood for pharmacogenetic testing will be obtained specifically to test 2 gene variants HSD3B1-(1245A) and HSD3B1-(1245C) which may predict corticosteroid sensitivity in asthma. Informed consent must be obtained for this testing.

[w] Date and time of sample collection will be recorded. Instructions for the proper collection, handling, labeling, and shipping of the samples are available in the study reference manual.

[x] FSH only for women to confirm post-menopausal state.

[y] Standard 12-lead ECG will be performed with the patient in the supine position using standardized equipment and will be reviewed locally and centrally.

[z] ECG will be performed in triplicate on DoR. Each ECG will be taken within 1 to 5 minutes of the previous one.

[aa] Vital signs should be taken with the patient seated, semi-recumbent or supine after approximately 5 minutes rest. Vital signs should include blood pressure (systolic/diastolic), pulse rate, respiratory rate, and body temperature. The same position and arm should be used for blood pressure readings as much as possible. If the opposite arm is used it will not be collected as a protocol deviation.

[bb] [redacted]

[cc] [redacted]

[dd] Patients should be trained on the proper use of the handheld device to measure lung function including performing readings prior to taking daily asthma maintenance medication and prior to taking rescue medication within 6 hours of testing (as possible). The patient should be retrained at each visit as indicated.

[ee] Review compliance with handheld device measurements and with diary entries, including the proper use in relation to asthma maintenance medication and rescue medication use/timing.

[ff] Patients who meet the requirements for randomization, after the procedures for specimen collection and other testing, will each receive 4 sc injections in the abdomen, administered by a qualified health care provider (according to local regulations) who is prepared to manage anaphylaxis, as described in the study reference manual. The kit number and location will be recorded in the source documents and entered in the CRF for each of the 4 injection site locations along with any injection site reactions evaluated at approximately 1 hour after dosing. If the patient develops clinical symptoms, vital signs should be recorded and the patient should be assessed for anaphylaxis/hypersensitivity reactions. Before leaving the clinic, patients will additionally be advised of symptoms/signs for which they should seek medical advice or medical treatment.

[gg] Evaluation of injection site for reaction will be performed at approximately 1 hour after dosing using the injection site CRF. Injection site findings will not be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess, etc.) or fulfill seriousness criteria; if fulfilled, they must be recorded and reported.

[hh]Rescue medication: Albuterol sulfate inhalation powder 117 µg (albuterol eMDPI) or equivalent albuterol/salbutamol will be distributed to patients at the start of the run-in period and throughout the study as needed. Patients may be given a second inhaler for work or school if required. Rescue medication will not be provided after week 16 (V9). Rescue medication should be collected when a patient completes week 16 (V9) and intermittently throughout the study whenever a patient requires a refill. The inhaler dose counter should be inspected, and the dose counter should be recorded, at each visit. Patients who require a new inhaler to maintain supply should return the current inhaler device, the dose counter should be recorded, and the inhaler stored for return as outlined in the study reference manual. Accountability for non-IMP rescue medication is required.

[ii] In the event of a CAE during the treatment period, Pulmonary function testing should be obtained if the investigator deems it is safe to do so. Blood samples to test TEV-53275 serum concentration, ADA and free and total serum IL-5 levels should be collected if possible and study procedures as outlined in V8 should be completed. CAEs that occur during the follow-up period should be noted and recorded but no further testing is indicated other than those at V10.

[jj] 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. Additionally, testing of patients who are asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center SOPs. The testing may be conducted by the central laboratory or locally depending on feasibility. PCR testing should be conducted to confirm any positive test for antigen (rapid testing).

β-HCG=beta human chorionic gonadotropin; ACQ-6=Asthma Control Questionnaire; ACT=Asthma Control Test; ADA=anti-drug antibody; AQLQ(S)=Standardized Asthma Quality of Life Questionnaire; CAE=clinical asthma exacerbation; CBC=complete blood count; COVID-19=coronavirus 2019; CRF=Case Report Form; CRSwNP=chronic rhinosinusitis with nasal polyps; DoR= day of randomization; ECG=electrocardiogram; eMDPI=electronic multidose dry powder inhaler; EoTV=end of treatment visit; EWV=early withdrawal visit; FEV_1=forced expiratory volume in 1 second; FSH=follicle stimulating hormone; HEENT=head, eyes, ears, nose, and throat; HFA=hydrofluoroalkane; HIV=human immunodeficiency virus; ICS=inhaled corticosteroid; IgE=immunoglobulin E; IL-5= interleukin 5; IMP=investigational medicinal product; IRT=interactive response technology; LABA=long-acting β adrenergic agonist; MDI=metered-dose inhaler; SABA=short-acting β-adrenergic agonist; sc=subcutaneous; [redacted]; [redacted]; SOP=standard operating procedure; V=visit; W=week; WOCBP=women of child-bearing potential.

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.

4.1. Patient Inclusion Criteria

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

a. The patient is capable of giving signed informed consent.

b. The patient is an adult female or male ≥18 years of age. Note: Age requirements are as specified or allowed by local regulations.

c. [Revision 1] The patient has a diagnosis of asthma for at least 6 months as defined by the National Institutes of Health (NIH) and has been stable without exacerbation or change in medications for at least 1 month.

d. The patient has an absolute blood eosinophil count ≥300 cells/µL demonstrated during the screening period. **Note: Rounding of the value (count) is not permitted.**

e. Severity of Disease: The patient has persistent asthma, with a trough FEV_1 ≥40% and ≤85% of the value predicted as per the National Health and Nutrition Examination Survey (Hankinson et al 1999, NHANES III 1998) and adjusted for ethnicity (Hankinson et al 2010). **Note: Patients who do not qualify for the study due to failure to meet baseline spirometry or fail to achieve spirometry consistent with the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria (Miller et al 2005) will be permitted to perform repeat spirometry during the screening period on 1 occasion and if criteria are not met, will be considered to have failed screening.**

f. Reversibility of Disease: The patient has demonstrated reversibility of ≥12% (increase) of FEV_1 and a minimum 200 mL increase from pre-albuterol/salbutamol FEV_1 approximately 30 minutes after 4 inhalations of albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) (90 µg ex-actuator) or equivalent during the screening period.

g. [Revision 1] Current Asthma Therapy: The patient has been maintained for at least 1 month on stable doses of:

   – medium or high dose ICS±another controller.

   – any fixed dose combination ICS (low, medium, or high) with LABA±another controller.

h. 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-human chorionic gonadotropin (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) prior to IMP administration and 30 weeks after the dose of IMP. Highly effective contraception includes:

- 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 14 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, except for hysteroscopic bi-tubal ligation for which a hysterosalpingogram (HSP) is required 3 months post procedure to assess surgical success
- 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.

i. 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 the follow-up procedures and assessments as specified, and be willing to return to the investigational center for further visits, as applicable.

j. The patient, as judged by the investigator, is able to continue their current asthma maintenance medications throughout the study.

4.2. Patient Exclusion Criteria

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

a. Life threatening asthma, defined as a history of asthma episode(s) requiring intubation and/or associated hypercapnea, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).

b. The patient has 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 screening period. Note: Patients who develop an upper respiratory infection/lower respiratory infection (URI/LRI) during the run-in period may rescreen 2 weeks after symptoms resolve and undergo coronavirus disease 2019 (COVID-19) testing as outlined in exclusion criteria “d”.

c. Patients with a confirmed infection with COVID-19 within 3 months prior to the screening visit.

d. 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 4 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. For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

e. The patient has an eosinophilic condition including hypereosinophilic syndrome, eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis (EGPA [Churg Strauss syndrome]), or allergic bronchopulmonary aspergillosis.

f. The patient has an active helminthic or parasitic infection currently or within the last 6 months.

g. The patient has a history of malignancy other than fully resected basal cell carcinoma of the skin.

h. The patient has any clinically significant, uncontrolled medical or psychiatric condition (treated or untreated) that would interfere with the study schedule or procedures, interpretation of efficacy results, or compromise the patient's safety. (Note: chronic obstructive pulmonary disease [emphysema], bronchiectasis requiring treatment, cystic fibrosis, chronic bronchitis, and other diseases of the lung that may complicate interpretation of the study results are prohibited).

i. The patient has known history of, or a positive test result for, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies (Ab), or human immunodeficiency virus (HIV) Types 1 or 2 Ab (according to 4th generation serology testing).

j. The patient is a pregnant or lactating woman, or plans to become pregnant during the study.

k. The patient has taken prohibited prior medications within the washout period. Prohibited medications are listed in Appendix G with the appropriate washout periods.

l. The patient has previously participated in a study with TEV-53275.

m. The patient has participated in another study of an IMP (or a medical device) within the previous 30 days or 5 half-lives of the IMP (whichever is longer) or is currently participating in another study of an IMP (or a medical device).

n. [Revision 1] The patient has been treated with a monoclonal antibody used to treat asthma or other inflammatory conditions within the washout period (5 half-lives), has demonstrated hypersensitivity or anaphylaxis to a monoclonal antibody (Appendix G) , or is currently using or has used a systemic immunosuppressive medication within the last 6 months. NOTE: Prior depemokimab exposure is prohibited without exception.

o. The patient has a known hypersensitivity to any components of the IMP stated or study supplied rescue medication.

p. The patient has a history of chronic alcohol or drug abuse within the previous 2 years.

q. [Revision 1] The patient currently smokes or has a smoking history of 10 pack years or more (a pack year is defined as smoking 1 pack of cigarettes [20 cigarettes]/day for 1 year), OR the patient used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco), OR the patient has smoked marijuana within 1 month, OR the patient has a history of "vaping" tobacco, marijuana, or any other substance within 24 months.

r. Vulnerable patients (eg, people kept in detention).

4.3. Randomization Criteria

The following criteria must be fulfilled at the randomization visit (day 0):

a. The patient continues to be in general good health, meeting the entry criteria.

b. The patient's average of 5 most recent **highest** daily trough values (from 3 attempts) for morning FEV_1 obtained at home (by handheld spirometry) over 7 days prior to V3 is within 40% to 80% predicted for age, height, sex, and race (Hankinson et al 1999, Hankinson et al 2010, NHANES III 1998). If rescue medication was taken within 4 hours of the FEV_1 assessment, or asthma maintenance medication was taken before the measurement, the data from that day should be excluded and data from a previous day during the 7-day period should be included.

c. The patient has an FEV_1 as assessed by clinic-based pulmonary function testing that is within 40% to 85% or the value predicted for age, height, sex, and race (Hankinson et al 1999, Hankinson et al 2010, NHANES III 1998).

d. The patient has demonstrated FEV_1 reversibility as required during the screening period.

e. The patient's ACQ-6 score assessed on V3 day 0 is $\geq$1.5.

f. The patient has remained on background asthma maintenance medication without changes during the run-in period other than study rescue medication (albuterol eMDPI [ProAir Digihaler for use as needed or equivalent albuterol/salbutamol depending on availability]) and albuterol/salbutamol used for reversibility testing.

g. The patient has had no exacerbation of asthma during the run-in period, defined as any worsening of asthma requiring significant treatment other than rescue medication (albuterol eMDPI [ProAir Digihaler for use as needed or equivalent albuterol/salbutamol depending on availability]). Significant treatment includes any of the following: use of systemic corticosteroids or the addition of ICS-containing asthma medications, LABA, long-acting muscarinic antagonist (LAMA), biologic or other non-corticosteroid asthma medications, emergency room/urgent care visit, or hospitalization for asthma. **Note: A single dose of nebulized albuterol/salbutamol will not meet the criteria for an asthma exacerbation. Emergency room/urgent**

care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.

h. The patient has complied with home spirometry and diary entry on at least 5 of the last 7 days prior to the visit including:
   - completion of daytime and night-time asthma symptom scores
   - completion of daytime and night-time rescue medication use, whether used or not
   - completion of the morning FEV_1 and PEF by handheld device
   - confirmed daily use of asthma maintenance medication as prescribed

i. The patient has not had an upper respiratory infection (URI) or lower respiratory infection (LRI) during the run-in period. Patients who develop a URI or LRI during the run-in period may be discontinued from the study and allowed to rescreen 2 weeks after resolution of symptoms. They must have a negative test for COVID-19 active infection.

j. The patient has used rescue medication or had a daytime or night-time asthma symptom score ≥1 on 3 or more days in the 7 days prior to the randomization visit as reported in the patient diary.

4.4. Withdrawal Criteria and Procedures for the Patient

Each patient is free to withdraw from the study at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur:

1. Patient withdraws consent or requests withdrawal from the study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined in this protocol. The decision to withdraw a patient should be discussed with the sponsor, for example, medications to treat an asthma exacerbation may not require that the patient be withdrawn from continued participation.
5. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
6. The sponsor requests withdrawal of the patient.
7. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient.

Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate.

Investigators should attempt to obtain information on patients in the case of withdrawal from the study. Results of any evaluations and observations, together with a narrative describing the

reason(s) for withdrawal from the study, must be recorded in the source documents. The CRF must document the primary reason for withdrawal from the study.

If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active COVID-19 (positive antigen tests must be confirmed by reverse transcription polymerase chain reaction [RT-PCR] testing), he/she may continue for scheduled visits when recovered (ie, after 10 days from the onset of symptoms, remains afebrile for 24 hours without using anti-pyretics and other symptoms are improving) (see Appendix G and Appendix N).

If the reason for withdrawal from the study is an adverse event and/or clinically significant abnormal laboratory test result, monitoring will be continued as applicable (eg, until the event has resolved, stabilized, or returned to baseline; or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

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

If a patient is withdrawn from the study for multiple reasons that also include adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be "need to take a prohibited medication", not the adverse event.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records and transcribed to the CRF. See Appendix E for information regarding how the study will define and address lost to follow-up patients to help limit the amount and impact of missing data.

4.5. Replacement of Patients

A patient who is randomized but does not complete the treatment period will not be replaced. For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

4.6. Rescreening

The screening visit will take place not more than approximately 4 weeks before the baseline/DoR visit (V3) and is limited to approximately 14 days duration. It is understood that not all procedures can be completed on the same day. In particular, the patient may need to return for repeat CBC testing as needed or to satisfy the medication wash out for pulmonary function testing or to undergo repeat pulmonary function testing.

