Statistical Analysis Plan

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

Study Number TV48574-AS-20031

NCT04545385

SAP Approval Date: 22 November 2021

Statistical Analysis Plan

Study Number TV48574-AS-20031

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

Proof of Concept Study (Phase 2a)

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

Approval Date: 22 November 2021

Sponsor

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

Prepared by: [redacted] and [redacted]
Teva Global Statistics

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV48574-AS-20031

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

Statistical Analysis Plan for:

- ☒ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Amendment: 0

Authors: [redacted], **Teva Global Statistics**

[redacted], **Teva Global Statistics**

Approver: [redacted] **Date**
[redacted], **Global Statistics**

Approver: [redacted] **Date**
[redacted], **Global Specialty R&D,**
[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACQ-6	Asthma Control Questionnaire 6-question version
ADA	antidrug antibodies
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
CAE	clinical asthma exacerbation
CRF	case report form
CI	Confidence interval
COVID-19	coronavirus disease 2019
CV	coefficient of variation
DoR	Day of randomization
e-diary	electronic diary
ECG	electrocardiogram/electrocardiography
EOS	end of study
EOT	end of treatment
ER	emergency room
ET	early termination
mITT	modified intent-to-treat
PEF	Morning peak expiratory flow
FeNO	Fractional exhaled nitric oxide
FEV_1	forced expiratory volume in the first second
FSH	follicle stimulating hormone
HBsAg	hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HIV	human immunodeficiency virus
HCV	hepatitis C virus
ICE	intercurrent events
ICS	inhaled corticosteroid
IMP	investigational medicinal product

Abbreviation	Term
ITT	intent-to-treat
JSRC	joint safety review committee
KM	Kaplan-Meier
LABA	Long-acting beta agonist
LoAC	loss of asthma control
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NRS	numerical response scale
PDAESI	protocol-defined adverse events of special interest
PP	per-protocol
Proof of concept	POC
R&D	Research and Development
RTSM	Trial Supply Management
SABA	short-acting beta agonist
SAP	statistical analysis plan
sc	subcutaneous(ly)
SD	standard deviation
SE	standard error
SI	standard international
SOC	system organ class
SOP	standard operating procedure
ULN	upper limit of normal
UN	unstructured covariance
WHO Drug	World Health Organization Drug Dictionary

INTRODUCTION

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study TV48574-AS-20031, [A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-low/non-T2 Severe Uncontrolled Asthma], and was written in accordance with [redacted] (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol (Protocol with Amendment 02 Approval Date: 28 April 2021**)** for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regard to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the clinical study report.

1. STUDY ENDPOINTS

1.1. Primary Efficacy Endpoints

The primary efficacy endpoint is the proportion of patients who experience loss of asthma control (LoAC) during the treatment period.

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

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

1.2. Secondary Efficacy Endpoints

Key secondary efficacy endpoints:

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

Other secondary efficacy endpoints:

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

1.3. Safety Endpoints

Safety and tolerability endpoints:

- Frequency of adverse events
- Change from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study
- Change from baseline in vital signs throughout the study
- Change from baseline in 12-lead electrocardiogram (ECG) findings throughout the study

- Use of concomitant medication
- Local tolerability
- Number (%) of patients who did not complete the study due to adverse events

1.4. Device-Related Events

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

1.5. Pharmacokinetic Assessment

Pharmacokinetic endpoints are

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

1.6. Immunogenicity Assessment Endpoints

Immunogenicity endpoints are

Assessment of treatment-emergent anti-drug antibody (ADA) responses: change from baseline and throughout the study

Impact of the presence of ADAs on pharmacokinetics and clinical safety (if possible).

Assessment of neutralizing ADA in ADA positive patients throughout the study

1.7. Estimand for Primary Efficacy Endpoint

An estimand, in general, includes 5 inter-related attributes – treatment condition, population of interest, variable (endpoint) of interest, intercurrent events (ICE) along with the strategy for handling ICE, and population-level summary for the endpoint. The four attributes of the estimand are defined as follows:

Treatment condition: TEV-48574 [redacted] vs. placebo administered bi-weekly in patients on stable background inhaled corticosteroids (ICS) / long-acting best agonist (LABA) in the first four weeks but with background asthma controllers withdrawn in a structured manner from week 4 to week 8.

Population: The patients with T2-low and non-T2 uncontrolled severe asthma met all inclusion criteria and met none of the exclusion criteria.

The intent-to-treat (ITT) analysis set as defined in Section 3.1 will be the primary analysis set for efficacy. In the data analyses, the treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

Variable: The proportion of patients who experience LoAC during the 16-week treatment period due to the initially randomized treatment as actually taken (Mallinckrodt, 2013).

Intercurrent events: Early treatment discontinuation will result in a lack of exposure to the initially randomized treatment and the patient being put on alternative medications. Observations after IMP discontinuations may not reflect the treatment effects of the initially randomized

treatment. In addition, an early discontinuation prior to week 16 without LoAC will result in a missing observation of the primary efficacy endpoint altogether.

As the strategy to handle the ICEs for the primary analysis, each patient's treatment period is defined as from the first dose to the last dose + 14 days. Patients who withdraw from the study prior to week 16 without LoAC or early terminated the study treatment without experiencing LoAC during the patient's treatment period will be analyzed as having experienced LoAC, if the assessed reason of discontinuation is lack of efficacy or due to an asthma-related adverse event. Patients who withdraw from the study without LoAC or early terminated treatments without experiencing LoAC during the patient's treatment period for other reasons will be analyzed as having not experienced LoAC.

Population-level summary: Numbers and proportions of patients who experience LoAC during the treatment period, adjusted proportions estimated from the logistic regression analysis in the treatment groups, as well as odds ratios between the two treatment groups estimated from the logistic regression analysis.

2. STUDY DESIGN

2.1. General Design

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

The study will consist of a 5-week period consisting of screening followed by a run-in, a 16-week treatment period, and an 8-week follow-up period.

Screening and run-in (5 weeks)

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

Treatment Period (16 weeks)

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

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

With randomization, patients enter the 16-week treatment period. The patients will receive the IMP [redacted]
Patients should be observed for 2 hours after the end of the first (loading dose) and second (first maintenance dose) administration of IMP and for 1 hour after the subsequent IMP administrations.

