Statistical Analysis Plan

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

SAP Approval Date: 22 June 2022

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Efficacy and Safety Study (Phase 2)

IND number: 138687; **EudraCT number: Not applicable**

Approval Date: 22 June 2022

Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **TV53275-AS-20033**

Study Title: **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**

Statistical Analysis Plan for:

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

Amendment: 0

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Approver: [redacted] **Date**
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Executed signature pages are maintained separately within the Trial Master File

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACQ-6	Asthma Control Questionnaire 6-question version
ACT	Asthma Control Questionnaire
ADA	antidrug antibodies
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AQLQ(S)	Standardized Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
BMI	body mass index
CAE	clinical asthma exacerbation
CRF	case report form
CI	Confidence interval
COVID-19	coronavirus disease 2019
CS	compound symmetry
CV	coefficient of variation
DoR	Day of randomization
e-diary	electronic diary
ECG	electrocardiogram/electrocardiography
eMDPI	electronic multidose dry powder inhaler
EoTV	end of treatment visit
PEF	Morning peak expiratory flow
FEV_1	forced expiratory volume in the first second
FSH	follicle stimulating hormone
FVC	forced vital capacity
HBsAg	hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HIV	human immunodeficiency virus
HCV	hepatitis C virus
ICE	Inter-current events
ICS	inhaled corticosteroid
IMP	investigational medicinal product
ITT	intent-to-treat

Abbreviation	Term
KM	Kaplan-Meier
LABA	long-acting β_2 agonist
LS	least square
MAR	a missing at random
MDPI	multidose dry powder inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputations
mITT	modified intent-to-treat
MCMC	Monte Carlo Markov Chain
MMRM	mixed model for repeated measures
MNAR	missing not at random
NRS	numerical response scale
PEF	peak expiratory flow
PDAESI	protocol-defined adverse events of special interest
PP	per-protocol
R&D	Research and Development
RTSM	Trial Supply Management
SAP	statistical analysis plan
sc	subcutaneous(ly)
SD	standard deviation
SE	standard error
[redacted]	[redacted]
SI	standard international
[redacted]	[redacted]
SOC	system organ class
SOP	standard operating procedure
ULN	upper limit of normal
UN	unstructured covariance
V	visit
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 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), and was written in accordance with GSD_SOP_702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol amendment 01 (Approval Date: 18 November 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.

When the study is terminated early due to futility at interim analysis or due to sponssor's strategic decision, the planned analyses may be simplified to present the necessary information for an abbreviated clinical study report (CSR). The Beyesian analysis for the primary efficacy endpoint and the statistical analyses for some of the secondary efficacy endpoints may not be conducted for the abbreviated CSR. The analysis plan will be followed where applicable.

1. STUDY ENDPOINTS

1.1. 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

1.2. [redacted]

[redacted]

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

[redacted]	[redacted]
	[redacted]

[redacted]	[redacted]

1.3. Estimand for Primary Efficacy Endpoint

1.3.1. Primary Estimand

An estimand, in general, includes 5 inter-related attributes – treatment condition, 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.

Treatment condition: TEV-53275 administered subcutaneously (sc) at doses of 600 mg or 1200 mg versus placebo as an add-on therapy to the patient's current stable isthma maintenance therapy.

Population of interest: Adult patients with moderate to severe asthma with an eosinophilic phenotype on asthma maintenance therapy

The primary 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 modified intent-to-treat (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, improvement in FEV_1 would be expected as rapidly as within 1 week for placebo patients placed on ICS (Szefler et al 1999). It has also been shown that patients placed on ICS with long acting beta-agonists can have significant improvement in serial FEV_1 measurements on the same day (Corren et al 2007, Pearlman et al 1999).In addition, improvement in FEV_1 can occur 1 day after treatment with ICS (Kerwin et al 2019). The inclusion of data after a patient receives additional maintenance 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 moderate or severe COVID-19 infections or any serious AE due to COVID-19: Since COVID-19 is a known respiratory disease which can adversely affect lung function, 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.

Missing data, including those as a result of ICE handling strategies, will be handled using a multiple imputation method in the Bayesian analysis, assuming a missing at random (MAR)mechanism. 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:

Posterior probability (TEV-53275 dose vs placebo >0).

As a sensitivity analysis, the reference-based multiple imputation method will be used as a missing data handling method to assess the robustness of the results under a missing not at random (MNAR) mechanism.

1.3.2. Secondary Estimand

A supplementary analysis will be conducted assessing a secondary estimand in the same treatment condition and patient population. The secondary estimand will assess the primary efficacy endpoint due to the initially randomized treatment regardless of actual treatments taken or any other occurrence of ICEs in the mITT population. The supplementary analysis will repeat the primary analysis including all observations retrieved after the occurrences of ICEs in the analysis as a means of handling the ICEs. Missing data will be handled in the same manner.