A patient who screen-fails may be permitted to rescreen once after 30 days duration if there is a reasonable expectation that this patient will become eligible for the study, including requirements for eosinophil counts and/or spirometry. The sponsor may grant permission to

rescreen more than once under extenuating circumstances and only with the approval of the sponsor's medical expert or delegate. Note: Patients who develop a URI/LRI during the run-in period may rescreen 2 weeks after symptoms resolve and after appropriate COVID-19 testing has been completed as specified. Additionally, patients who fail randomization for reasons other than spirometry requirements may be rescreened once.

4.7. Screening Failure

Screen failure occurs when a patient who consents to participate in the clinical study is not subsequently entered into the run-in period because that patient did not meet inclusion criteria, met exclusion criteria, or withdrew consent. Patients who enter the run-in period but who do not meet the criteria for randomization or withdraw consent will be considered randomization failures.

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

5. TREATMENTS

Investigational medicinal products in this study include TEV-53275 (test IMP) and matching placebo (placebo IMP). Patients will receive 4 injections (3 ml each) of test IMP and/or placebo IMP, administered by a qualified health care provider (according to local regulations) who is prepared to manage anaphylaxis, to achieve the following doses administered on a single occasion:

- TEV-53275 600 mg sc
- TEV-53275 1200 mg sc
- Placebo sc

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

Other study provided medications (short-acting bronchodilators) are considered non-IMP in this study (see Section 5.4 for details).

5.1. Investigational Medicinal Products Used in the Study

Investigational medicinal product is defined as the test IMP and matching placebo IMP.

5.1.1. Test Investigational Medicinal Product

TEV-53275 is provided as a liquid solution with a nominal concentration of 100 mg/mL. Refer to Table 3 for specific details regarding TEV-53275. Additional details may be found in the pharmacy manual and in the IB for TEV-53275.

5.1.2. Placebo Investigational Medicinal Product

Placebo IMP is provided as a liquid solution in the same formulation as TEV-53275, except for absence of active protein. Refer to Table 3 for specific details regarding placebo IMP.

Table 3: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	TEV-53275	TEV-53275 Placebo
Formulation	[redacted]	[redacted]
Unit dose strength(s)/Dosage level(s)	300 mg/vial	Vehicle buffer absent of protein
Route of administration	sc injection	sc injection
Dosing instructions/Dosing schedule/Titration periods/Treatment periods	As instructed in the clinical protocol and pharmacy manual	As instructed in the clinical protocol and pharmacy manual
Packaging	Type 1 glass vial with butyl rubber stopper and crimp seal with a plastic flip-off cap	Type 1 glass vial with butyl rubber stopper and crimp seal with a plastic flip-off cap
Manufacturer	Teva Branded Pharmaceutical Products R&D, Inc., West Chester, Pennsylvania, USA	Teva Branded Pharmaceutical Products R&D, Inc., West Chester, Pennsylvania, USA
Storage conditions	2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze	2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze

IMP=investigational medicinal product; INN=international nonproprietary name; sc=subcutaneous; USA=United States of America.

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

5.2.1. 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.

The IMPs (TEV-53275 and placebo IMP) must be stored at a controlled temperature (2°C to 8°C) in a secure area. The site should have a process for monitoring the storage temperature of unused IMP.

5.2.2. 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.

5.2.3. 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 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, institution, or the head of the medical institution (where applicable) 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. Empty, partially used, and unused IMP will be disposed of or returned to Teva or its designee.

Further guidance and information (including non-IMP rescue medication) are provided in the pharmacy manual.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The doses administered in this study (600, 1200 mg TEV-53275) were selected on the basis of pharmacokinetic and safety data from the healthy volunteer Phase 1 study, TV53275-PK-10152 (Section 1.2.2.1), in which single sc doses of TEV-53275 up to 1800 mg administered in Part A, and dose levels of 450 or 900 mg administered sc every 28 days 3 times in Part B, were shown to be well tolerated; the available anti-IL-5 mAb data; and the modeling and simulation of TEV-53275 pharmacokinetic and pharmacodynamic data obtained in Study TV53275-PK-10152.

To support the proposed dose selection, a pharmacokinetic/pharmacodynamic analysis was conducted to characterize the TEV-53275 exposure/blood eosinophil suppression data collected from Study TV53275-PK-10152.

Firstly, a potential therapeutic dose was estimated from the pharmacokinetic/pharmacodynamic data collected in Study TV53275-PK-10152. After treatment with TEV-53275, the blood eosinophils from all treated cohorts were reduced by approximately 75% from baseline. The lowest levels were reached within 1 week with a dose-dependent duration of eosinophil suppression, from which the blood eosinophil counts rebounded earlier in individuals from lower dose cohorts than higher dose cohorts. The data were characterized by an indirect-response model (ePD Report #0220-2). The IC_{50} was estimated (1.11 µg/mL) with acceptable precision

(15.3% standard error of the mean [SEM]), and with a serum concentration resulting in 90% reduction of maximum inhibitory effect (IC_{90}) of TEV-53275 of 10 µg/mL. The efficacious dose projection strategy aimed to maintain TEV-53275 concentrations in 90% of the patient population above the IC_{90} for the study duration, and was estimated to be a 600-mg dose every 12 weeks (Q12W).

In a second step, insights from reslizumab were used to guide the selection of the proposed high dose, 1200 mg Q12W. An exposure-response relationship has been demonstrated for reslizumab-treated patients (Bjermer et al 2016). For example, reslizumab 3.0 mg/kg iv improved lung function and various measures of asthma control and quality of life to a greater degree than reslizumab 0.3 mg/kg, even though both doses demonstrated a significant reduction in eosinophil counts compared to placebo. In addition, treatment of moderate to severe asthma with reslizumab 3.0 mg/kg iv demonstrated reduction in asthma exacerbations, improvement in lung function, and a reduction in eosinophils (Castro et al 2015); however, when evaluated by the sc route, reslizumab 110 mg sc dosing failed to demonstrate a significant reduction in exacerbations even though eosinophil reductions and improvements in lung function, asthma control, and quality of life measures (Bernstein et al 2020) were demonstrated. Overall, data show that while suppression of eosinophils can be achieved with minimal dose levels of reslizumab, clinically meaningful improvement in lung function, asthma control, quality of life, and reduction of exacerbations in patients with severe eosinophilic asthma required significantly higher and increasing exposures to reslizumab.

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

Advantages of placebo-controlled trials are summarized in the ICH E10 Choice of Control Group and Related Issues in Clinical Trials Guideline and include minimizing investigator and patient bias. Studies may use a placebo-controlled design when the risk of serious harm including death or irreversible morbidity (ICH E10) is low and the patient's full informed consent is obtained.

A placebo control design is scientifically appropriate as placebo will be compared to TEV-53275 as add-on therapy in patients with moderate to severe eosinophilic asthma. The study includes close daily remote monitoring of each patient's safety electronically with predefined alert criteria to capture patients with worsening asthma by monitoring daily lung function measurements, rescue medication use, and asthma symptoms. 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.

5.4. Other Medicinal Products/Non-Investigational Medicinal Products

Note that other medicinal products, ie, rescue medication (albuterol eMDPI [ProAir Digihaler or equivalent albuterol/salbutamol depending on availability]), are mandated for use in this study; however, for the purposes of this study it is considered a non-IMP. In addition, patients will maintain their usual asthma maintenance medication.

5.5. Treatment After the End of the Study

At week 16 (EoTV; V9), 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. No additional extension or compassionate use of TEV-53275 is planned after completion of this study.

5.6. Restrictions

Patients will be required to comply with restrictions detailed below.

5.6.1. Activity

Patients must remain seated, semi-recumbent, or supine as needed for assessments or other procedures, including dosing.

Patients are not to engage in strenuous exercise within 5 days prior to the dose of IMP and should avoid strenuous exercise for 48 hours prior to any clinic visit.

5.6.2. Tobacco

Use of tobacco products will not be allowed from screening until after the final follow-up visit. Patients are not eligible to participate if they have used tobacco products within the year prior to screening.

5.6.3. Blood Donation

Patients may not donate blood during the study.

5.7. Prior and Concomitant Medication or Therapy

Any prior or concomitant therapy, medication (including prior asthma medication), or procedure a patient has had from 30 days before screening through the end of the study will be recorded in the source documentation and in the CRF. Trade name and INN (if available), indication, dose, and start and end dates of the administered medication or treatment will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug).

Prohibited and restricted medications are listed in Appendix G.

At each visit at the investigational center after the screening visit, the investigator will ask patients whether they have had any change in maintenance medication (including asthma maintenance medication), taken any other medications, including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit.

Concomitant medication and treatment will be recorded until the follow-up visit.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

5.8. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance with this protocol from the start of the screening/run-in period through the follow-up 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. The Independent Ethics Committee/Institutional Review Board (IEC/IRB) should be notified if

required by local regulation. Compliance with the patient diary will be deemed adequate if 80% of the data is captured through V9.

5.9. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled, parallel-group study.

Patients and investigators will remain blinded to IMP assignment during the study. Patients who meet all inclusion criteria, none of the exclusion criteria and all of the randomization criteria will be randomly assigned to 1 of 2 treatment groups or placebo in a 1:1:1 ratio and will be stratified by prior asthma maintenance therapy (ICS and low dose ICS/LABA will be stratified separately from the medium and high dose ICS/LABA [2 separate strata]) and absolute eosinophil count (300 to <400, ≥400 cells/μL). Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients (may be adjusted based on the interim analysis) on medium or high dose ICS/LABA will be included and screening may be adjusted as needed to meet these criteria. This system is used to ensure a balance across treatment groups; no effort will be made to maintain a balance among treatment groups within an investigational center.

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 sponsor's clinical personnel (and delegates) involved in the study will be blinded to the identity of the IMPs until the database is locked for analysis and the IMP assignment is known. However, if a prioritized sample analysis is needed, bioanalytical and/or clinical pharmacology personnel may be unblinded.

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.

5.10. Maintenance of Randomization and Blinding

5.10.1. 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 last patient completes V9), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignments according to the processes defined in the relevant SOP. An interim analysis is planned for this study. The details for maintaining the study blind will be outlined in the charter for the interim analysis.

5.10.2. 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 sample 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).

In case of an emergency, serious adverse event, or pregnancy (see Section 7.1.5 and Section 7.2), 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 system, 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 for safety reasons, 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 blinded 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.

5.11. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 157.5 mL.

Details on blood volumes to be collected during the study are provided in the informed consent form (ICF) and study reference manual.

6. ASSESSMENT OF EFFICACY

Data from any efficacy assessments performed after the specified time will not be collected on the CRF; in the event, however, that such data are collected, these data will not be analyzed. For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

6.1. Assessments of Efficacy

Refer to Table 2 for the timing of assessments and procedures. See Appendix B for a detailed description of assessments and procedures.

6.1.1. Pulmonary Function Testing

Pulmonary function testing (spirometry and reversibility testing) will be conducted in the morning between 0530 and 1100 during the screening period and V3, and 0530-1100±1 hour (subsequent visits) on study-provided spirometry equipment. Testing will be performed in the clinic unless specified as by handheld device, which will be provided to patients upon entering the run-in period for the assessment of lung function.

Lung function will be measured using standard spirometry consistent with ATS/ERS 2005 procedural guidelines (Miller et al 2005). The FEV_1 is the volume of air that can be forcibly exhaled from the lungs in the first second, measured in liters. The forced vital capacity (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 at 25% to 75% of FVC. The National Health and Nutrition Survey III reference equations (NHANES III 1998) will be used with adjustments for ethnicity (Hankinson et al 1999, Hankinson et al 2010).

At the screening visit, FEV_1 will be measured immediately before and 30 (±15) minutes after administration of 4 inhalations of albuterol/salbutamol HFA MDI (90 µg ex-actuator) or equivalent. The spirometry equipment will provide the reversibility as a percent value. This value should not be rounded. FEV_1 reversibility ≥12% and a 200-mL increase from baseline FEV_1 is required.

The FEV_1 stability limit (clinic-based spirometry) will be calculated from each patient at the randomization visit (V3) using the following equation:

- best pre-albuterol/salbutamol $FEV_1 \times 80\%$

This value will be used for the remainder of the study and will be used to determine alert criteria for worsening asthma. The FEV_1 stability limit is automatically calculated and stored in the spirometry software. If a patient falls below the FEV_1 stability limit, an alert will be generated.

The FEV_1 stability limit for the handheld device will be 80% of the value obtained at the screening visit (using the clinic-based equipment value) and for the run-in period and 80% of the baseline value as determined by the handheld device for the treatment period.

FEV_1 and PEF in between visits will be measured using the handheld device (as above) each morning before the patient takes their asthma maintenance medication. Patients should avoid taking morning rescue medication within 6 hours of the measurement whenever possible. PEF is

the maximum speed of exhalation. PEF will be measured by the patient and will be recorded automatically in the database.

6.1.2. Clinical Asthma Exacerbation

For this study, a CAE is defined as worsening asthma requiring treatment with a systemic corticosteroid for ≥3 days, emergency room visit resulting in systemic corticosteroid treatment, or 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 electronic diary/handheld spirometer) and require the addition of maintenance medications (other than systemic corticosteroids) to control the patients asthma symptoms based on the investigator's judgment.

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

The asthma exacerbation start and stop dates will be collected in order to determine the exacerbation duration. The start date of an asthma exacerbation will be the start date of the initial medical intervention (ie, use of systemic corticosteroids [oral or injection] asthma-specific hospital admission, or asthma-specific emergency department visit resulting in systemic corticosteroid treatment, whichever comes first). The stop date is the last day of systemic corticosteroids or the last day of an asthma-specific hospitalization whichever is later.

In the event of a CAE, 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-53275 serum concentration, ADA, and free and total serum IL-5 levels should be collected if possible.

6.1.3. Asthma Control Days

An asthma control day is defined as a day on which the patient uses zero puffs of inhaled SABA, has no night-time awakenings, and experiences no asthma exacerbations.