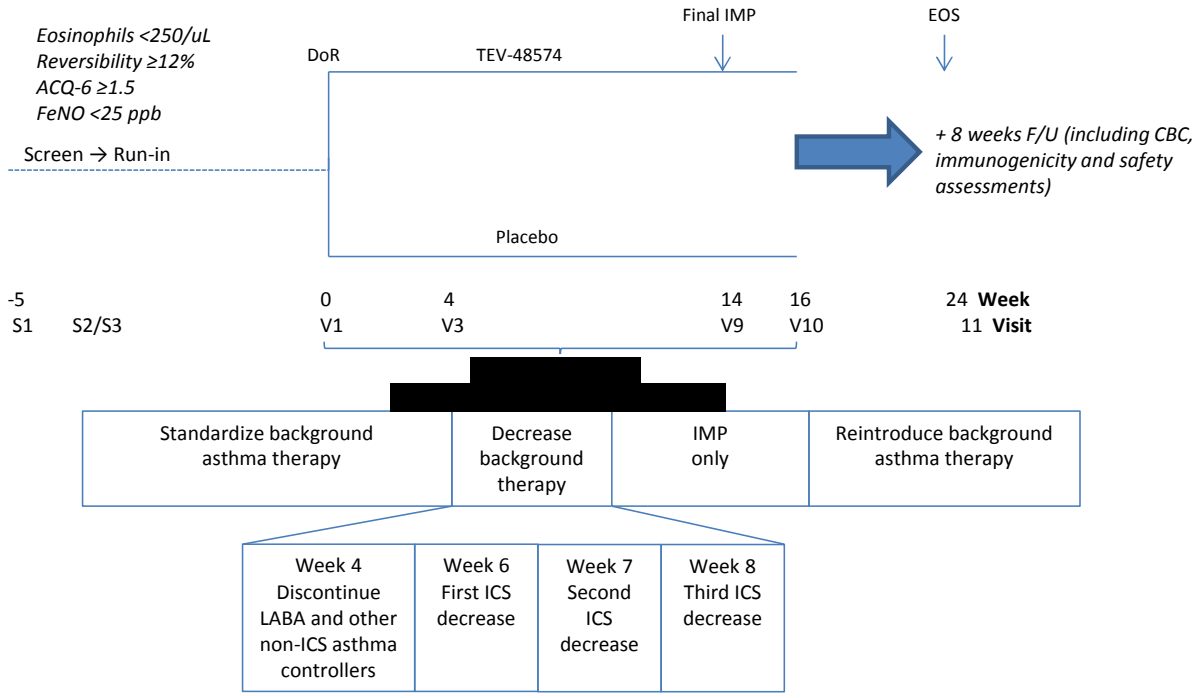
Follow-up Period (8 weeks)

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

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

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

Figure 1: Overall Study Schematic Diagram



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

2.2. Randomization and Blinding

This is a randomized, double-blind study. Patients who meet all inclusion criteria, none of the exclusion criteria, and all of the randomization criteria will be randomly assigned to receive TEV-48574 or placebo to match TEV-48574 in a 1:1 ratio to the following regimens administered sc every 2 weeks:

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

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

The study patients and the clinical team at the site will be blinded to treatment assignment until the database is locked for analysis. Individuals who may not be blinded include (but are not

limited to) the bioanalytical scientists, pharmacokineticists, and biostatisticians who are not directly involved in study conduct.

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

2.3. Joint Safety Review Committee

A Joint Safety Review Committee (JSRC) will convene and review all available safety data at specific stages of the study and will recommend proceeding with the study as planned, performing modifications, suspending study until further notice, or prematurely terminating the study.

Details are in JSRC Charter.

2.4. Sample Size and Power Considerations

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

Sample size calculations were performed based on the following considerations:

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

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

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

An unblinded interim analysis is planned to re-assess the sample size and conduct a futility analysis as described in Section 13. If the sample size increases as a result of the interim analysis, the number of evaluable patients would be expected to increase proportionately.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

An unblinded interim analysis is planned after the first 40-52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely. The main purposes of the interim analysis include sample size re-assessment and futility analysis. The details are in Section 13 and the Interim Analysis Charter.

2.5.2. Final Analyses and Reporting

All final analyses identified in this SAP will be performed after the final database lock.

3. ANALYSIS SETS

3.1. Intent-to-Treat Analysis Set

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

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

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

3.2. 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 sensitive analysis.

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

For the actual treatment assignment, a patient is assigned to the placebo group if the patient only received placebo doses. If a patient received at least one dose of active IMP, the actual treatment received for the patient will be the active IMP treatment group.

3.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients that did not experience any important protocol deviation prior to LoAC (if any) or the end of the treatment period, whichever comes first. The list of important deviations identified as having the potential to influence and/or bias the primary efficacy results are:

- Receive any dose of study drug by error, eg. randomized to receive test IMP but received dose(s) from placebo IMP, versa vise
- Did not complete planed study treatments (8 doses in total) for reason other than LoAC related
- Use of prohibited medications

A complete list of important deviations resulting in exclusion of patients from the PP analysis will be determined and documented at the end of the study based on a team review of accumulated blinded study data.

3.5. Pharmacokinetic Analysis Set

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

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include count (n), mean, SD, standard error (SE), median, minimum, and maximum. In addition, for TEV-48574 concentration, percentage coefficient of variation (%CV) and geometric mean will also be calculated. Descriptive statistics for categorical variables include patient counts and percentages, and a missing category will be displayed as appropriate.

Summaries of potentially clinically significant abnormal values for clinical laboratory tests and vital signs values will include all postbaseline values (including scheduled, unscheduled, and early withdrawal visits).

4.2. Specification of Baseline Values

Unless otherwise noted, the baseline for clinic visit variables will be the last observed value before the first dose of study drug. The baseline for absolute eosinophil count will be the average of measurements prior to the administration of the first IMP.

The baseline for hand-held spirometry parameters and e-diary variables will be the average of the values over the 7 days preceding day of randomization.

4.3. Handling Withdrawals and Missing Data

For all safety 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.

Dates that have incomplete information (the month and year or just the year is available) will be estimated for the purpose of calculating variables that are dependent on time if necessary. Day will be estimated as the first day (01) of the month (if month and year of partial date are available) or middle (July 1) of the year (if only year is available), unless otherwise noted. The imputations for partial dates are only for calculation purpose. Original date variables will not be modified. Listings will list dates as collected.

4.4. Study Days and Visits

For by-visit summaries, if there are multiple assessments at a postbaseline visit then the last non-missing assessment at that visit will be used for the summary (this includes scheduled and unscheduled assessments), except for triplicate ECG assessments (see Section 8.9 for further details).

Study visits are in Table 1. See the study protocol Table 2 to 4 for details.