6.1.4. Asthma Control Test

The Asthma Control Test (ACT) is a patient self-administered tool for identifying those with poorly controlled asthma comprising 5 items, with 4-week recall (on symptoms and daily functioning) (Nathan et al 2004, Schatz et al 2006). It assesses the frequency of shortness of breath and general asthma symptoms, the use of rescue medications, the effect of asthma on daily functioning, and the overall self-assessment of asthma control measured on a 5-point scale (for symptoms and activities: 1=all the time to 5= not at all; for asthma control rating: 1=not controlled at all to 5=completely controlled). Total scores range from 5 (poor control of asthma) to 25 (complete control of asthma), with higher scores reflecting greater asthma control. An ACT score >19 indicates well-controlled asthma.

6.1.5. Asthma Symptom Score

The asthma symptom score will be determined from the information recorded in the asthma control diary. A Likert-style scale will be used to quantify symptomatology. This scale has been

used previously to assess changes in asthma symptoms in response to novel asthma treatments (Shapiro et al 2000).

Asthma symptom scores should be determined twice daily, in the morning and evening:

Daytime Symptom Score (determined in the evening)

0=No symptoms during the day

1=Symptoms for 1 short period during the day

2=Symptoms for 2 or more short periods during the day

3=Symptoms for most of the day which did not affect my normal daily activities

4=Symptoms for most of the day which did affect my normal daily activities

5=Symptoms so severe that I could not go to work or perform normal daily activities

Night-time Symptom Score (determined in the morning)

0=No symptoms during the night

1=Symptoms causing me to wake once (or wake early)

2=Symptoms causing me to wake twice or more (including waking early)

3=Symptoms causing me to be awake for most of the night

4=Symptoms so severe that I did not sleep at all

Symptom-free days are defined as 24-hour periods with asthma symptom score of 0.

Asthma control days are defined as 24-hour periods with asthma symptom scores of 0 and no rescue medication use.

6.1.6. Asthma Rescue Medication Use

The number of times asthma rescue medication (number of inhalations/puffs) is used will be assessed (eg, by reviewing the electronic diary or if required due to missing data in the diary, by site tracking of the inhalation counter on the inhaler). Note: SABA therapy used for reversibility testing should not be included in this measure.

6.1.7. Asthma Control Composite Score

The weekly asthma control composite score will be based on the following, modified from O'Byrne et al (2018) to include daily morning FEV_1 instead of PEF:

1. Two or more of the following criteria are fulfilled
   - ≤2 days with a daily asthma symptom score >1
   - ≤2 days of albuterol/salbutamol used as rescue medication up to a maximum of 4 occasions per week (multiple occasions per day are counted as separate occasions)
   - morning FEV_1 ≥80% predicted for each day (by handheld device)

And

2. Both of the following criteria are fulfilled:

- no night-time awakenings due to asthma
- no use of asthma maintenance medications

6.1.8. Standardized Asthma Quality of Life Questionnaire

The Standardized Asthma Quality of Life Questionnaire AQLQ[S]) (patients ≥18 years of age version) will be self-administered by patients. The questionnaire is a tool to measure the impact of asthma on a patient's quality of life (physical, emotional, social, and occupational). The aim of the questionnaire is to evaluate the problems that are most troublesome to patients in their day to day lives. The questionnaire contains 32 items with a 2-week recall period and uses a 7-point Likert scale (7=not impaired at all to 1=severely impaired). Scores range from 1 to 7, with higher scores indicating better quality of life.

6.1.9. Asthma Control Questionnaire

The ACQ-6 is a validated asthma assessment tool that has been widely used (Juniper et al 1999). The 6 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.

6.1.10. [redacted]

[redacted]

6.1.11. [redacted]

[redacted]

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, local tolerability at the injection site, clinical laboratory test results, vital signs measurements, electrocardiogram (ECG) findings, physical examination findings, and use of concomitant medications. Refer to Table 2 for the timing of assessments and procedures. For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

7.1. Adverse Events

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 and which does not necessarily have to have a causal relationship with this treatment.

In this study, any adverse event occurring after the patient has signed the ICF through the end of the study should be recorded and reported as an adverse event.

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-53275. 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:

- inter-current illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of pre-existing conditions
  (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event)
- drug 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, or require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant
  (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events)

Asthma manifestation, worsening and exacerbation are an efficacy variable for this study and should be captured on the asthma exacerbation CRF; accordingly, asthma exacerbations should not be recorded as adverse events unless they meet the criteria for 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 to the end of the study. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered until the end of the study.

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. For serious adverse events, the serious and protocol defined adverse event of special interest form (SAE/PDAESI form) must be completed and the serious adverse event should be reported within 24 hours of when the investigator becomes aware of the serious adverse event (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the study period defined above (defined period).

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

Further details are given in the Safety Monitoring Plan.

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 an adverse event to an IMP suspect, as applicable in the report, will be captured separately. Determination of this relationship will be made according to the criteria in Table 4.

Table 4: The Relationship of an Adverse Event to the IMP 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.	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. • 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. • It does not reappear or worsen when the IMP 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 IMP/non-IMP administration 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. • 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 upon discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as that time period from signature of the ICF to the end of the follow-up period. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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 pre-existing condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is 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 intensive treatment in an emergency room or at home for allergic bronchospasm; 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 >3 × upper limit of normal (ULN)
  - total bilirubin increase of >2 × 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.

Asthma manifestation, worsening and exacerbation are an efficacy variable for this study and should be captured on the asthma exacerbation CRF; accordingly, asthma exacerbations should not be recorded as adverse events unless they meet the criteria for a serious adverse event.

7.1.5.2. Expectedness

In this study, the reference safety information (RSI) for determination of expectedness of suspected serious adverse reactions for the IMP is included in the IB. A serious adverse event that is not included in the relevant RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

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. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP to that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee, ie, a Clinical Research Organization (CRO) in a country without a sponsor LSO (the email address will be provided on the SAE report form).

The following information should be provided to record the event accurately and completely:

- 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, or reasonable possibility, as described in Table 4)

Additional information includes:

- 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, and regimens)
- treatment of 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 the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP.

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 local regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

The sponsor's GPSP will submit the XML of SUSARs to the EMA in an unblinded manner, when applicable and according to local regulations. Submission of SUSARs to the FDA using MedWatch forms is done by the Regulatory Affairs department upon receipt from the LSO.

Blinding will be maintained for all study 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 safety management plan (SMP).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed 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-53275 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 consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-53275

7.1.6. Protocol-Defined Adverse Events of Special Interest for Reporting to the Global Patient Safety & Pharmacovigilance Department

For the purposes of this protocol, the following are considered PDAESI for expedited reporting to the GPSP department:

- systemic severe reactions (including anaphylaxis) that follow the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) Second Symposium on Anaphylaxis (Sampson et al 2006, [Appendix H]).
- opportunistic infections as listed in the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (Appendix I).
- helminth infections
- malignancies (including non-melanoma skin cancer)

The process for reporting these PDAESI is the same as that for reporting a serious adverse event (see Section 7.1.5.3). These events can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.1.7. Protocol-Defined Adverse Events of Special Interest that do not Require Reporting to the Global Patient Safety & Pharmacovigilance Department

Injection site findings will be assessed using a standardized scale as described in Section 7.8. Injection site findings will not be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess, etc.) or fulfill seriousness criteria; if fulfilled, they must be recorded and reported as specified in Section 7.1.2.

7.1.8. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the CRO medical monitor 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. Pregnancy

Any female patient becoming pregnant during the study will be discontinued from the study.

All pregnancies of women participating in the study that occur during the study, or within 5 half-lives after IMP administration, or is reported to the investigator, are to be reported immediately to the CRO medical monitor, and the investigator must provide the sponsor (LSO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (Section 7.1.5.3.1) but using the pregnancy form.

The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no protocol-related procedures were applied.

All female patients 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.

Since there is no evidence of reproductive risk, human mutagenicity or genotoxicity for this IMP, female partners will not be asked to sign an ICF to monitor the outcome of the pregnancy.

If the pregnancy in the woman 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.

7.3. 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 as a protocol deviation and in the patients' source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria, all instances of incorrect IMP administration should be categorized as "Noncompliance to Investigational Medicinal Product (IMP)."

The following are types of medication errors and special situations:

- 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.
- overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the protocol or authorized product information as applicable. 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.
- misuse: Any intentional therapeutic use of a drug product in an inappropriate way or opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects. Examples: under usage, erratic or disorganized use, inappropriate use (for anxiety), use in conjunction with alcohol or illegal substances, overuse.

- abuse: Any intentional, nontherapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect, or intentional use of an opioid for a nonmedical purpose, such as euphoria or altering one's state of consciousness.
- off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the protocol or authorized product information as applicable.
- occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
- breastfeeding: Suspected adverse events which occur in infants following exposure to a medicinal product from breast milk.

7.4. Clinical Laboratory Tests

All clinical laboratory test results outside 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 an 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 result triggering the work-up is an adverse event. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

Details of clinical laboratory tests will be included in the study reference manual.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

7.4.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 2. Clinical laboratory tests will be performed using the central laboratory. Details are provided in Appendix A. Specific serum chemistry, hematology and coagulation laboratory tests to be performed are listed in Table 5.

Table 5: Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation
Calcium (Ca) Phosphorous Sodium (Na) Potassium (K) Chloride (Cl) Creatinine Creatinine phosphokinase (CPK) Glucose Blood urea nitrogen (BUN) Alanine aminotransferase (ALT/SGPT) Aspartate aminotransferase (AST/SGOT) Gamma-glutamyl transpeptidase (GGT) Alkaline phosphatase (ALP) Bicarbonate Protein, total Albumin Bilirubin, total	Hematocrit (Hct) Hemoglobin (Hb) Red blood cell (RBC) count White blood cell (WBC) count Platelet count Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Mean Platelet Volume (MPV) Red Cell Distribution Width (RDW) CBC, Nucleated RBC (%, abs) WBC Differential - Basophils (%, abs) - Eosinophils (%, abs) - Immature granulocyte (%, abs) - Lymphocytes (%, abs) - Monocytes (%, abs) - Neutrophils, Total (%, abs)

7.4.2. Other Clinical Laboratory Tests

7.4.2.1. Serology Tests

At screening, patients will be tested for HBsAg, antibodies to HCV, and HIV Types 1 and 2. Patients with confirmed positive results will not be eligible to participate in the study.

7.4.2.2. Follicle Stimulating Hormone

At screening, women who have been amenorrheic for at least 1 year without an alternative medical cause will have a serum 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).

7.4.2.3. Human Chorionic Gonadotropin Tests

β-HCG tests in urine will be performed for women of childbearing potential as detailed in Table 2.

7.4.2.4. COVID-19 Testing

Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center SOPs. The testing may be conducted by the central laboratory or locally depending on feasibility. The

testing may be conducted by the central laboratory or locally depending on feasibility. Positive tests that measure COVID-19 antigen must be confirmed by RT-PCR.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

7.5. Physical Examinations

Physical examinations will be performed at the time points detailed in Table 2. Height in centimeters and weight in kilograms will be recorded at screening. Weight only will be measured at other times specified. Body mass index will be determined.

A full physical examination will include, at a minimum, head, eyes, ears, nose, and throat (HEENT), chest, cardiovascular, abdominal, skin examination and abbreviated neurological examination including cranial nerves, deep tendon reflexes and strength. A brief physical examination will include, at a minimum, chest, cardiovascular, abdominal, and skin examinations.

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 the source document, and monitored as described in Section 7.1.2.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

7.6. Vital Signs

Vital signs (pulse rate, blood pressure [systolic/diastolic], respiratory rate, and body temperature) will be measured at the time points detailed in Table 2. All vital signs results outside 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

Before blood pressure and pulse are measured, the patient must rest in a supine, semi-recumbent or seated position for at least 5 minutes. The same position and arm should be used as much as possible each time vital signs are measured for a given patient. If the opposite arm is used it will not be collected as a protocol deviation. For any abnormal vital signs value, the measurement should be repeated as soon as possible. Any vital signs 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.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

7.7. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 2. Where triplicate measurements are required (DoR), each ECG will be taken within 1 to 5 minutes of the previous one.

Standard ECGs parameters will be recorded using a centralized process and the ECG will be interpreted locally by the principal investigator (or qualified physician). Additionally, a qualified

central reader will interpret all ECG. In cases of disagreement, the interpretation by the central reader should be used. All ECG results outside the reference ranges will be judged by the investigator (or qualified physician) 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 (or qualified physician) as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

7.8. Assessment of Local Tolerability and Pain

Local tolerability at the injection site (erythema, ecchymosis, induration, tenderness, warmth, swelling, and pain) will be assessed using standardized scales. Patient reported pain at the injection 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, where 0 is 'No pain' and 10 is 'Worst possible pain'?".

The assessments will be performed at approximately 1 hour after dosing (Table 2).

Severity of local tolerability symptoms should be assessed as described in Table 6. Erythema, ecchymosis, and induration will be considered only if they reach a diameter of at least 5 mm. The surface diameter in millimeters will be recorded and erythema, induration, and ecchymosis at the injection site will be graded according to the diameter measurements: Absent, 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.

In cases where symptoms do not resolve, assessments will proceed at each ambulatory visit. Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication. In case the site(s) of injection need visual representation, in addition to comments in the source documents, the injection site(s) may be photographed along with a metric ruler and patient identification number for later review. Any features that could be used to identify the patient will not be captured on the photograph.

Table 6: Severity Assessment of Local Tolerability

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

Injection site findings will not be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess, etc.) or fulfill seriousness criteria; if fulfilled, they must be recorded and reported as specified in Section 7.1.2.

8. ASSESSMENT OF PHARMACOKINETICS, IMMUNOGENICITY, BIOMARKERS, AND PHARMACOGENETICS

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

8.1. Pharmacokinetic Assessment

Blood samples will be collected via venipuncture at the time points detailed in Table 2 for measurements of serum concentration of TEV-53275. 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-53275 using an appropriate validated method. Blood samples from patients who received placebo may not be analyzed.

Blood volumes are provided in the ICF and study reference manual.

Details on sample handling, storage, shipment, and analysis are given in the study reference manual.

8.2. [redacted]

8.3. Immunogenicity

Blood samples (12 mL) for assessment of ADA response will be taken at the time points indicated in Table 2.

Additionally, efforts should be made to collect ADA samples when a severe hypersensitivity reaction (eg, anaphylaxis) is suspected, or an asthma exacerbation, a serious adverse event, or an immunogenicity-related adverse event is observed, as close to the onset of the event as possible, at the resolution of the event, and at 30 days following the event onset, if possible. Antibodies to TEV-53275 will be evaluated in serum samples of patients treated with TEV-53275. All samples collected for detection of antibodies to TEV-53275 may also be evaluated for TEV-53275 serum concentration to facilitate interpretation of the antibody data. Antibodies may be further characterized including evaluation of TEV-53275-neutralizing antibodies (if possible).

When a number of assessments are to be conducted at the same time point, the immunogenicity blood sample should be taken after other assessments. The date and time 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-53275 will be performed using validated methods by or under the supervision of the sponsor. Blood samples from patients who received placebo may not be analyzed for the presence of ADAs.

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-53275.

Details on sample handling, storage, shipment, and analysis are given in the study reference manual.

8.4. [redacted]

8.4.1. [redacted]

[redacted]

8.5. Pharmacogenetic Assessment

Whole blood (2.5 mL) will be collected at baseline/DoR. More details regarding pharmacogenetic analyses are provided in Appendix J and the study reference manual.

Pharmacogenetic data will be kept confidential and stored separately.

HSD3B1 genetic alleles (associated with steroid resistance/responses) will be studied to determine the relative frequency of allele status in randomized patients and to assess the differential effect of IMP with respect to HSD3B1 allele status.

This testing requires informed consent to be obtained. Patients may decline this testing while still participating in the study.

Pharmacogenetic analyses may be presented in a separate analytical plan and report at the end of the study.

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. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report (CSR).

[redacted]

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

9.1. Sample Size and Power Considerations

The sample size is calibrated based on simulation studies to assess the operating characteristics of the following Bayesian success criterion for the final analysis of the primary efficacy endpoint: adjusted mean change from baseline at week 12 in trough FEV_1:

[redacted]

Data from previous internal clinical studies of another anti-IL5 biologic treatment (CinqAir®[1]) in patients with persistent eosinophilic asthma were used to derive the expected range of treatment effects of TEV-53275 versus placebo and the standard deviation estimate of 0.350 L for the primary efficacy endpoint, when TEV-53275 is given as an add-on maintenance therapy on top of the background ICS or ICS/LABA treatments.

The statistical software FACTS v6.4 was used for conducting the simulations assuming a 15% dropout rate for the placebo group and an 8% dropout rate for each of the TEV-53275 treatment groups.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients.

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

[1] CinqAir® is a registered to Teva Pharmaceutical Industries Ltd.

9.2.2. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP.

The mITT analysis set will serve as the primary analysis set for efficacy analyses.

9.2.3. 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, patients will be assigned to the treatment they actually received regardless of which treatment they were randomized, unless otherwise specified.

9.2.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients without important protocol deviations. Important protocol violations will be determined before unblinding and will include incorrect IMP received by a patient.

The PP analysis will serve as a supportive analysis for the primary efficacy analysis as well as the secondary efficacy analysis.

9.2.5. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include those patients in the safety analysis set who have at least 1 available serum concentration value.

9.2.6. Anti-drug Antibody Analysis Set

The ADA analysis set (for anti-TEV-53275 antibodies) will include those patients treated with TEV-53275 in the safety analysis set.

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 statistical analysis plan.

9.4. Study Population

The ITT analysis set (Section 9.2.1) 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 PP analysis set, and patients who complete the study (see Section 3.1 for definition of end of study) will be summarized. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

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. The presence of restrictive alleles will be summarized by treatment group using patient counts and percentages.

Generally, for continuous variables, descriptive statistics (number [n], mean, standard deviation, 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. Efficacy Analysis

9.5.1. Primary Efficacy Endpoints

The primary endpoint is the change from baseline in clinic-based standardized baseline-adjusted trough (pre-bronchodilator) morning FEV_1 at week 12.

9.5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- overall weekly well-controlled asthma status defined by the asthma control composite score and weekly asthma control status (Yes versus No) from week 1 through 12 and overall weekly well-controlled asthma status from week 1 through 16
- overall changes from baseline in the weekly average of daily morning trough (pre-rescue bronchodilator) FEV_1 as measured by a handheld device over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16
- overall changes from baseline in weekly average of rescue medication use over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16
- changes from baseline in percentage of asthma control days (no symptoms and no rescue medication use) over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16
- change from baseline in clinic-based standardized baseline-adjusted morning trough FEV_1 at week 16
- proportions of patients who achieve clinic-based FEV_1 $\geq$80% predicted at weeks 12, 16, and at endpoint
- proportions of patients who achieve forced expiratory flow at 25% to 75% of FVC (FEF_{25-75}) $\geq$70% predicted at weeks 12, 16, and at endpoint
- time to first CAE throughout the study
- changes from baseline in Asthma Control Questionnaire (ACQ-6) at weeks 12 and 16
- changes from baseline in ACT at weeks 12 and 16
- changes from baseline in Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) at weeks 12 and 16

- proportions of patients who achieve FEV_1:FVC ratio ≥0.80 at weeks 12, 16, and at endpoint

9.5.3. [redacted]

[redacted]

[redacted]

[redacted]

9.5.4. Planned Method of Analysis

The mITT and PP analysis sets will be used for the efficacy analyses. The mITT analysis set will serve as the primary efficacy analysis population, while the PP analysis set will serve as the supportive population for the primary efficacy endpoint as well as the secondary efficacy endpoints.

Descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum for continuous variables, and patient counts and percentage for categorical variables) will be provided for each efficacy variable by visit or week, as appropriate. Summaries will be presented by treatment group.

All statistical tests will be conducted at the two-sided 0.05 significance level.

Unless otherwise specified, baseline value is defined as the last available value before the administration of IMP.

9.5.4.1. Primary Efficacy Analysis

Primary Efficacy Analysis: An estimand, in general, includes 4 inter-related attributes – population of interest, variable (endpoint) of interest, inter-current events (ICE) along with the strategy for handling ICE, and population-level summary for the endpoint.

The estimand selected for the primary efficacy endpoint will assess the change from baseline in morning trough FEV_1 at week 12 due to the initially randomized treatment as actually taken (Mallinckrodt 2013) in the mITT population. This estimand assesses the treatment efficacy at week 12 attributable to the initially randomized medication.

Inter-current events (ICEs) that are expected to affect the efficacy endpoint will include:

1. Instances where a patient experiences worsening of asthma or an asthma exacerbation and the patient is placed on systemic corticosteroids, or additional asthma therapy treatment. In such cases, the investigators will be instructed to encourage the patient to continue in the study and return for planned visits until study completion in order to collect safety data after additional maintenance treatments are used. However, for these patients, improvement in FEV_1 would be expected as rapidly as 1 day after treatment with ICS (Kerwin et al 2019) and within 1 week after a patient receives the ICS/LABA treatment (Corren et al 2007, Pearlman et al 1999). The inclusion of data after a patient receives alternative medications would potentially bias the treatment response estimates due to initially randomized study medications. Therefore, for the primary analysis, the strategy to handle these ICEs will be to exclude observations after the use of asthma maintenance medications (regardless of availability of data obtained afterwards).
2. Confirmed COVID-19 infections: Since COVID-19 is a known respiratory disease which can adversely affect lung functions as a result, the same strategy for handling such ICEs will be applied in the primary analysis. Observations that occurred after the diagnosis of COVID-19 infections will not be used in the primary analysis.

The population-level summaries would be the Bayesian estimates of mean changes from baseline at week 12 for the treatment groups and corresponding 95% credible intervals, as well as posterior probability of treatment effect between each of the TEV-53275 treatment groups vs placebo being greater than 0, ie:

[redacted]

[redacted]

9.5.4.2. Sensitivity/Supportive Analysis

9.5.4.2.1. Supportive Analysis

The frequentist approach will be used for analyzing the primary efficacy endpoint as a supportive analysis. The same estimand with respect to study population, efficacy endpoint and ICEs along with the same handling strategies will be applied. The population-level summary statistics will be the least squares means in the treatment groups derived from the mixed-effects model for repeated measures (MMRM).

The MMRM model will include baseline morning trough FEV_1, the randomization stratification factors (prior therapy use and baseline EOS levels), visit (weeks 2, 4, 8, 12, and 16), treatment group, and visit-by-treatment group interactions. Contrasts for pairwise treatment comparisons of interest will be constructed. The unstructured covariance matrix will first be used; however, in case of convergence issues, the compound symmetry covariance matrix structure will be used instead.

Missing data are expected to occur due to early dropouts from study or "analysis dropouts" resulting from the use of additional or alternative medications and COVID-19 infections, as mentioned above. We plan to use the reference-based multiple imputations method (Mallinckrodt et al 2017) to handle the missing data problem. This approach imputes missing data based on regression models from the placebo-treated patient data, representing a missing not at random (MNAR) mechanism. It is expected to yield a conservative treatment effect estimate as compared to the estimate obtained from multiple imputations (MI) under a missing at random (MAR) mechanism. This approach has recently been successfully applied in a Phase 3 pediatric trial comparing fluticasone propionate multidose dry powder inhaler (MDPI) with fluticasone propionate/salmeterol MDPI (Study FSS-AS-30003). More details on implementing the reference-based MI will be provided in the protocol and statistical analysis plan.

The Rubin's method will be used to combine estimates from multiply-imputed datasets. The final estimated treatment differences will be presented together with the 2-sided 90% CI and p-values.

9.5.4.2.2. Sensitivity Analyses

The primary efficacy analysis and supportive analysis will be repeated using the PP population.

Other sensitivity analyses will be conducted by evaluating the impact of missing data on the supportive MMRM analysis using a 2-dimensional "tipping-point", multiple-imputation approach under the MNAR assumption. Shifts to the distributions of missing observations in

both the placebo and active treatment arms will be applied to represent different degrees of effect losses. More details will be provided in the statistical analysis plan.

Sensitivity analysis using all data, including retrieved observations following alternative medication use will be run to assess the robustness of study results to a different estimand.

9.5.4.3. Secondary Efficacy Analysis

For the overall weekly asthma control status from week 1 through 12, the weekly binary endpoints from week 1 through 12 will be analyzed using the repeated measures logistic regression with treatment group, baseline status, prior therapy use, week, and week-by-treatment group interactions in the model and with an unstructured covariance matrix. In the case of convergence issues with the unstructured covariance form, the exchangeable covariance matrix will be used. The overall probability estimate of weekly asthma control over 12 weeks in each treatment group, as well as the overall estimate of odds ratio of weekly asthma control over 12 weeks, comparing each TEV-53275 treatment group versus placebo with corresponding 95% CI and p-value will be derived.

Using the mITT analysis set, each of the following secondary efficacy endpoints will be summarized descriptively and analyzed using a MMRM including baseline value, randomization stratification factors, visit/week, treatment group, and visit/week -by-treatment group interactions in the model with an unstructured covariance matrix:

- overall changes from baseline in weekly average of daily morning trough (pre-rescue bronchodilator) FEV_1 as measured by handheld device over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16
- overall changes from baseline in weekly average of rescue medication use over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16
- changes from baseline in clinic-based standardized baseline-adjusted morning trough FEV_1 at week 16
- changes from baseline in ACQ-6 at weeks 12 and 16
- changes from baseline in ACT at weeks 12 and 16
- changes from baseline in AQLQ(S) at weeks 12 and 16

For weekly binary endpoints, such as the following:

- proportions of patients who achieve clinic-based FEV_1 $\geq$80% predicted at weeks 12, 16, and at endpoint
- proportions of patients who achieve forced expiratory flow at 25% to 75% of FVC (FEF_{25-75}) $\geq$70% predicted at weeks 12, 16, and at endpoint
- proportions of patients who achieve FEV_1:FVC ratio $\geq$0.80 at weeks 12, 16, and at endpoint

The repeated measures logistic regression model with treatment group, corresponding baseline parameter value, prior therapy use, week, and week-by-treatment group interactions in the model and with an unstructured covariance matrix will be used. In the case of convergence issues with the unstructured covariance form, the exchangeable covariance matrix will be used. The weekly

probability estimates of achieving the improvement criterion in each treatment group, as well as the estimates of weekly odds ratios comparing each TEV-53275 treatment group versus placebo with corresponding 95% CI and p-values will be derived.

All repeated measures model will be run including measurements at all visits/weeks through week 16.

For changes from baseline in weekly average of rescue medication use over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16, and changes from baseline in percentage of asthma control days (no symptoms and no rescue medication use) over 12 weeks from week 1 through 12 and over 16 weeks from week 1 through 16, Wilcoxon rank-sum test will be used stratified on randomization stratification factors.

The frequency of CAEs will be analyzed using a negative binomial regression method including randomization stratification factors and treatment group in the model and the logarithm of follow-up time as an offset variable. The ratio of CAE rate between the treatment groups and its 95% CI will be estimated from the negative binomial regression model. Treatment effects will be tested using the likelihood-based Chi-square test.

The Kaplan-Meier method will be used to estimate and compare the distributions of time to the first CAE between treatment groups. Distribution difference will be compared by a log rank test adjusting for the randomization stratification factors.

9.5.4.4. [redacted]

[redacted]

9.5.4.4.1. [redacted]

[redacted]

9.6. Multiple Comparisons and Multiplicity

No adjustments will be made for the preplanned multiple comparisons/endpoints.

9.7. Safety and Tolerability Analysis

The secondary safety and tolerability endpoints are:

- frequency of adverse events
- changes from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study
- changes from baseline in vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) throughout the study
- changes 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

Safety analyses will be performed on the safety analysis set (Section 9.2.3).

Safety assessments and time points are provided in Table 2.

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), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of all adverse events, serious adverse events and adverse events leading to withdrawal will be presented.