Table 1: Study Visits

Study Period	**Screening & Run-in**		**Treatment Period (Visits 1 -10)**										**Follow -up**
Visit #	**S1**	**S2/3**	**V1** DoR	**V2**	**V3**	**V4**	**V5** Phone	**V6**	**V7**	**V8**	**V9**	**V10** EOT	**V11** EOS
Week	**-5**		**0**	**2**	**4**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**24**
Study Day	**-**		**1**	**15**	**29**	**43**	**50**	**57**	**71**	85	**99**	113	**169**

DoR=Day of Randomization; EOT=End of Treatment; EOS=End of Study.

'Last Assessment' may be derived for analysis purpose and is defined as the last observed postbaseline data during the treatment period. For patients who withdraw from the study early, their data at the early withdrawal visit will be excluded from the by-visit summaries but will be included in the Last Assessment summaries.

Study days are numbered relative to the first day of the IMP administration. The start of treatment (day 1) is defined as the date on which a patient takes the first dose of the IMP, as recorded on the case report form (CRF). Days will be numbered relative to treatment start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the first day of the IMP administration and day –1 being the day before the first day of the IMP administration).

5. STUDY POPULATION

5.1. General

The ITT analysis set (see Section 3.1) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and all patients. All data will be listed and sorted by treatment group and subject identifying number.

5.2. Patient Disposition

Data from patients screened, patients screened but not randomized, patients randomized to treatment in the study, patients randomized but not treated, patients in the safety analysis set, patients in the per-protocol analysis set, patients who completed the treatment period (week 16), patients who completed the study (see Section 2.1 for definition of study completion), and patients who did not complete treatment but were followed up until end of study will be summarized. Data from screen failures, patients who did not complete the treatment period and patients who did not complete the study will also be summarized by reason for withdrawal using descriptive statistics.

This summary will include all patients.

5.3. Demographics and Baseline Characteristics

The demographic data will be collected at the screening visit after the patient signs the informed consent form. Patient demographic data including age, age group (<65 years vs ≥65 years), gender, race, race group (white or other), ethnicity, baseline weight (kg), baseline weight group (<75 kg vs ≥75 kg), baseline height (cm), baseline body mass index (BMI; kg/m^2), and baseline BMI group (<30 vs ≥30) will be summarized using descriptive statistics for the ITT, safety and PP analysis sets.

Baseline characteristics including asthma history and ECG findings at screening will be summarized for the ITT analysis set using descriptive statistics. No inferential analyses will be performed.

Asthma history includes

- Months since asthma diagnosis
- The duration of asthma
- The number of inpatient hospitalization due to asthma over the past 12 months
- Months since most recent inpatient event
- The number of emergency department visit due to asthma over the past 12 months
- Months since most recent emergency department visit
- the number of times oral corticosteroids were prescribed for asthma in the last 18 months
- Months since last prescription of corticosteroids

The month will be calculated as (date of informed consent - the date of the event + 1)/30.44. Rules for handling partial dates are in Section 4.3.

5.4. Medical History

All medical history abnormalities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Patients are counted only once in each SOC and only once in each preferred term.

5.5. Prior Therapy and Medication

All prior medications or therapy will be coded using the World Health Organization Drug Dictionary of medical codes (WHO Drug). The incidence of prior medications or therapy will be summarized by therapeutic class and preferred term using descriptive statistics. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the administration of the first dose of the IMP.

5.6. Childbearing Potential and Methods of Contraception

Information related to reproductive system findings will be collected at the screening visit. Data will be listed.

5.7. Physical Examinations

Patients with at least 1 abnormal finding (overall) and abnormal findings for each category at the baseline will be summarized and listed.

5.8. Study Protocol Deviations

Data from patients with any important protocol deviations during the study will be summarized overall and for each category using descriptive statistics. All study protocol deviations will be listed.

6. EFFICACY ANALYSIS

6.1. General

The ITT analysis set (Section 3.1) will be used for all efficacy analyses unless otherwise noted. Summaries will be presented by treatment group. The mITT and per-protocol analysis sets (Section 3.4) will be used as supplementary analysis for the primary analysis. All efficacy related data will be listed using ITT analysis set unless otherwise specified.

The baseline for clinic visit variables will be the last observed value before the first dose of study drug.

The baseline for spirometry parameters and e-diary variables will be based on the daily average of the values over the 7 days preceding day of randomization.

6.1.1. Analysis Windows for E-diary Data

For the purpose of analysis, the analysis windows for the treatment period will be derived for data collected on e-diary and with hand-held spirometry daily if applicable.

Postbaseline monthly (4-week) analysis windows during the treatment period will be determined based on the actual dosing day as follows:

- Month 1/Weeks 1 to 4: from the day of 1st IMP administration to the day before 3rd IMP administration (visit 3/week 4 dosing);
- Month 2/Weeks 5 to 8: from the 3rd IMP administration (visit 3/week 4 dosing) to the day before the 5th IMP administration (visit 6/week 8);
  Note, Visit 5/Week 7 is a non-dosing visit.
- Month 3/Weeks 9 to 12: from the 5th IMP administration (visit 6/week 8) to the day before the 8th MP administration (visit 8/week 12);
- Month 4/Weeks 12 to 16: from the 8th IMP administration (visit 8/week 12) to the day of the EOT visit (visit 10/week 16);

Notes:

There will be no IMP administration at visit 10; for patients who withdraw from the study early, the end day for the last window will be the day before EOT/early termination (ET); a 4-week analysis window may contain <28, 28, or >28 days.

Postbaseline weekly analysis windows during the treatment period will be derived based on the study days as follows:

Week x: day (x-1)*7 + 1 to day x*7

Eg. Week 1 is study days 1 to 7; Week 2 is study days 8 to 14, etc.

A post-treatment analysis window will be from the day after the EOT visit to the day of the EOS visit (visit 11/week 24).

6.2. Primary Efficacy Endpoint and Analysis

6.2.1. Definition

The primary efficacy endpoint is the proportion of patients who experience loss of asthma control (LoAC) during the treatment period.

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

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

LoAC will be determined and recorded by investigator from study sites. A patient who meets criteria for LoAC will discontinue IMP, and resume or increase background asthma controller therapies, but will remain in the study. LoAC events will be treated by the investigator according to local standard of care.

6.2.2. Primary Efficacy Analysis

The primary analysis will compare rates of LoAC between treatment groups using logistic regression with fixed effect for treatment, age group (<65 years vs ≥65 years) and gender, as well as baseline FEV_1 and baseline weight as covariates. Patients who withdraw from the study before the week 16 or early terminated the study treatment due to lack of efficacy, LoAC, or an asthma-related adverse event will be analyzed as having experienced LoAC. Patients who withdraw from the study before the week 16 without LoAC or early terminated from the study treatment without experiencing LoAC during the patient's treatment period (Section 1.7) for other reasons will be analyzed as not experiencing LoAC. Asthma-related adverse events will be determined by blinded data reviews prior to the final database lock.

The treatment effect will be tested at a one-sided alpha of 0.1.

The primary analysis will be performed on the ITT analysis set. The rates of LoAC for each treatment group, confidence intervals, and p-value will be displayed.

Example SAS code for Logistic Regression

PROC GENMOD DATA =*name*;
CLASS TRTP AGEGR1 SEX;
MODEL AVALC = TRTP FEV1 WEIGHT AGEGR1 SEX / **DIST**=**BIN TYPE3**;
RUN;

Where AVALC denotes the responses with 'yes' for LoAC and 'no' for not having LoAC; TRTP denotes the planned treatment group; AGEGR1 denotes age group; in bold are the SAS key words.

6.2.3. Subgroup Analysis

Sub-group analyses will be performed on the primary endpoint and key secondary endpoints for gender, baseline BMI (<30 vs ≥30), baseline weight (<75 kg vs ≥75 kg) and age group (<65 years vs ≥65 years).

Sub-group analysis will be based on ITT and PP analysis sets.

6.2.4. Sensitivity Analysis for the Primary Efficacy Endpoint

As a supplementary analysis, the primary analysis will be repeated on mITT analysis set and the per-protocol analysis set as defined in Section 3.4. In addition, a sensitivity analysis will be performed using multiple imputations method, when there are more than 5% early discontinuations from the study before week 16 due to reasons other than lack of efficacy or asthma-related AEs in either treatment group.

6.2.4.1. Sensitivity Analysis Using Multiple Imputations

Patients who discontinued the treatment or the study before week 16 without LoAC due to lack of efficacy or asthma-related AEs will be considered as having experienced an LoAC, the same imputation method as used in the primary efficacy analysis.

For patients who discontinued the study before week 16 without LoAC for reasons other than lack of efficacy or due to asthma-related AEs, multiple imputations will be used from a Bernoulli distribution with the probability estimated from a logistic regression model from the observed LoAC data given the treatment group, sex, age group (<65 years vs ≥65 years), baseline FEV_1, and baseline weight. A total of 100 datasets will be imputed and each will be analyzed with the logistic regression model the way as for the primary analysis. The final estimates will be obtained using Rubin's method. The details are as follows:

Step 1: Estimate the probabilities for Bernoulli distribution

The SAS procedure in Section 6.2.2 will be used to obtain the probability estimates from a logistic regression model. The following statement will be added to SAS procedure:

ODS OUTUT ParameterEstimates=pest;

Estimates from PROC GENMOD along with patients' data will be used to calculate the probability, the p used for Bernoulli distribution, for each patient.

Observed data will be duplicated 100 times creating 100 sets of data. In each dataset, the SAS function **RAND**("**Bernoulli**", p) will be used to determine LoAC status (1=having LoAC, 0=not having LoAC) for patients with missing data due to reasons other than lack of efficacy or due to asthma-related AEs.

Step 2: Analysis

The 100 sets of data will be analyzed in a manner analogous to the analysis as described in Section 6.2.2 adding a by-statement for imputation to the SAS procedure.

The results from the 100 analyses will be combined using Rubin's formulae in the following SAS procedure.

PROC MIANALYZE DATA=diff;

MODELEFFECTS estimate;

STDERR stderr;

RUN;

6.3. Key Secondary Efficacy Endpoints and Analyses

The key secondary efficacy endpoints are listed in Section 1.2. Analyses will be based on the ITT analysis set.

6.3.1. Time from Randomization to LoAC During Treatment Period

The time (days) from randomization to LoAC during the treatment period is the interval from the randomization to the occurrence of the LoAC.

The observation for each patient is the interval from randomization to the occurrence of the LoAC, or censoring, whichever occurs earlier and an indicator whether or not the observation is for a LoAC case or censoring.

The observations are derived as:

1. Time to event or censoring: the date of censoring or the date of LoAC, whichever occurs earlier - the date of randomization + 1.
2. Indicator variable: 1 if a LoAC case is observed; 0 otherwise.

Patients who withdraw from the study before the week 16 or discontinue treatment due to lack of efficacy, LoAC, or an asthma-related adverse event will be analyzed as having experienced LoAC at the time of the withdrawal or treatment discontinuation.

Patients who withdraw from the study before week 16 without LoAC or early withdraw from treatment without LoAC during the treatment period (section 1.7) for other reasons will be analyzed as being right-censored at the time of withdrawal.

Patients who completed treatment without experiencing LoAC will be right-censored at the time of treatment completion.

The Kaplan-Meier (KM) method will be used to estimate and compare the distributions of time to LoAC between treatment groups. A one-sided log-rank test will be provided to compare the hazard ratio (TEV-48574/placebo) between the TEV-48574 and placebo groups.

Example SAS code for hazard ratio

ODS OUTPUT PARAMETERESTIMATES=*name*;
PROC PHREG DATA= *NAME*;
MODEL AVALN*CENSOR(**1**)= TRTPN/**RISKLIMITS**;
RUN;

Notes, for the hazard ratio of active/placebo, the TRTPN should have a value 2 for active and 1 for placebo.

Example SAS code for log-rank test

ODS OUTPUT HOMTESTS=*name* (**WHERE**=(**UPCASE**(**TEST**) = "**LOG-RANK**"));

PROC LIFETEST DATA=*name*;
TIME AVALN*CENSOR(**1**);
STRATA TRTP;
RUN;

Example SAS code for KM estimates

ODS OUTPUT PRODUCTLIMITESTIMATES=*name* QUARTILES=*name*
CENSOREDSUMMARY = *name*;

PROC LIFETEST DATA=*name* **OUTSURV**=*name* **TIMELIST**=**x TO y BY n** ;
TIME AVALN*CENSOR(**1**);
BY TRTP;
RUN;

Where AVALN denotes the time-to-event (days); CENSOR denotes censoring (1= censoring and 0=event); TRTP/TRTN denote the planned treatment group.

6.3.2. Asthma Control Questionnaire 6-Question Version (ACQ-6) at End of Treatment (EOT) and Throughout Study

The ACQ-6 is a validated asthma assessment tool that has been widely used. Six questions are self-assessments (completed by the patient). Each item on the ACQ-6 has a possible score ranging from 0 to 6, and the total score is the mean of all responses (See Appendix E of the study protocol). ACQ-6 will be administered at the sites at screening, run-in, all on-site visits during treatment period (visits 1, 2, 3, 4, 6, 7, 8, 9, and 10), and follow-up visit (visit 11).

The analysis will be based on ITT and PP analysis sets.