Values and changes from baseline in clinical laboratory, ECG, and vital signs measurement data (including the incidence of abnormalities) will be summarized descriptively.

Local tolerability at the injection site (erythema, ecchymosis, induration, tenderness, warmth, swelling, and pain) will be assessed using standardized scales and summarized descriptively.

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

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, 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.

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.

9.8. Pharmacokinetic Analysis

Summaries of TEV-53275 serum concentrations will be presented by nominal time point and dose. Plots of individual TEV-53275 serum concentrations will be presented by actual day

(linear and log scales). Plots of mean or median TEV-53275 serum concentrations will be presented by nominal day (linear and log scales).

9.9. Pharmacodynamic/Biomarker Analysis

Blood eosinophil count and serum IL-5 (free and total) levels will be summarized by treatment and time point using descriptive statistics. Individual data will be listed.

9.10. [redacted]

[redacted]

9.11. Immunogenicity Analysis

Anti-TEV-53275 antibody information, the number and percent of patients positive for ADA and their antibody titers, and the number of ADA positive patients who are positive for neutralizing antibody, will be described. The impact of the presence of ADA on pharmacokinetics, efficacy, and clinical safety will be evaluated, if appropriate, and results will be provided in the CSR.

9.12. Ancillary Studies Analysis

During the run-in and treatment periods of this study, patients will be supplied with ProAir Digihaler. Data from these inhalers will be collected centrally. [redacted]

9.13. Planned Interim Analysis

The final primary efficacy analyses will be performed when all patients have completed V9 (week 16) or withdrawn from the study. An unblinded interim analysis is planned, when approximately 120 patients (40 patients per arm) have completed the week 8 visit or withdrawn from the study, to assess the early efficacy data. The objectives of the unblinded interim efficacy analysis are: 1) to detect an early efficacy success signal; 2) to conduct a formal futility analysis, so that the study may be terminated early if both TEV-53275 dose groups are futile, ie, meet the futility criterion., and; 3) to evaluate early stopping criteria. The statistical analysis and the success and futility criteria are specified in Section 9.13.1 below.

[redacted]

[redacted]

Further, due to challenges in patient enrollment in the face of the COVID-19 pandemic, the feasibility of an early stopping of the trial with smaller sample sizes may also be evaluated during the interim analysis. The feasibility analysis will be described in the statistical analysis plan.

9.13.1. The Unblinded Interim Efficacy Analysis

For the early efficacy success and futility analysis, the week 8 efficacy endpoint, ie, change from baseline at week 8 in morning trough FEV_1 will be analyzed. The same Bayesian analysis for the final primary efficacy analysis will be applied and both the early success and futility criteria will be based on the derived posterior probability of the TEV-53275 dose group performing better than the placebo group in improving the week 8 endpoint.

Early efficacy success

The early efficacy success will be assessed in the TEV-53275 1200 mg treatment group with the success defined as meeting the following criterion:

Posterior probability (TEV-53275 1200 mg treatment effect vs placebo >0 at interim analysis) >0.95.

The early success threshold value of 0.95 is set higher than the final analysis success threshold of 0.85 to demonstrate an unequivocal evidence of TEV-53275 1200 mg treatment efficacy success compared to placebo at the interim analysis.

[redacted]

Other efficacy endpoints, such as changes from baseline in morning trough FEV_1 at weeks 1, 2, 4, 12 and week 16 will be summarized descriptively by treatment group to provide supportive data.

It is of note that meeting the interim efficacy success criterion will not result in terminating the study early. The early efficacy success result, combined with satisfactory safety data, may assist with preparation / initiation of further safety and efficacy studies, and enable communications with regulatory agencies regarding further clinical development.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Meeting the study futility criterion may result in early termination of the study due to futility.

The execution of the unblinded interim analysis

The unblinded interim analysis will be conducted by independent, unblinded statistician(s) and programmer(s) who are not part of the study team, following the pre-specified algorithms and rules. An independent unblinded data review committee will be set up to review the unblinded interim efficacy analysis results. 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. In order to maintain the study blind and the study conduct integrity, a data review charter will be finalized prior to the interim analysis, which specifies the processes for securely unblinding interim analysis results. The processes will be followed to ensure that the study blind will be maintained in the blinded study personnel who are involved in managing the study activities until the study is unblinded at the final analysis. This charter will also detail the blinded safety review.

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 statistical analysis plan, 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 C for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, audit and inspection.

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

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

Details are given in the study reference 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 IEC/IRB, and with competent authorities.

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC/IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix L 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 FDA3454 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.

14. PUBLICATION POLICY

See Appendix M for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 01 Dated 18 November 2021

The primary reason for this amendment is to modify the entry/eligibility criteria to assist with recruitment rates; to clarify that study sample size may be adjusted based on the results of an interim analysis, using unblinded efficacy data; and to clarify that the interim analysis will include an unblinded futility analysis. Additionally, the amendment contains a clarification of collection of blinded/unblinded blood counts at baseline and updates to the COVID-19 monitoring criteria. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (eg, typos and punctuation) have been made to the protocol (and protocol synopsis, as appropriate). Table 2 has been revised to reflect the described changes.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Title Page		
EudraCT number: ~~Not Applicable~~ 2021-001439-22	**EudraCT number: 2021-001439-22**	Added EudraCT study identifier.
3 Study Design		
3.1 General Study Design and Study Schematic Diagram		
Patients may be eligible to participate if they have a diagnosis of asthma for at least 6 months and their current asthma maintenance therapy has been stable for at least ~~3 months~~ **1 month** and includes 1 of the following (see Appendix F).	Patients may be eligible to participate if they have a diagnosis of asthma for at least 6 months and their current asthma maintenance therapy has been stable for at least 1 month and includes 1 of the following (see Appendix F).	Updated to improve patient enrollment.
Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients **(may be adjusted based on the interim analysis)** on medium or high dose ICS/LABA will be randomized and stratified across all treatment arms. Screening may be adjusted as needed to meet these criteria as much as possible.	Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients (may be adjusted based on the interim analysis) on medium or high dose ICS/LABA will be randomized and stratified across all treatment arms. Screening may be adjusted as needed to meet these criteria as much as possible.	Clarification.
3.2 Planned Number of Patients and Countries		
Approximately 860 patients will be screened to achieve approximately 300 randomized patients, **which may be adjusted based on an interim analysis**. Details on the definition of evaluable patients and sample size are given in Section 9.	Approximately 860 patients will be screened to achieve approximately 300 randomized patients, which may be adjusted based on an interim analysis. Details on the definition of evaluable patients and sample size are given in Section 9.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Table 2: Study Procedures and Assessments		
See new wording column	Table 2 (Study Procedures and Assessments) has been revised as described below: • Hematology (CBC with differential) – assessment added to V3 • Hematology (blinded CBC with differential) – assessment deleted from V3	Correction.
Footnote b: The screening visit will take place not more than approximately 4 weeks before the baseline/DoR visit (V3) and is limited to **approximately** 14 ~~±2~~ days duration. It is understood that not all procedures can be completed on the same day. In particular, the patient may need to return for repeat CBC testing as needed or to satisfy the medication wash out for pulmonary function testing or to undergo repeat pulmonary function testing.	Footnote b: The screening visit will take place not more than approximately 4 weeks before the baseline/DoR visit (V3) and is limited to approximately 14 days duration. It is understood that not all procedures can be completed on the same day. In particular, the patient may need to return for repeat CBC testing as needed or to satisfy the medication wash out for pulmonary function testing or to undergo repeat pulmonary function testing.	Clarification.
Footnote r: Blinded CBC with differential count will be drawn at visits ~~from~~ **after** V3 ~~and~~ onward to maintain study blinding. The eosinophil and monocyte counts will not be reported to the study personnel.	Footnote r: Blinded CBC with differential count will be drawn at visits after V3 onward to maintain study blinding. The eosinophil and monocyte counts will not be reported to the study personnel.	Correction.
4 Selection and withdrawal of patients		
4.1 Patient Inclusion Criteria		
c. **[Revision 1]** The patient has a diagnosis of asthma for at least 6 months as defined by the National Institutes of Health (NIH) and has been stable without exacerbation or change in medications for at least ~~3 months~~ **1 month**.	c. [Revision 1] The patient has a diagnosis of asthma for at least 6 months as defined by the National Institutes of Health (NIH) and has been stable without exacerbation or change in medications for at least 1 month.	Updated to improve patient enrollment.
g. **[Revision 1]** Current Asthma Therapy: The patient has been maintained for at least ~~3 months~~ **1 month** on stable doses of: - medium or high dose ICS±another controller. - any fixed dose combination ICS (low, medium, or high) with LABA±another controller.	g. [Revision 1] Current Asthma Therapy: The patient has been maintained for at least 1 month on stable doses of: - medium or high dose ICS±another controller. - any fixed dose combination ICS (low, medium, or high) with LABA±another controller.	Updated to improve patient enrollment.

Original text with changes shown	New wording	Reason/Justification for change
4.2 Patient Exclusion Criteria		
n. **[Revision 1]** The patient has been treated with a monoclonal antibody **used to treat asthma or other inflammatory conditions within the washout period (5 half-lives), has demonstrated hypersensitivity or anaphylaxis to a monoclonal antibody (Appendix G),**or is currently using or has used a systemic immunosuppressive medication within the last 6 months. **NOTE: Prior depemokimab exposure is prohibited without exception.**	n. [Revision 1] The patient has been treated with a monoclonal antibody used to treat asthma or other inflammatory conditions within the washout period (5 half-lives), has demonstrated hypersensitivity or anaphylaxis to a monoclonal antibody (Appendix G), or is currently using or has used a systemic immunosuppressive medication within the last 6 months. NOTE: Prior depemokimab exposure is prohibited without exception.	Updated to improve patient enrollment.
q. **[Revision 1]** The patient currently smokes or has a smoking history of 10 pack years or more (a pack year is defined as smoking 1 pack of cigarettes [20 cigarettes]/day for 1 year), OR the patient used tobacco ~~**or marijuana**~~ products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco), **OR the patient has smoked marijuana within 1 month**, OR the patient has a history of "vaping" tobacco, marijuana, or any other substance within 24 months.	q. [Revision 1] The patient currently smokes or has a smoking history of 10 pack years or more (a pack year is defined as smoking 1 pack of cigarettes [20 cigarettes]/day for 1 year), OR the patient used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco), OR the patient has smoked marijuana within 1 month, OR the patient has a history of "vaping" tobacco, marijuana, or any other substance within 24 months.	Clarification.
4.4 Withdrawal Criteria and Procedures for the Patient		
If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active COVID-19 **(positive antigen tests must be confirmed by reverse transcription polymerase chain reaction [RT-PCR] testing)**, he/she may continue for scheduled visits when recovered ~~**recovered (ie, negative real-time polymerase chain reaction [RT-PCR] test for COVID-1) assuming he/she has no protocol violations including use of disallowed medication**~~ **(ie, after 10 days from the onset of symptoms, remains afebrile for 24 hours without using anti-pyretics and other symptoms are improving)** (see Appendix G and Appendix N.	If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active COVID-19 (positive antigen tests must be confirmed by reverse transcription polymerase chain reaction [RT-PCR]) testing), he/she may continue for scheduled visits when recovered (ie, after 10 days from the onset of symptoms, remains afebrile for 24 hours without using anti-pyretics and other symptoms are improving) (see Appendix G and Appendix N).	Updated to align with current guidelines.

Original text with changes shown	New wording	Reason/Justification for change
4.6 Rescreening		
A patient who screen-fails may be permitted to rescreen once **after 30 days duration** if there is a reasonable expectation that this patient will become eligible for the study, **including requirements for eosinophil counts and/or spirometry**. The sponsor may grant permission to rescreen more than once under extenuating circumstances and only with the approval of the sponsor's medical expert or delegate. Note: Patients who develop a URI/LRI during the run-in period may rescreen 2 weeks after symptoms resolve and after appropriate COVID-19 testing has been completed as specified. **Additionally, patients who fail randomization for reasons other than spirometry requirements may be rescreened once.**	A patient who screen-fails may be permitted to rescreen once after 30 days duration if there is a reasonable expectation that this patient will become eligible for the study, including requirements for eosinophil counts and/or spirometry. The sponsor may grant permission to rescreen more than once under extenuating circumstances and only with the approval of the sponsor's medical expert or delegate. Note: Patients who develop a URI/LRI during the run-in period may rescreen 2 weeks after symptoms resolve and after appropriate COVID-19 testing has been completed as specified. Additionally, patients who fail randomization for reasons other than spirometry requirements may be rescreened once	Updated to improve patient enrollment.
5 Treatments		
5.8 Procedures for Monitoring Patient Compliance		
The investigator will be responsible for monitoring patient compliance with this protocol from the start of the screening/run-in period through the follow-up 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. The Independent Ethics Committee/Institutional Review Board (IEC/IRB) should be notified if required by local regulation. **Compliance with the patient diary will be deemed adequate if 80% of the data is captured through V9.**	The investigator will be responsible for monitoring patient compliance with this protocol from the start of the screening/run-in period through the follow-up 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. The Independent Ethics Committee/Institutional Review Board (IEC/IRB) should be notified if required by local regulation. Compliance with the patient diary will be deemed adequate if 80% of the data is captured through V9.	Clarification.
5.9 Randomization and Blinding		
Patients who meet all inclusion criteria, none of the exclusion criteria and all of the randomization criteria will be randomly assigned to 1 of 2 treatment groups or placebo in a 1:1:1 ratio and will be stratified by prior asthma maintenance therapy (ICS and low dose ICS/LABA will be stratified separately from the medium and high dose ICS/LABA [2 separate strata]) and absolute	Patients who meet all inclusion criteria, none of the exclusion criteria and all of the randomization criteria will be randomly assigned to 1 of 2 treatment groups or placebo in a 1:1:1 ratio and will be stratified by prior asthma maintenance therapy (ICS and low dose ICS/LABA will be stratified separately from the medium and high dose	Correction for consistency within the protocol and clarification sample size may be adjusted based on interim analysis.