The changes from baseline in ACQ-6 total score at EOT will be analyzed using an analysis of covariance (ANCOVA) method. The model will include treatment as the fixed effect and baseline weight, age group (<65 years vs ≥65 years), gender, and baseline value of ACQ-6 total score as covariates. LS mean and SE for each treatment group, LS means and corresponding 95% confidence intervals for the treatment differences (TEV-48574 - placebo), and the associated p-values from the overall results for treatment comparisons.

For patients who did not complete the treatment period, data from the early termination (ET) visit will be used for the analysis. For patients who are lost-to-follow-up (no ET assessment) prior completion of the treatment period, the last assessment during the treatment period will be used for the analysis.

Example SAS code for ANCOVA

PROC MIXED DATA=<name>;

CLASS TRTP AGEGR1 SEX;

MODEL CHG= BASE TRTP WEIGHT AGEGR1 SEX /**S**;

LSMEANS TRTP /**DIFF=CONTROL** (“Placebo”) **CL ALPHA**=0.05;

ODS OUTPUT LSMEANS= <name> **DIFFS**= < name> ;

RUN;

Where TRTP denotes the planned treatment group; CHG denotes the change from baseline at EOT; BASE denotes the baseline ACQ-6 total score;

The changes from baseline in ACQ-6 total score **throughout the study** will be analyzed using the mixed model for repeated measures (MMRM) with treatment group, visit, treatment and visit interaction, and baseline value of ACQ-6 total score as fixed effects and patient as a random effect. The unstructured covariance structure (UN) will be used to model intra-subject correlation. LS mean and SE for each treatment group, LS means and corresponding 95% confidence intervals for the treatment differences (TEV-48574 - placebo), and the associated p-values from the overall results for treatment comparisons.

Notes, if UN dose not converge, compound symmetry (CS) will be used.
Data from visits 2 to 10 except visit 5 (phone contact, no data will be collected) will be included in the analysis model.
Per the ICE handling strategy, for patients who did not complete the treatment period, observations after the end of the treatment period will be discarded and treated as missing obseravtions.

The overall and by-visit results will be presented. The endpoint will be measured by the overall results. Descriptive statistics from each visit will be provided.

Example SAS codes for MMRM analysis:

PROC MIXED DATA=<name> **METHOD=REML**;

CLASS USUBJID TRTP AVISIT AGEGR1 SEX;

MODEL CHG=BASE TRTP WEIGHT AGEGR1 SEX AVISIT TRTP*AVISIT/**S;**

REPEATED AVISIT/ **SUB**=USUBJID **TYPE=UN**;

LSMEANS TRTP TRTP*AVISIT/ **DIFF CL** DDFM=KR **ALPHA=0.05**;

ODS OUTPUT LSMEANS= <name> **DIFFS**= < name> ;

RUN;

Where TRTP denotes the planned treatment group; AVISIT denotes the visits; BASE denotes the baseline ACQ-6 total score; CHG denotes the change from baseline at each visit.

6.3.3. Forced Expiratory Volume in First Second (FEV_1) (% Predicted, L) at EOT and Throughout Study

Spirometry will be performed both at the site and by hand-held spirometer. On-site spirometry will include full-flow volume loops (FVC, FEV_1, FEV_1/FVC, $FEF_{25\%-75\%}$ and PEF) and reversibility testing at all visits during treatment period except the phone visit. Hand-held spirometry (FEV_1, PEF) will be performed daily.

Analyses will be based on-site FEV_1.

The change from baseline in FEV_1 **at EOT** will be analysis using ANCOVA in a manner analogous to the analysis as described in Section 6.3.2 using the same algorithm for patients who did not complete the treatment period or patients who are lost-to-follow-up (no ET assessment) prior completion of the treatment period.

The changes from baseline in FEV_1 **throughout study** will be analyzed using analyzed using MMRM in a manner analogous to the analysis as described in Section 6.3.2. Per the ICE handling strategy, for patients who did not complete the treatment period, observations after the end of the treatment period will be discarded and treated as missing observations.

The baseline FEV_1 will be used in the analysis models.

6.3.4. Use of SABA Quick Relief Medication at EOT and Throughout Study

The number of inhalations/puffs of SABA/quick-relief inhaler will be recorded in the e-diary daily. Study sites will monitor rescue medication use during the study visits screening and run-in visit, all visits during treatment period, and follow-up visit. Study sites are also responsible for responding to asthma specific alert criteria related to SABA/quick-relief inhaler use.

Analysis windows throughout the study for during the treatment period and post-treatment (follow-up period) will be derived for each patient using algorithm detailed in Section 6.1.1.

The daily average of the inhalations/puffs of SABA/quick-relief inhaler in each monthly analysis window will be calculated using formula below:

$$\frac{\sum inhalations/puffs\ in\ an\ analysis\ window}{number\ of\ \ days\ \ in\ an\ analysis\ window}$$

The baseline daily average of use of SABAs will be calculated based on the data from 7 days preceding day of randomization similarly.

The change from baseline in the daily average of the uses of SABA quick relief medication at EOT will be analysis using ANCOCA in a manner analogous to the analysis as described in Section 6.3.2. For patients who did not complete the treatment period, the last analysis window during the treatment period will be used. For patients who are lost-to-follow-up (no ET assessment) prior completion of the treatment period, the last analysis window during the treatment period will be used for the analysis.

The change from baseline in the daily average of the use of SABA quick relief medication throughout study will be analyzed using MMRM in a manner analogous to the analysis as described in Section 6.3.2. Per the ICE handling strategy, for patients who did not complete the treatment period, observations after the end of the treatment period will be discarded and treated as missing observations.

The baseline daily average of use of SABAs will be included in the analysis models.

In additional, weekly analysis windows (weeks 1 to 8) will be derived for each patient using algorithm detailed in Section 6.1.1. The daily average of the inhalations/puffs of SABA/quick-relief inhaler in each weekly analysis window will be calculated similarly using formula above. The change from baseline in the daily average of the use of SABA quick relief medication during weeks 1 to 8 will be analyzed using MMRM similarly.

6.4. Other Secondary Efficacy Endpoints and Analyses

The other secondary efficacy endpoints are listed in Section 1.2. Analyses will be based on the ITT analysis set.

6.4.1. Proportion of Patients Who Have a CAE During Treatment Period

A clinical asthma exacerbation (CAE) during the treatment period CAE is defined as a worsening of asthma symptoms resulting in any of the following:

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

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

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

CAEs will be assessed at visits (screening and run-in, visits during treatment period, follow-up).

Proportion of patients who have a CAE during the treatment period will be analyzed in a manner analogous to the analysis for LoAC as described in Section 6.2.2. Similar approach for handling ICEs will be applied.