Original text with changes shown	New wording	Reason/Justification for change
eosinophil count (~~300 to 400 cells/µL, >400 cells/µL~~ **300 to <400 cells/µL, ≥400 cells/µL**). Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients **(may be adjusted based on the interim analysis)** on medium or high dose ICS/LABA will be included and screening ~~will~~ **may** be adjusted as needed to meet these criteria.	ICS/LABA [2 separate strata]) and absolute eosinophil count (300 to <400 cells/µL, ≥400 cells/µL). Approximately 90 patients who have been maintained on medium or high dose ICS or low dose ICS/LABA and approximately 210 patients (may be adjusted based on the interim analysis) on medium or high dose ICS/LABA will be included and screening may be adjusted as needed to meet these criteria.	
5.11 Total Blood Volume		
The total blood volume to be collected for each patient in this study is approximately ~~183.5~~ **157.5** mL.	The total blood volume to be collected for each patient in this study is approximately 157.5 mL.	Correction for miscalculation of the total blood volume collected for each patient.
7 Assessment of Safety		
7.4.2.4 COVID-19 testing		
Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center SOPs. The testing may be conducted by the central laboratory or locally depending on feasibility. ~~based on RT-PCR analysis. If a patient has a~~ **pP**ositive tests **that measure** COVID-19 antigen ~~test the result~~ must be confirmed ~~based on~~ **by** RT-PCR~~ analysis~~.	Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center SOPs. The testing may be conducted by the central laboratory or locally depending on feasibility. The testing may be conducted by the central laboratory or locally depending on feasibility. Positive tests that measure COVID-19 antigen must be confirmed by RT-PCR.	Clarification.
9 Statistics		
9.1 Sample Size and Power Considerations		
[redacted]	[redacted]	Clarification.
9.5.4.1 Primary Efficacy Analysis		
where "IG"(a,b) is the inverse gamma	where "IG"(a,b) is the inverse gamma	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
distribution. **To handle missing data with a multiple imputation approach, ~~T~~the** linear regression model **which** fits a simple linear model from the data at previous visits (yi,) **will be used: ~~where t=baseline, 2, 4, ….10 and stratification variables s:~~** $$Y_i \mid y_{i,T} \sim \alpha_t + \beta_t y_{i,t} + \eta s + N(0, \lambda_t^2),$$ **where T=12 and s represents the stratification variables. The ~~with~~ priors for regression model parameters are:**	distribution. To handle missing data with a multiple imputation approach, the linear regression model, which fits a simple linear model from the data at previous visits (yi,), will be used: $$Y_i \mid y_{i,T} \sim \alpha_t + \beta_t y_{i,t} + \eta s + N(0, \lambda_t^2),$$ where T=12 and s represents the stratification variables. The priors for regression model parameters are:	
9.13 Planned Interim Analysis		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
9.13.1 The Unblinded Interim Efficacy Analysis		
[redacted] See new wording column	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
	[redacted]	

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
Appendix A. Clinical Laboratories and other Departments and Institutions		
See new workings column	Appendix A (Clinical) has been revised as described below: • Sponsor's Medical Expert/Contact Point …Further Information on the Study - Added: [redacted], Respiratory R&D Teva Branded Pharmaceutical Products R&D, Inc [redacted] Email: [redacted] • Study Principle Investigator – removed • Pharmacogenetics/Biomarker Evaluation – Added:	Updated the contacts for Sponsor Medical Expert and Pharmacogenetics/Biomarker Evaluation.

Original text with changes shown	New wording	Reason/Justification for change
	GENEWIZ 111 Corporate Boulevard Suite H Loading Dock South Plainfield, NJ 07080 USA	
Appendix B. Study Procedures and Assessments		
2. Procedures During the Run-in Period (Visit 2; 14±2 Days) • patient to complete the Asthma Control Questionnaire (ACQ-6) ~~to confirm eligibility (ACQ-6 score of ≥1.5 is required)~~	2. Procedures During the Run-in Period (Visit 2; 14±2 Days) • patient to complete the Asthma Control Questionnaire (ACQ-6)	Correction for consistency within the protocol; ACQ-6 score of ≥1.5 is not required at visit 2. Per the randomization criteria, this is a requirement at visit 3.
3.Procedures During Baseline Visit for Double-Blind Treatment Period (Visit 3 Day 0) • hematology (~~blinded~~ CBC with differential analysis)	3.Procedures During Baseline Visit for Double-Blind Treatment Period (Visit 3 Day 0) • hematology (CBC with differential analysis)	Clarification.
Appendix D. Ethics		
Informed Consent ~~Adult patients with a legally acceptable representative should provide informed consent according to national and local requirements.~~	Not applicable; text was deleted.	Removed due to conflict with Inclusion Criterion a, the patient is capable of giving signed informed consent.
Appendix G. List of Prohibited Medications		
See new wording column	Appendix G (List of prohibited medications) has been revised as described below: • Monoclonal antibody therapy – Washout period update to; Prohibited within 5 half-lives • Leukotrine modifiers (eg, montelukast, zileuton) – removed from table • Inhaled marijuana – Washout period update to; 1 month	Provides consistency with exclusion criteria and clarifies that leukotrienes are permitted during the study.
Footnote b ~~Previous exposure or treatment with monoclonal antibody therapy whether investigational or maintenance therapy.~~ **Patients with history of hypersensitivity/anaphylaxis to any monoclonal antibody are excluded from participating. Monoclonal antibodies used to treat non-inflammatory or non-malignant conditions (ie, migraine headache) may be allowed after**	Footnote b Patients with history of hypersensitivity/anaphylaxis to any monoclonal antibody are excluded from participating. Monoclonal antibodies used to treat non-inflammatory or non-malignant conditions (ie, migraine headache) may be allowed after consultation with the study medical monitor. **Note: previous depemokimab exposure is prohibited without**	Updated to provide consistency with exclusion criteria.

Original text with changes shown	New wording	Reason/Justification for change
consultation with the study medical monitor. Note: previous depemokimab exposure is prohibited without exception.	**exception.**	
Appendix N. Management of Study Activities During COVID-19 Outbreaks		
Section 1.3.1 Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) The protocol also states that if a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, he/she should be tested for active COVID-19. If the patient tests positive for active COVID-19 **(positive antigen testing must be confirmed by reverse transcription polymerase chain reaction [RT-PCR]),** he/she may continue for scheduled visits when recovered (ie, ~~after a negative RT-PCR test for COVID-19~~**10 days after onset of symptoms, is afebrile for 24 hours without use of anti-pyretics and demonstrates improvement in other symptoms),** assuming he/she has no protocol violations including use of disallowed medications (see Section 4.4).	Section 1.3.1 Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) The protocol also states that if a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, he/she should be tested for active COVID-19. If the patient tests positive for active COVID-19 (positive antigen testing must be confirmed by reverse transcription polymerase chain reaction [RT-PCR]), he/she may continue for scheduled visits when recovered (ie, 10 days after onset of symptoms, is afebrile for 24 hours without use of anti-pyretics and demonstrates improvement in other symptoms), assuming he/she has no protocol violations including use of disallowed medications (see Section 4.4).	Updated to align with current guidelines.
Section 3.1 General Study Design and Study Schematic Diagram; Section 3.5. Schedule of Study Procedures and Assessments; Appendix B. Study Procedures and Assessments by Visit If the patient tests positive for active COVID-19, he/she may continue for scheduled visits when recovered, **as specified above** ~~**(ie, after testing negative for active COVID-19)**~~, assuming he/she has no protocol violations including use of disallowed medications (see Section 4.4). Where appropriate, remote assessment of safety via telephone and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends his/her next scheduled visit. All other tests (including safety laboratory tests, pharmacokinetics, ADA, and biomarkers) are to be conducted once the patient can return to the study center for his/her next scheduled visit unless collected at a local laboratory or home nurse visit depending on availability and local regulation. Samples from patients with known **active** COVID-19 infection	Section 3.1 General Study Design and Study Schematic Diagram; Section 3.5. Schedule of Study Procedures and Assessments; Appendix B. Study Procedures and Assessments by Visit If the patient tests positive for active COVID-19, he/she may continue for scheduled visits when recovered, as specified above, assuming he/she has no protocol violations including use of disallowed medications (see Section 4.4). Where appropriate, remote assessment of safety via telephone and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends his/her next scheduled visit. All other tests (including safety laboratory tests, pharmacokinetics, ADA, and biomarkers) are to be conducted once the patient can return to the study center for his/her next scheduled visit unless collected at a local laboratory or home nurse visit depending on availability and local regulation. Samples from patients	Updated to align with current guidelines.

Original text with changes shown	New wording	Reason/Justification for change
should not be collected.	with known active COVID-19 infection should not be collected.	
Section 4.4 Withdrawal Criteria and Procedures for the Patient If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active COVID-19 **(confirmed by RT-PCR)**, he/she may continue for scheduled visits when recovered, **as specified above** ~~(ie, tests negative for active COVID-19)~~, assuming he/she has no protocol violations including use of disallowed medications (Appendix G).	Section 4.4 Withdrawal Criteria and Procedures for the Patient If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active COVID-19 (confirmed by RT-PCR), he/she may continue for scheduled visits when recovered, as specified above, assuming he/she has no protocol violations including use of disallowed medications (Appendix G).	Updated to align with current guidelines.
Section 7 Assessment of Safety **Active COVID-19 cases will be monitored throughout the study. If a total number of COVID-19 infections are confirmed in randomized patients who received IMP (placebo or TEV-53275) and related to an SAE to reach a minimum threshold (based on total randomized patients, detailed in the medical monitoring plan), the Pharmacovigilance physician in consultation with the Clinical Study Physician will determine if an unblinded review of the cases is warranted to ensure patient safety. Any unblinded review will be conducted by appropriate personnel that are not connected with the study.**	Section 7 Assessment of Safety Active COVID-19 cases will be monitored throughout the study. If a total number of COVID-19 infections are confirmed in randomized patients who received IMP (placebo or TEV-53275) and related to an SAE to reach a minimum threshold (based on total randomized patients, detailed in the medical monitoring plan), the Pharmacovigilance physician in consultation with the Clinical Study Physician will determine if an unblinded review of the cases is warranted to ensure patient safety. Any unblinded review will be conducted by appropriate personnel that are not connected with the study.	To provide clarification secondary to updated FDA COVID-19 guidance.
Section 7.4.2.4 COVID-19 Testing Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center **standard operating procedures** (SOPs). The testing may be conducted by the central laboratory or locally depending on feasibility. **Positive tests that measure COVID-19 antigen must be confirmed by RT-PCR.**	Section 7.4.2.4 COVID-19 Testing Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center standard operating procedures (SOPs). The testing may be conducted by the central laboratory or locally depending on feasibility. Positive tests that measure COVID-19 antigen must be confirmed by RT-PCR.	Updated to align with current guidelines.

16.2. Administrative Letter 01 Dated 23 March 2021

ADMINISTRATIVE LETTER 01

Study number: TV53275-AS-20033

Clinical Study Protocol

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Efficacy and Pharmacodynamics of TEV-53275 Administered Subcutaneously in Adult Patients with Persistent Eosinophilic Asthma

Version date 22 December 2020

IND number: 138687 EudraCT number: 2021-001439-22

23 March 2021

Dear Investigator:

The purpose of this letter is to provide the EudraCT number for this study and to correct for inconsistencies/editorial errors in the protocol related to duration of patient participation, stratification of absolute blood eosinophil counts, total blood volume, Asthma Control Questionnaire 6 (ACQ-6) score at Visit 2, and informed consent procedures.

Table 1 below summarizes the relevant sections and page numbers to be revised, the existing protocol text and the new wording, and the reason for the change. Where applicable, the actual changes to the text are shown (revisions and additions are shown in bold and underline; deletions are shown in strikethrough).

These changes 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 IRB/IEC for review and acknowledgement.

Please feel free to contact the study Global Clinical Operations (GCO) project manager, [redacted] (at [redacted] or [redacted]) if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

[redacted], Clinical Development
Respiratory

Table 1: Revisions and Clarifications to the TV53275-AS-20033 Clinical Study Protocol - Administrative Letter 01

Item Number	Item	Section/Table/Page Number(s)	Current Wording	New Wording	Reason for Change
1	EudraCT number	Page 1 and Synopsis, Page 5	EudraCT number: ~~Not Applicable~~ **2021-001439-22**	EudraCT number: 2021-001439-22	Added EudractCT study identifier.
2	Total duration of patient participation	Synopsis, Page 13	The total duration of patient participation in the study is planned to be approximately ~~36~~ **34** weeks including up to an approximate 2-week screening period, approximately a 2- ~~to 4-~~ week run-in period, a 16-week treatment period, and a follow-up visit 14 weeks after the final treatment visit.	The total duration of patient participation in the study is planned to be approximately 34 weeks including up to an approximate 2-week screening period, approximately a 2-week run-in period, a 16-week treatment period, and a follow-up visit 14 weeks after the final treatment visit.	Correction for consistency within the protocol; the duration of the Run-in period is 2 weeks, with a total study duration of 34 weeks.
3	Stratification of absolute blood eosinophil counts	Synopsis, Page 12, and Section 5.9, Page 74	absolute eosinophil count ~~(300 to 400 cells/µL, >400 cells/µL~~ **300 to <400 cells/µL, ≥400 cells/µL**).	absolute eosinophil count (300 to <400 cells/µL, ≥400 cells/µL).	Correction for consistency within the protocol; the blood eosinophil count strata are defined as 300 to <400 cells/µL and ≥400 cells/µL.
4	Total blood volume	Section 5.11, Page 75	The total blood volume to be collected for each patient in this study is approximately ~~183.5~~ **157.5** mL.	The total blood volume to be collected for each patient in this study is approximately 157.5 mL.	Correction for miscalculation of the total blood volume collected for each patient.