6.4.2. Time from Randomization to First CAE During Treatment Period

CAEs are a subset of LoAC events. Asthma exacerbation is defined as a worsening of asthma symptoms (examples are described below) resulting in any of the following:

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

CAEs will be assessed at screening and run-in visit, all visits during treatment period, and follow-up visit.

Time from randomization to first CAE during the treatment period will be analyzed in a manner analogous to the analysis of the time to LoAC as described in Section 6.3.1. Patients who early terminated from the study or treatment due to lack of efficacy or asthma-related AEs will be also treated as CAE. Patients who withdraw from the study before week 16 without LoAC or early withdraw from treatment without LoAC during the treatment period for other reasons will be analyzed as being right-censored at the time of withdrawal. Patients without CAE will be right-censored at the time of treatment completion.

6.4.3. Number of Nighttime Awakenings Due to Asthma During Treatment Period

Patients will record nighttime awakenings due to asthma in the e-diary daily. Sites will check the records of nighttime awakenings during the all study visits (screening and run-in), treatment period and follow-up visit.

Monthly analysis windows during the treatment period will be derived for each patient using algorithm detailed in Section 6.1.1. The monthly number of nighttime awakenings due to asthma during the treatment period will be calculated and normalized to 28 using the formula below.

$$\frac{\sum days\ nighttime\ awakenings\ during\ an\ analysis\ window}{Days\ with\ assessments\ recorded\ in\ the\ eDiary\ during\ an\ analysis\ window} \times 28$$

The baseline will be calculated based on the data from 7 days preceding day of randomization and be normalized to 28 days similarly.

The change from baseline in the monthly numbers of nighttime awakenings due to asthma during treatment period will be analyzed using MMRM in a manner analogous to the analysis as described in Section 6.3.2. Baseline monthly number of nighttime awakenings due to asthma will be included in the analysis model.

In additional, weekly analysis windows (weeks 1 to 8) will be derived for each patient using algorithm detailed in Section 6.1.1. The weekly number of nighttime awakenings due to asthma during weeks 1 to 8 will be calculated using the formula below:

$$\frac{\sum days\ nighttime\ awakenings\ during\ an\ analysis\ window}{Days\ with\ assessments\ recorded\ in\ the\ eDiary\ during\ an\ analysis\ window} \times 7$$

The baseline will be calculated based on the data from 7 days preceding day of randomization similarly. The change from baseline in the weekly numbers of nighttime awakenings due to asthma during weeks 1 to 8 will be analyzed using MMRM similarly. Per the ICE handling strategy, for patients who did not complete the treatment period, observations after the end of the treatment period will be discarded and treated as missing observations.

6.4.4. Percent Decrease in ICS Dose During Treatment Period

Inhaled corticosteroid (ICS) use will be recorded as one of asthma medications in the prior and concomitant medication data on the CRF.

Monthly analysis windows during the treatment period will be derived for each patient using algorithm detailed in Section 6.1.1. The monthly ICS usage in an analysis window will be the summation of reported usages in the analysis window.

The baseline will be the summation of reported usage from 28 days preceding day of randomization.

The percent decrease in ICS usage in an analysis window will be calculated using the formula below:

$$\frac{baseline\ value - postbaseline\ value}{baseline\ value} \times 100\%$$

The percent decreases and changes from baseline in monthly ICS usage during the treatment period will be analyzed using MMRM in a manner analogous to the analysis as described in Section 6.3.2. Baseline daily ICS usage will be used in the analysis model.

In additional, weekly analysis windows (weeks 1 to 8) will be derived for each patient using algorithm detailed in Section 6.1.1. The weekly ICS usage in each weekly analysis window will be the summation of reported usages in the analysis window. The baseline will be the summation

of reported usage from 7 days preceding day of randomization. The percent decrease in ICS usage in a weekly analysis window will be calculated similarly using formulas above. The percent decreases and changes from baseline in monthly ICS usage during weeks 1 to 8 will be analyzed using MMRM similarly. Per the ICE handling strategy, for patients who did not complete the treatment period, observations after the end of the treatment period will be discarded and treated as missing observations.

6.4.5. Other Lung Function Parameters as Assessed by Hand-Held Spirometry at End of Treatment and Throughout the Study

Spirometry will be performed both at the site and by hand-held spirometer.

On-site spirometry will include full-flow volume loops (FVC, FEV_1, FEV_1/FVC, $FEF_{25\%-75\%}$ and PEF) and reversibility testing at visit 1 (DoR), visit 3, visit 6, visit 8, and visit 10 during the treatment period. Changes from baseline in these parameters at EOT and throughout the study will be analyzed in a manner analogous to the analysis as for FEV_1 described in Section 6.3.3.

Hand-held spirometry (FEV_1, PEF) will be performed daily. Monthly analysis windows during the treatment period and post-treatment (follow-up period) will be derived for each patient using algorithm detailed in Section 6.1.1. The monthly average of FEV_1 and PEF during each analysis window will be calculated using the formula below:

$$\frac{\sum an\ efficacy\ variable\ during\ an\ analysis\ window}{Number\ of\ Days\ in\ the\ analysis\ window}$$

The baseline will be calculated based on the data from 28 days preceding day of randomization similarly.

The change from baseline in the monthly averages of hand-held spirometry FEV_1 and PEF values at EOT will be analysis using ANCOVA in a manner analogous to the analysis as described in Section 6.3.2. For patients who did not complete the treatment period, the last analysis window during the treatment period will be used. For patients who are lost-to-follow-up (no ET assessment) prior completion of the treatment period, the last analysis window during the treatment period will be used for the analysis.

The changes from baseline in monthly averages of hand-held spirometry FEV_1 and PEF values throughout study will be analyzed using analyzed using MMRM in a manner analogous to the analysis as described in Section 6.3.2. The corresponding baseline value will be included in the analysis models. Per the ICE handling strategy, for patients who did not complete the treatment period, observations after the end of the treatment period will be discarded and treated as missing observations.

In additional, weekly analysis windows (weeks 1 to 8) will be derived for each patient using algorithm detailed in Section 6.1.1. The weekly average of FEV_1 and PEF during each analysis window will be calculated similarly using the formula above. The baseline will be the summation of reported usage from 7 days preceding day of randomization. The changes from baseline in weekly averages of hand-held spirometry FEV_1 and PEF values during week 1 to 8 will be analyzed using analyzed using MMRM similarly.

6.4.6. Fractional Exhaled Nitric Oxide Throughout the Study

The concentration of nitric oxide in exhaled breath (FeNO) will be measured at screening, run-in, all on-site visits during treatment period (visits 1, 2, 3, 4, 6, 7, 8, 9, and 10), and follow-up visit (visit 11).