Item Number	Item	Section/Table/Page Number(s)	Current Wording	New Wording	Reason for Change
5	Asthma Control Questionnaire 6 (ACQ-6) score at Visit 2	Appendix B, Page 117	Patient to complete the Asthma Control Questionnaire (ACQ-6) ~~to confirm eligibility. (ACQ-6 score of ≥1.5 is required)~~	Patient to complete the Asthma Control Questionnaire (ACQ-6).	Correction for consistency within the protocol; ACQ-6 score of ≥1.5 is not required at Visit 2. Per the randomization criteria, this is a requirement at Visit 3.
6	Informed consent for adult patients with legally acceptable representative	Appendix D, Page 127	~~Adult patients with a legally acceptable representative should provide informed consent according to national and local requirements.~~	N/A; text was deleted.	Removed due to conflict with Inclusion Criterion a, The patient is capable of giving signed informed consent.

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. [redacted], Clinical Development Phone: [redacted] Cell: [redacted] Email: [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 address of the local safety officer/contract research organization (LSO/CRO) provided on the SAE report form. In the event of difficulty transmitting the form, contact an email address as indicated in the safety management plan (SMP).	[redacted] [redacted], Respiratory R&D Teva Branded Pharmaceutical Products R&D, Inc [redacted] Email: [redacted]
Contract Research Organization	ICON Clinical Research South Country Business Park Leopardstown Dublin 18, Ireland
Central Clinical Laboratory	PPD Clinical Labs 2 Tesseneer Drive Highland Heights, Kentucky, 41076 USA
Central Spirometry, eDiary, Central Electrocardiogram Evaluation	eResearch Technology GmbH Sieboldstrasse 3 97230 Estenfeld Germany
Bioanalytical Pharmacokinetics Evaluation	Teva Branded Pharmaceutical Products R&D, Inc.
Bioanalytical Immunogenicity Evaluation	Teva Branded Pharmaceutical Products R&D, Inc.
Pharmacogenetics/Biomarker Evaluation	GENEWIZ 111 Corporate Boulevard Suite H Loading Dock South Plainfield, NJ 07080 USA
Randomization and Trial Supply Management (RTSM) vendor	Parexel 2520 Meridian Parkway Research Triangle Park Suite 200, Durham, NC 27713 USA

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

The following study procedures and assessments by visit are a summary of the specific requirements listed in Table 2 and associated footnotes.

1. **Procedures for Screening (Visit 1; Up to 2-week Period)**

The screening visit (V) (V1) will take place not more than approximately 4 weeks before the baseline visit (V3). The following procedures will be performed at V1:

- obtain signed and dated informed consent before any study-related procedures are performed
- demographics
- review inclusion and exclusion criteria
- medical history
- asthma history, including duration, current medication, and history of exacerbations in the last year
- prior medication and treatment history. Note: any prior or concomitant therapy, medication, or procedure a patient has had 30 days before screening will be recorded in the source documentation and in the case report form (CRF)
- brief physical examination including (at minimum) chest, cardiovascular, abdominal and skin examinations
- record height in centimeters
- record weight in kilograms
- pulmonary function testing with reversibility:

  pulmonary function testing (spirometry) and reversibility testing will be conducted in the morning between 0530 and 1100 hours. Patients are required to withhold asthma maintenance medications for approximately 24 hours prior to lung function testing for once daily medications, 12 hours for twice daily or more frequently dosed medications. If the patient has taken asthma maintenance medication within 24±2 hours (daily dosed) or 12±2 hours (dosed twice daily or more frequently) or SABA rescue medication within 6 hours of the planned pulmonary function testing or ICS/LABA used as rescue medication within 12 hours of the planned pulmonary function testing, the visit must be rescheduled. Patients who meet the pre-albuterol/salbutamol lung function requirements and demonstrate reversibility ≥12% and a 200 mL increase from pre-albuterol/salbutamol FEV_1 approximately 30 minutes after 4 inhalations of albuterol/salbutamol HFA MDI (90 µg ex-actuator) or equivalent may enter the run-in period if they meet other eligibility requirements as specified. Patients may repeat pulmonary function testing (spirometry) and reversibility testing once during the screening period as needed to qualify
- hematology (CBC with differential analysis)

- serum chemistry

  Note: an absolute eosinophil count of ≥300 cells/μL is required to be included in the study. Given the known variability in this measure, the eosinophil count (CBC) may be repeated once during screening (total of 2 attempts during screening period), at the discretion of the investigator in order to fulfill this inclusion criterion. Historical eosinophil counts will not qualify a patient to participate.

  Laboratory testing, medical history assessments, serum collection for biomarkers, physical examination, and other assessments as noted in Table 2 will be completed during the screening period and may be conducted at more than one visit.

- obtain a blood sample for serum biomarker banking from patients who provided informed consent
- obtain a blood sample for serology testing (Hepatitis B, Hepatitis C, and human immunodeficiency virus [HIV] testing)
- urinalysis
- urine pregnancy test for women of childbearing potential (β HCG)
- serum follicle stimulating hormone (FSH) test, as applicable
- obtain vital signs
- COVID-19 symptoms inquiry. Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of the visit or as required by health authorities, local ethics committees, or study center SOPs

2. **Procedures During the Run-in Period (Visit 2; 14±2 Days)**

Visit 2 is the beginning of the run-in period. The following procedures will be performed during the run-in period:

- confirm eligibility to enter the run-in (inclusion/exclusion criteria)
- measure and record vital signs
- patient to complete the Asthma Control Questionnaire (ACQ-6)
- distribute handheld device and electronic diary
- conduct training for handheld device and electronic diary use
- dispense rescue medication
- inquire about clinical asthma exacerbation (CAE) during the screening period
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

3. **Procedures During Baseline Visit for Double-Blind Treatment Period (Visit 3, Day 0)**

The baseline/randomization visit (V3) will occur after a minimum of 14±2 days after entering the run-in period. Patients who meet the inclusion and exclusion criteria to enter the run-in period will continue to V3, when baseline assessments will be conducted.

At this visit the patient's diary data should be reviewed prior to formal lung function testing, laboratory testing and the various questionnaires to ensure compliance with diary entries and to determine if lung function, symptoms and rescue medication use meet the randomization criteria. If the patient fails to meet the diary requirements, the patient will be considered a randomization failure. Further procedures for V3 will only be conducted for patients who meet the diary requirements.

The following procedures will be performed:

- review inclusion and exclusion criteria
- review randomization criteria
- review compliance with diary and study randomization requirements
- full physical examination (to include, at a minimum, head, eyes, ears, nose, and throat [HEENT], chest, cardiovascular, abdominal, skin, and neurological examination)
- pulmonary function testing (spirometry)
- hematology (CBC with differential analysis)
- fasting serum chemistry tests
- obtain a blood sample for Phadiatop Allergy Test and Total IgE
- obtain a blood sample for pharmacogenetics (confirm patient has provided informed consent for this procedure)
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for serum anti-drug antibody (ADA) assay
- obtain a blood sample for biomarker interleukin 5 (IL-5) analysis
- urinalysis
- urine pregnancy test for women of childbearing potential (β HCG)
- 12-lead electrocardiogram (|ECG) in triplicate. Each ECG will be taken within 1 to 5 minutes of the previous one.
- vital signs measurements
- [redacted]
- complete ACQ-6
- Asthma Control Test (ACT)

- Standardized Asthma Quality of Life Questionnaire (AQLQ[S])
- [redacted]
- conduct training on handheld device and review diary use and compliance
- perform randomization and treatment assignment in interactive response technology (IRT) after confirming eligibility including diary and pulmonary function testing, ACQ 6 score and the remaining randomization criteria have been met.
- investigational medicinal product (IMP) dosing (**Note:** dosing may not occur until all clinical laboratory samples, and questionnaires have been completed). Doses will be administered by a qualified health care provider (according to local regulations) who is prepared to manage anaphylaxis
- postdose observation period of 1 hour
- injection site evaluation
- dispense rescue medication (if needed)
- collect rescue medication
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

4. **Procedures During Double-Blind Treatment Period (Visits 4 through 7)**

a. Visit 4 (Week 1 [Days 3±2])

The following procedures will be performed:

- pulmonary function testing (spirometry)
- hematology (blinded CBC with differential analysis)
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for serum biomarker (IL-5) analysis
- dispense/collect rescue medication (if needed)
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

b. Visit 5 (Week 2 [Day 14±2])

The following procedures and assessments will be performed:

- brief physical examination (to include, at a minimum, chest, cardiovascular, abdominal, and skin examinations)
- pulmonary function testing (spirometry)
- hematology (blinded CBC with differential analysis)
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for serum biomarker (IL-5) analysis
- vital signs measurements
- complete ACQ-6
- review compliance with diary and study requirements
- dispense/collect rescue medication (if needed)
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

c. Visit 6 (Week 4 [Day 28±2])

The following procedures and assessments will be performed:

- brief physical examination (to include, at a minimum, chest, cardiovascular, abdominal, and skin examinations)
- pulmonary function testing (spirometry)
- hematology (blinded CBC with differential analysis)
- serum chemistry tests
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for biomarker (IL-5) analysis
- urine pregnancy test for women of childbearing potential (β HCG)
- vital signs measurements
- complete ACQ-6
- complete ACT
- review compliance with diary and study requirements
- dispense/collect rescue medication (if needed)
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications

- COVID-19 symptoms inquiry

d. Visit 7 (Week 8 [Day 56±2]):

The following procedures and assessments will be performed:

- brief physical examination (to include, at a minimum, chest, cardiovascular, abdominal, and skin examinations)
- pulmonary function testing (spirometry)
- hematology (blinded CBC with differential analysis)
- serum chemistry tests
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for biomarker (IL-5) analysis
- urine pregnancy test for women of childbearing potential (β HCG)
- vital signs measurements
- complete ACQ-6
- complete ACT
- review compliance with diary and study requirements
- dispense/collect rescue medication (if needed)
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

5. **Procedures During Visit 8 (Week 12 [Day 84±2])**

The following procedures will be performed:

- brief physical examination
- pulmonary function testing
- hematology (blinded CBC with differential analysis)
- serum chemistry tests
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for biomarker (IL-5) analysis
- urine pregnancy test for women of childbearing potential (β HCG)
- vital sign measurements
- [redacted]

- complete ACQ-6
- complete ACT
- complete AQLQ(S)
- [redacted]
- review compliance with diary and study requirements
- dispense/collect rescue medication (if needed)
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

6. **Procedures During Visit 9 (Week 16 [Day 112±2]) (End of Treatment Visit)**

The following procedures will be performed:

- full physical examination (to include, at a minimum, HEENT, chest, cardiovascular, abdominal, skin, and neurological examination)
- weight (kg)
- pulmonary function testing
- hematology (blinded CBC with differential analysis)
- fasting serum chemistry tests
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for serum anti-drug antibody (ADA) assay
- obtain a blood sample for biomarker (IL-5) analysis
- urinalysis
- urine pregnancy test for women of childbearing potential (β HCG)
- 12-lead ECG
- vital sign measurements
- complete ACQ-6
- complete ACT
- complete AQLQ(S)
- collect handheld device and electronic diary
- collect rescue medication
- discuss ongoing asthma treatment

- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

7. **Procedures During Telephone Follow-up (Weeks 20 [Day 140±2], 24 [Day 168±2], 28 [Day 196±2])**

Patients will be contacted approximately monthly by telephone to inquire about CAEs, adverse events, concomitant medications and COVID-19 symptoms.

8. **Procedures During Visit 10 (Week 30 [Day 210±5]) (Follow-up Visit)**

Patients will return to the investigational center, whereupon the following procedures will be performed:

- brief physical examination (to include, at a minimum, chest, cardiovascular, abdominal, and skin examinations)
- hematology (blinded CBC with differential analysis)
- serum chemistry tests
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for ADA assay
- obtain a blood sample for biomarker (IL-5) analysis
- urine pregnancy test for women of childbearing potential (β HCG)
- vital signs measurements
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

9. **Unscheduled Visits**

An unscheduled visit may be performed at any time during the study at the patient's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits may include:

- vital signs measurement
- assess CAEs
- inquire about adverse events

- inquire about concomitant medications
- COVID-19 symptoms inquiry

Other procedures and assessments may be performed at the discretion of the investigator.

10. **Early Withdrawal Visit**

Patients who withdraw consent or patients who are unable to continue participation in the study should participate in the Early Withdrawal Visit (EWV) whenever possible.

Procedures performed during the EWV may include:

- full physical examination
- weight (kg)
- pulmonary function testing
- hematology (blinded CBC with differential analysis)
- serum chemistry tests
- obtain a blood sample for pharmacokinetics (serum IMP concentration)
- obtain a blood sample for ADA assay
- obtain blood for serum biomarker (IL-5) analysis
- urinalysis
- urine pregnancy test for women of childbearing potential (β HCG)
- 12-lead ECG
- vital signs measurement
- [redacted]
- complete ACQ-6
- complete ACT
- complete AQLQ(S)
- [redacted]
- collect handheld device and electronic diary
- collect rescue medication
- assess CAEs
- inquire about adverse events
- inquire about concomitant medications
- COVID-19 symptoms inquiry

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Important 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 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 nonadherence 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 by investigational center personnel. 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.

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or 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.

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 informed consent form 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 monitors are to visit the investigator before, during, and after the study to ensure adherence to the protocol, to ensure that all data are correctly and completely recorded and reported, and to confirm that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitors 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.

For details of the management of study activities during COVID-19 outbreaks, see Appendix N.

APPENDIX D. 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. Informed consent may be conducted by an electronic platform (ie, eConsent) if allowed by local regulation and as implemented during the study.

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 informed consent form, 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 informed consent forms, 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.