The changes from baseline in FeNO **throughout study** will be analyzed using analyzed using MMRM in a manner analogous to the analysis as described in Section 6.3.2. The baseline FeNo will be used in the analysis model. Per the ICE handling strategy, for patients who did not complete the treatment period, observations after the end of the treatment period will be discarded and treated as missing observations.

7. MULTIPLE COMPARISONS AND MULTIPLICITY

As there are only 2 treatment groups and one primary analysis test in this study, no multiplicity correction is necessary. Secondary endpoints will be considered as hypothesis-generating.

8. SAFETY ANALYSIS

8.1. General

The safety analysis set (Section 3.3) will be used for all safety analyses. Summaries will be presented using descriptive statistics by treatment group as actually received unless otherwise stated. All data will be listed using ITT analysis set unless otherwise specified.

8.2. Duration of Exposure to Study Drug

The patients will receive the IMP loading dose on the day of randomization (visit 1) and the subsequent corresponding IMP maintenance dose every 2 weeks (visits 2 to 4 and visits 6 to 9) for a total of 8 doses ([redacted]).

Duration of the treatment period (days), the number of doses received, and reasons for IMP not administrated (adverse event or other) will be summarized using descriptive statistics.

Duration of the treatment period (days) for a patient is defined as the number of days a patient is in the treatment period and calculated as the date of last IMP administration – the date of first IMP administration + 14.

IMP administration, IMP accountability data, and medical device malfunction data will be listed using safety analysis set.

8.3. Adverse Events

Adverse events will be recorded from time informed consent is obtained through the end of study participation.

All adverse events will be coded using MedDRA. Each patient will be counted only once in each preferred term or SOC category for the analyses of safety. Summaries will include treatment-emergent adverse events which are defined as adverse events occurring at or after the first dose of the IMP through the end of the follow-up visit. Listings will include all adverse events recorded.

Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (defined as related or with missing relationship) (overall and by severity), adverse events determined by the investigator to be related to the medical device, or the study inhaler (defined as related or with missing relationship), serious adverse events, and adverse events causing drug withdrawal or discontinuation from the study. Adverse events with the missing flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non-serious adverse events.

Summaries for clinical asthma exacerbation related adverse events, loss of asthma control related adverse events, injection site reaction adverse events, protocol-defined adverse events of special interest (PDAESI), PDAESI require completion of suspected anaphylaxis will also be presented.

Listings for deaths, serious adverse events, adverse events leading to drug withdrawn or the study discontinuation, clinical asthma exacerbation related adverse events, loss of asthma control

related adverse events, injection site reaction adverse events, PDAESI, and PDAESI require completion of suspected anaphylaxis, adverse event required concomitant or additional treatment will be presented. In addition, listings for MedDRA dictionary terms for adverse event descriptions and adverse event preferred terms by patient number and treatment group will be presented.

Adverse events for patients who did not meet screening criteria will be listed.

In additional, adverse events and serious adverse events occurred during the 10 weeks period after the last dose of IMP will be summarized using descriptive statistics. These adverse events will be presented in a patient listing as well. Injection Site Assessments

Local tolerability assessments will be performed after each administration of IMP (visits 1 to 4 and visits 6 to 9) and include administration site findings and pain. Administration site findings (erythema, ecchymosis, induration, tenderness, warmth, and swelling) will be assessed using the scales provided in Table 2. Pain at the administration site will be reported using 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?"

Table 2: Administration Site Finding Severity Assessment

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

The injection site assessments (erythema, ecchymosis, induration, tenderness, warmth, and swelling) at each visit will be summarized using descriptive statistics. For NRS-11 scale, the worst pain score overall and the pain score at each visit will be summarized descriptively. The data will be listed using safety analysis set.

8.4. Hypersensitivity/Anaphylaxis

The event of anaphylaxis is considered as a PDAESI. The information about all suspected anaphylaxis and hypersensitivity events will be recorded on the Suspected Anaphylaxis CRF. PDAESI will be summaries (Section 8.3).

Suspected anaphylaxis data will be listed.

8.5. Deaths

If any patient dies during the study, all relevant information will be discussed in the patient narrative included in the clinical study report.

8.6. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up) of the study protocol. Clinical laboratory tests will be performed using the central laboratory.

Laboratory test results will be presented in standard international (SI) units in summaries. Laboratory values and changes from baseline to each visit and Last Assessment will be summarized using descriptive statistics. Shifts (below [low], within [normal], and above [high] the normal range) from baseline to each postbaseline visit and the Last Assessment will be summarized using patient counts. Baseline is defined as the last observed data before the administration of the first dose of the IMP (also see Section 4.2).

The potentially clinically significant abnormal values will be derived using criteria specified in Table 3 based on all postbaseline values (including scheduled, unscheduled, and withdrawal visits). The overall incidence of potentially clinically significant abnormal values will be summarized for laboratory variables using descriptive statistics by treatment group. Listings for patients who have potentially clinically significant abnormal laboratory data will be presented.

Table 3: Criteria for Potentially Clinically Significant Laboratory Values

Test	Criterion value
Serum chemistry	
Alanine aminotransferase (ALT)	≥3x ULN
Aspartate aminotransferase (AST)	≥3x ULN
Alkaline phosphatase (ALP)	≥3x ULN
Gamma-glutamyl transpeptidase (GGT)	≥3x ULN
Lactate dehydrogenase (LDH)	≥3x ULN
Blood urea nitrogen (BUN)	≥10.71 mmol/L
Creatinine	≥177 μmol/L
Bilirubin (total)	≥34.2 μmol/L
Hematology	

Test		Criterion value
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L
	Women	≤95 g/L
WBC counts		≤3 x 10^9/L ≥20 x 10^9/L
Eosinophils		≥10%
Absolute neutrophil count (ANC)		≤1 x 10^9/L
Platelet counts		≤75 x 10^9/L ≥700 x 10^9/L
Urinalysis		
Hemoglobin		≥2 unit increase from baseline
Glucose		≥2 unit increase from baseline
Ketones		≥2 unit increase from baseline
Total protein		≥2 unit increase from baseline

ULN=upper limit of normal range; WBC=white blood cell

8.6.1. Other Clinical Laboratory Tests

At screening, patients will be tested for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (HCV), human immunodeficiency virus (HIV) types 1 or 2, and Tuberculosis test.

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

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

At screening, women who have been amenorrheic for at least 1 year without an alternative medical cause will have a serum follicle stimulating hormone (FSH) assessment to confirm postmenopausal status.

Other clinical laboratory tests results will be listed.

8.6.2. Laboratory Values Meeting Hy's Law Criteria

All occurrences of possible drug-induced liver injury that meet Hy's law criteria as defined in the Section 7.1.5.1 of the study protocol will be included in serious adverse events reporting.