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, 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 E. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- the investigational center must attempt to contact the patient and 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.
- in cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

APPENDIX F. LIST OF INHALED CORTICOSTEROID THERAPY REQUIRED FOR INCLUSION INTO THE RUN-IN PERIOD

Asthma maintenance therapy[a]	Daily dose (mcg/day) Medium dose	Daily dose (mcg/day) High dose
Fluticasone propionate HFA pMDI	>250 mcg (metered dose[b]) >220 mcg (delivered dose)	>500 mcg (metered dose) > 440 mcg (delivered dose)
Fluticasone propionate DPI	>250 mcg (metered dose)	>500 mcg (metered dose)
Fluticasone propionate DPI (Amonair®/AirDuo®)	226 mcg (metered dose)	464 mcg (metered dose)
Fluticasone furoate DPI	100 mcg	200 mcg
Beclomethasone dipropionate DPI (EASYHALER®) (Orion Corporation)	>500 mcg (metered dose)	>1000 mcg (metered dose)
Beclomethasone dipropionate HFA pMDI (QVAR®)	>200 mcg (metered dose) >160 mcg (delivered dose)	>400 mcg (metered dose) >320 mcg (delivered dose)
Budesonide DPI	>400 mcg (metered dose) >320 mcg (delivered dose)	>800 mcg (metered dose) >640 mcg (delivered dose)
Mometasone furoate DPI	200 mcg	400 mcg
Mometasone furoate HFA pMDI	>200 mcg	>400 mcg
Ciclesonide HFA pMDI	>160 mcg (delivered dose)	>320 mcg (delivered dose)

Source: Adapted from Global Initiative for Asthma (2020).

[a] Does not include ICS/LABA used as rescue medication.

[b] Consult prescribing information to determine metered or delivered dose if required.

DPI=dry powder inhaler HFA=hydrofluoroalkane (HFA); ICS=inhaled corticosteroid; pMDI=pressurized metered dose inhaler;LABA=long-acting β_2 agonist.

NOTE: low dose ICS/LABA fixed dose combinations are allowed.

APPENDIX G. LIST OF PROHIBITED MEDICATIONS

Type of Medication or Drug[a]	Washout Period before Study Visit V2 (Unless Otherwise Specified)
Monoclonal antibody therapy[b]	Prohibited within 5 half-lives
Any other investigational drug	30 days or 5 half-lives (whichever is longer)
Inhaled or oral cromolyn	14 days
Corticosteroids (oral, iv, intra-articular, or intramuscular)	30 days
Topical dermatologic corticosteroids (intermediate to high potency, eg, CUTIVATE® [PharmaDerm], ELOCON® [Schering Corporation] or triamcinolone cream, lotion or ointment)[c]	14 days
Decongestants (eg, pseudoephedrine, phenylpropanolamine, or phenylephrine)	Discontinue 24 hours before any visit where pulmonary function will be assessed
Immunosuppressive therapy (eg, methotrexate, gold, or azathioprine)	6 months
Immunotherapy[d]	Initiation within 90 days or clinically meaningful change in dose within 30 days
Inhaled anticholinergic (anti-muscarinic) medication (eg, tiotropium, umeclidinium, glycopyrrolate)	7 days prior to lung function testing during the screening period and through week 16 (V9)
Oral β_2-agonists (tablets, syrup)	7 days
Oral or nasal antihistamines (eg, loratadine, diphenhydramine, or cetirizine)	Chronic stable doses are allowed and are anticipated to remain stable throughout the treatment period (week 16 [V9])
Inhaled marijuana	1 month
Vaping nicotine/marijuana or any other substance	24 months

[a] Medications prohibited during the study through week 16 (V9) and required washout periods are listed. Patients who require addition of asthma medications during the study to control asthma prior to the week 16 visit (V9) are allowed but will be recorded as a protocol deviation.

[b] Patients with history of hypersensitivity/anaphylaxis to any monoclonal antibody are excluded from participating. Monoclonal antibodies used to treat non-inflammatory or non-malignant conditions (ie, migraine headache) may be allowed after consultation with the study medical monitor. **Note: previous depemokimab exposure is prohibited without exception.**

[c] Low-potency topical corticosteroids are allowed and may include (as examples) hydrocortisone cream 2.5% or lower, Desonide gel or foam 0.05%, fluocinolone acetonide cream or solution 0.01%, or alclometasone dipropionate 0.05% cream or ointment.

[d] Patients who have been treated with immunotherapy and the treatment is expected to remain stable during the study may participate in the study.

ICS=inhaled corticosteroid; iv=intravenous; LABA=long-acting β-adrenergic agonist; V=visit.

APPENDIX H. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

As detailed by Sampson et al 2006, anaphylaxis is broadly defined as, "a serious allergic reaction that is rapid in onset and may cause death." Diagnostic criteria defined by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network during the second symposium on the definition and management of anaphylaxis, modified from Sampson et al 2006, are as follows:

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue, uvula) and at least 1 of the following:
   - respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen* for that patient (minutes to several hours):
   - involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure *to a known allergen* for that patient (minutes to several hours):
   - adults: systolic BP of <90 mm Hg or >30% decrease from that person's baseline

In the event of suspected severe hypersensitivity (including anaphylaxis), vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator.

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
- Hepatitis C
- Herpes simplex
- 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

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 Adults and Adolescents with HIV". 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. PHARMACOGENETIC ASSESSMENTS

Blood samples (2.5 mL) for pharmacogenetic assessments will be collected at the randomization visit (V3) from all patients in the study who signed the informed consent form (ICF) for the pharmacogenetic assessments. Each patient will sign a separate ICF for the genetic assessment. Participation in the genetic research is optional. Patients who do not wish to participate in the genetic research may still participate in the study. Pharmacogenetic data will be kept confidential and stored separately.

Pharmacogenetic assessment potentially includes the association of DNA variations in the IL-5 gene with clinical responses to TEV-53275 (eg, efficacy, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features).

IL-5 sequence may be studied in addition to other potential genes in relation with respiratory disease or with the TEV-53275. The final list of genes that might be investigated will be selected at a later stage before the analysis to allow the list to be updated with new scientific information. Genetic analysis could also include a sequencing of the whole genome if required. Pharmacogenetic assessment may be performed based on study results. Samples will be used only for investigations related to respiratory diseases and/or response to related investigational drugs. Pharmacogenomic assessment may occur after this clinical study is completed.

Details on processes for collection and shipment of these samples can be found in the study reference manual.

APPENDIX K. PRODUCT COMPLAINTS

Clinical Product Complaints

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 or other retrievable item, it is required that the device (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.

1. **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
- 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.

2. **Handling of Investigational Medicinal Product(s) 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, 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.

3. **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).

4. **Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, 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.

APPENDIX L. 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 informed consent forms
- 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 M. PUBLICATION POLICY

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator, if applicable, will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

APPENDIX N. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19 OUTBREAKS

This appendix addresses the modifications 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 who were impacted by COVID-19.

The following sections of the protocol are affected:

Section 1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

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 COVID-19 will be excluded from entering run-in period and will not be randomized into the study as they would meet exclusion criterion "d", which excludes patients with "clinical symptoms that may indicate COVID-19 infection, and/or patients who in the investigator's opinion are at high risk of exposure to COVID-19 within 4 weeks before screening or during screening/run-in". Such patients will be tested for active COVID-19 infection and will only be included if they test negative for COVID-19. Furthermore, exclusion criterion "c" stipulates:

- The patient has a suspected bacterial or viral infection (including COVID-19) of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the screening period. Note: Patients who develop an upper respiratory infection/lower respiratory infection (URI/LRI) during the run-in period may rescreen 2 weeks after symptoms resolve and undergo COVID-19 testing as outlined in exclusion criteria "d".

Older adults and people of any age who have serious underlying medical conditions, including moderate to severe asthma, may be at higher risk for a more severe COVID-19 course when infected (Centers for Disease Control and Prevention [CDC] Coronavirus [COVID-19]).

The protocol also states that if a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, he/she should be tested for active COVID-19. If the patient tests positive for active COVID-19 (positive antigen testing must be confirmed by reverse transcription polymerase chain reaction [RT-PCR]), he/she may continue for scheduled visits when recovered (ie, 10 days after onset of symptoms, is afebrile for 24 hours without use of anti-pyretics and demonstrates improvement in other symptoms), assuming he/she has no protocol violations including use of disallowed medications (see Section 4.4).

Section 3.1. General Study Design and Study Schematic Diagram; Section 3.5. Schedule of Study Procedures and Assessments; Appendix B. Study Procedures and Assessments by Visit

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 continue with daily hand-held spirometry measurements and e-diary completion, and scheduled adverse event and concomitant medication monitoring. Patient questionnaires may be completed with the assistance of study center personnel where permitted by licensing agreements. If the patient tests positive for active COVID-19, he/she may continue for scheduled visits when recovered, as specified above, assuming he/she has no protocol violations including use of disallowed medications (see Section 4.4). Where appropriate, remote assessment of safety via telephone and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends his/her next scheduled visit. All other tests (including safety laboratory tests, pharmacokinetics, ADA, and biomarkers) are to be conducted once the patient can return to the study center for his/her next scheduled visit unless collected at a local laboratory or home nurse visit depending on availability and local regulation. Samples from patients with known active COVID-19 infection should not be collected.

In the event that a patient completes the run-in but cannot come to the site for the day of randomization (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. Rescreening of the patient will also be allowed.

Modifications to other procedures and assessments (electrocardiogram [ECG], laboratory sample collection, pharmacokinetic sampling, etc.) will be performed per implemented contingency measures according to sponsor instructions and the corresponding manual. For example, if central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or dispatch a home health nurse to perform the assessments, but only after consultation with the sponsor and as allowed by local regulation.

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 original protocol instructions will be followed whenever the modified instructions are not required.

Section 4.2 Patient Exclusion Criteria; Section 4.3. Randomization Criteria; Section 5.7. Prior and Concomitant Medication or Therapy

In the event that new COVID-19 therapies or vaccines become available during the study, the eligibility criteria and list of prohibited medications can be updated to reflect these developments. If a patient receives new COVID-19 therapies not in compliance with the eligibility criteria and list of prohibited medications current 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 4.4. Withdrawal Criteria and Procedures for the Patient

If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active COVID-19 (confirmed by RT-PCR), he/she may continue for scheduled visits when recovered, as specified above, assuming he/she has no protocol violations including use of disallowed medications (Appendix G).

Where appropriate, remote assessment of safety via telephone and/or VC, with VC being the preferred method, is recommended until the patient attends his/her next scheduled visit. All other tests (including safety laboratory tests, pharmacokinetics, ADA, and biomarkers) are to be conducted once the patient can return to the study center for his/her next scheduled visit.

Section 4.5 Replacement of Patients

In the event of an emergency situation (eg, COVID-19 outbreaks), if 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 6. Assessment of Efficacy

In the event of an emergency situation (eg, COVID-19 outbreaks), if 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 efficacy via telephone call and/or VC, with VC being the preferred method, may be allowed. Uploaded electronic diary data for rescue medication usage, daytime and night-time asthma symptom scores, and uploaded hand-held spirometry data will be reviewed remotely. Telephone/VC assessment by the investigator will be assessed at the scheduled visit. Clinic-based forced expiratory volume in 1 second (FEV_1) assessments will not be possible unless a satisfactory home spirometry device that is generally equivalent can be implemented. The results of the clinical asthma exacerbation (CAE) inquiry will be entered directly into the CRF per the usual process. Questionnaire data will be completed and entered into the CRF per the usual process or will be collected by validated paper questionnaire and entered into the database by the study personnel.

Preferably, the original protocol instructions will be followed whenever the new instructions are not required.

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 original 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), if 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 (as well as inquiries regarding adverse events and use of concomitant medication) via telephone call and/or VC, with VC being the preferred method, may be allowed. The results will be directly entered into the CRF per the usual process.

Modifications to other procedures and assessments (ECG, laboratory sample collection, pharmacokinetic sampling, etc.) will be performed per implemented contingency measures according to sponsor instructions and the corresponding study reference manual. For example, if central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or dispatch a home health nurse to perform the assessments, but only after consultation with the sponsor and as allowed by local regulation.

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 original protocol instructions will be followed whenever the modified instructions are not required.

Active COVID-19 cases will be monitored throughout the study. If a total number ofCOVID-19 infections are confirmed in randomized patients who received IMP (placebo or TEV-53275) and related to an SAE to reach a minimum threshold (based on total randomized patients, detailed in the medical monitoring plan), the Pharmacovigilance physician in consultation with the Clinical Study Physician will determine if an unblinded review of the cases is warranted to ensure patient safety. Any unblinded review will be conducted by appropriate personnel that are not connected with the study.

Section 7.4. Clinical Laboratory Tests

If central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or arrange a home health visit to perform the assessments after discussion with and approval by the sponsor and as allowed by local regulation.

Section 7.4.2.4. COVID-19 Testing

Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit where spirometry assessments are to be conducted or as required by health authorities, local ethics committees, or study center standard operating procedures (SOPs). The testing may be conducted by the central laboratory or locally depending on feasibility. Positive tests that measure COVID-19 antigen must be confirmed by RT-PCR.

Section 7.5. Physical Examinations; Section 7.6. Vital Signs; Section 7.7. Electrocardiography; Section 7.8. Assessment of Local Tolerability and Pain

After consultation with the sponsor and as allowed by local regulation, at home health visits may be used to perform safety assessments such as physical examinations, vital signs, ECG, and local tolerability, and nursing assessments to determine any new adverse events. The patient will continue with daily hand-held spirometry measurements and e-diary completion during this time.

Section 8. Assessments of Pharmacokinetics, Immunogenicity, Biomarkers, and Pharmacogenetics

If pharmacokinetic, immunogenicity, and/or biomarker samples cannot be collected due to limitations in the 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 laboratory and will not be shipped to Teva bioanalytical laboratories nor analyzed. Teva bioanalytical laboratories will be informed by the sponsor within

approximately 1 week of any patients confirmed COVID-19 positive after samples have been collected.

Section 9. Statistics

Sensitivity and supplementary analyses may be conducted to evaluate the impact of the change to remote monitoring (telephone calls and VC visits) and the impact of COVID-19 outbreaks on study endpoints, eg, as follows:

1. A sensitivity analysis which will include eligible home-based efficacy assessment values for those who cannot be remotely evaluated due to outbreak emergency situations.
2. A sensitivity analysis which will treat the efficacy assessment values collected through remote evaluation as missing and apply the usual missing data handling approach (reference-based multiple imputation).

In addition, the amount of home-based efficacy assessments and missing data due to the outbreak will be monitored continuously and the sample size will be re-assessed to ensure sufficient study power.

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 the 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 C. 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 the 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/IEC approval. Details will be provided in the monitoring plan.