8.7. Physical Examinations

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

Abnormal physical examination findings will be listed and summarized descriptively.

Height and weight will be obtained at the at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up) of the study protocol. Data will be summarized and listed with vital signs data.

8.8. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 2 (screening and run-in), Table 3 (treatment period), and Table 4 (follow-up) of the study protocol. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2 of the protocol.

Vital signs (including weight) values and changes from baseline to each visit and the Last Assessment will be summarized using descriptive statistics. The incidence of potentially clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics. Baseline is defined as the last observed data before the administration of the first dose of the IMP (also see Section 4.2).

Table 4 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column. The potentially clinically significant abnormal vital signs values will include all postbaseline values (including scheduled, unscheduled, and early withdrawal visits) for the summaries.

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15 bpm
	≤50 bpm	Decrease of ≥15 bpm
Systolic blood pressure	≥180 mm Hg	Increase of ≥20 mm Hg
	≤90 mm Hg	Decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15 mm Hg
	≤50 mm Hg	Decrease of ≥15 mm Hg

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Temperature	≥38.3°C	Change of ≥1.1°C

Bpm=beats per minute

Height will be measured at screening visit, and data will be listed in the vital sign listing.

8.9. Electrocardiography

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

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

- abnormal and not clinically significant
- abnormal and clinically significant

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

At DoR visit, triplicate measurements are required, each ECG will be taken within 1 to 5 minutes of the previous one. For analysis purpose, the mean of recorded results from the 3 measurements will be calculated and used for the analysis.

Baseline is defined as the last observed data before the administration of the first dose of the IMP. If the last observed data is at DoR visit, the mean of the 3 measurements will be used as the baseline ECG results and the worst value of the 3 recorded findings will be used as the baseline ECG finding.

ECG variable results and changes from baseline to each visit and the Last Assessment will be summarized using descriptive statistics.

Baseline ECG findings and shifts (normal, abnormal not clinically significant, and abnormal clinically significant) from baseline to each visit, overall (worst value for a patient), and the Last Assessment will be summarized using patient counts.

8.10. Concomitant Medications or Therapies

Concomitant medications, treatments, or procedures will be collected up to the end of study.

All concomitant medications will be coded using the WHO Drug. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. The concomitant medications will include all medications taken after administration of the first IMP.

Asthma medications will be summarized by the medication class separately.

9. TOLERABILITY VARIABLES AND ANALYSIS

Number (%) of patients who did not complete the study due to adverse events will be summarized descriptively.

10. PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) ANALYSIS

Pharmacokinetic serum concentration results for TEV-48574 will be tabulated descriptively and listed at each planned sampling time point using pharmacokinetic analysis set.

PK/PD analyses are outside of the scope of this SAP.

11. BIOMARKER ANALYSIS

Biomarker analysis is outside of the scope of this SAP.

Listing of patients' biomarker data may be provided if applicable.

12. IMMUNOGENICITY ANALYSIS

Immunogenicity analyses are outside of the scope of this SAP.

Listing(s) of patients with positive ADA sample(s) and patient ADA status will be provided if applicable.

13. PLANNED INTERIM ANALYSIS

An unblinded interim analysis is planned after the first 40-52 randomized patients have completed the treatment period, experienced LoAC, or withdrawn from the study completely. The main purposes of the interim analysis include a sample size re-assessment and a futility analysis, which will be described in sections 13.1 and 13.2 below.

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

13.1. Sample Size Re-Assessment

The assumed LoAC event rate in the placebo group is 0.270. If the actual placebo event rate is lower than expected, the study will be underpowered to detect a 60% reduction in event rate. At the interim analysis, if the observed placebo event rate is lower than expected, and the observed treatment effect is at least a 40% reduction (event rate ratio ≤0.6), the sample size may be increased by up to 50 additional randomized patients, from the initially planned 124 to up to 174. This procedure corresponds to a Promising Zone methodology and does not increase the Type I error rate (Mehta and Pocock 2011). Using an exhaustive enumeration of all possible trial outcomes, it is verified that the type I error rate is preserved when the interim unblinded sample size re-assessment is implemented:

Table 5: Calculated Type 1 Error Rates with or without Sample Size Re-assessment

True Placebo Event Rate	Fixed Sample Size Design	Adaptive Sample Size Design
0.12	10.5%	9.5%
0.15	10.3%	9.7%
0.18	10.3%	10.0%
0.21	10.4%	10.2%
0.24	10.2%	10.1%
0.27	10.1%	10.0%
0.30	10.3%	10.3%
0.33	10.6%	10.6%
0.36	10.7%	10.7%
0.39	10.3%	10.3%
0.42	9.7%	9.7%
0.45	9.2%	9.2%

13.2. Futility Analysis

The interim futility analysis comprises a statistical comparison between treatment group versus placebo in LoAC rate using logistic regression among the randomized patients who have completed the treatment period, experienced LoAC, or withdrawn from the study completely at time of the interim analysis. The logistic regression model will include fixed effect for treatment, age group (<65 years vs ≥65 years) and gender, as well as baseline FEV_1 and baseline weight as covariates. A one-sided p-value above 0.5 will be declared as treatment efficacy futility, which could potentially result in early termination of the trial. According to simulation analyses, this cutoff value yields a correct early termination rates under the null hypothesis of 0.43 (40 patients) and 0.44 (52 patients) and controls incorrect early termination rate under the alternative hypothesis at approximately and 0.06 (40 patients) and 0.04 (52 patients). The following table provides the correct early termination rates (under the alternative hypothesis) and the incorrect early termination rates (under the null hypothesis) at different interim analysis time points and using different p-value cut-offs, calibrated through simulations. The placebo LoAC rate is assumed to be 0.27.

Table 6: Correct and Incorrect Early Termination Rates

Interim Analysis Sample Size (Total)	P-Value Cut-Off	Correct Early Termination Rate	Incorrect Early Termination Rate
20	>0.5	0.40	0.12
20	>0.33*	0.60	0.25
30	>0.5	0.42	0.08
30	>0.33	0.58	0.18
40	>0.5	0.43	0.06
40	>0.33	0.57	0.13
52	>0.5	0.44	0.04
52	>0.33	0.56	0.09

*0.33 cut-off shown for comparison purposes only; the actual futility cut-off is $p > 0.5$

14. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

15. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

None.

16. REFERENCES

1. Mallinckrodt C. Choosing primary estimands and analyses. In: Preventing and treating missing data in longitudinal clinical trials: A practical guide. New York: Cambridge University Press, 2013;103-10.
2. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda, F et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-66.
3. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med 2018;378(26):2486-2496.
4. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med 2011;30(28):3267-84.