More details will be in sections Section 6.2.2 and Section 6.2.4.

2. STUDY DESIGN

2.1. General 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 (see Appendix F in the study protocol):

- 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/end of treatment visit (EoTV)]. 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

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.

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

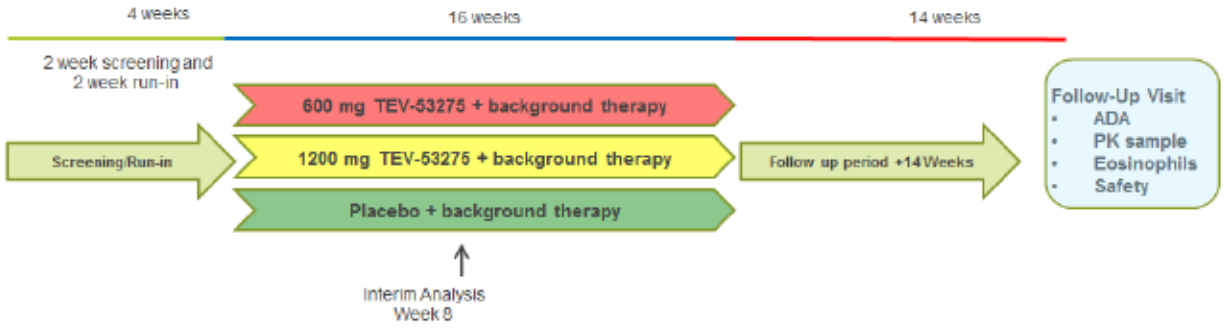
The randomization visit (V3) will occur after a minimum of 14±2 days after entering the run-in period. At this visit the patient's diary data should be reviewed prior to formal lung function testing, laboratory testing and the various questionnaires to ensure compliance with diary entries and to determine 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

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 of the study protocol.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



ADA=anti-drug antibody; PK=pharmacokinetics.

2.2. Randomization and Blinding

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

Patients who meet all of the randomization criteria will be randomly assigned to 1 of 2 treatment groups or placebo in a 1:1:1 ratio, stratified based on maintenance therapy and screening eosinophil count:

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

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). The stratifications are:

- ICS alone (medium or high dose) or low dose ICS/LABA and eosinophil count<400 cells/uL
- ICS alone (medium or high dose) or low dose ICS/LABA and eosinophil count≥400 cells/uL

- medium or high dose ICS/LABA and eosinophil count<400 cells/uL
- medium or high dose ICS/LABA and eosinophil count≥400 cells/uL

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.

2.3. Data Monitoring Committee

There is no independent Data Monitoring Committee to review ongoing safety data.

Data review committees will be set up to review the planned interim analysis results, the process for which will be described in a separate document (the interim analysis charter).

2.4. 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]

With the same base assumptions (treatment effect=0.1L and SD=0.35L), the comparison between the 1200 mg treatment group vs placebo using a two-sample t-test at one-sided alpha of

2 CinqAir® is a registered to Teva Pharmaceutical Industries Ltd.

15% would provide a study power of 80.6%. The statistical software East version 6.5 was used for the calculation.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

An 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 safety data (blinded data) and early efficacy signal (unblinded data). 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.

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

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 a partial dose of IMP.

The mITT analysis set will serve as the primary analysis set for efficacy analyses. In the mITT analysis set, patients will be assigned to the treatment they were randomized, regardless of which treatment they actually received.

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

The actual treatment group assignment for safety analyses is based on the actual TEV-53275 dose received by the patient:

- The patient is assigned to TEV-53275 1200 mg treatment group, if the patient received TEV-53275, and the recorded dose was > 750 mg; The patient is assigned to TEV-53275 600 mg treatment group, if the patient received TEV-53275, but the recorded dose was ≤ 750 mg;
- The patient is assigned to placebo treatment group, if patient only received placebo.

3.4. 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 determined to impact efficacy assessments. These important protocol deviations will be determined before unblinding for the final analysis and will be documented separately. The list will include, but are not limited to, 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.

3.5. 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.

3.6. 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.

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-53275 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 specified, baseline value is defined as the last observed value before the administration of 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

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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.

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 8.10 for further details).

Study visits are in Table 2 of the study protocol.

'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

Study population summaries will be based on the ITT analysis set (see Section 3.1), 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 ITT, mITT, safety and PP analysis sets and other analysis sets (Section 3), and patients who complete the double-blind treatment period and complete the study (see Section 2.1 for definitions of the double-blind treatment period and end of study) will be summarized. Data from screen failures, patients who did not complete the double-blind 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 height (cm), baseline body mass index (BMI; kg/m^2), and baseline BMI group (<30 vs ≥30), randomization stratification variables per IRT and per CRF: prior therapy (medium- and high-dose ICS alone and low-dose ICS/LABA vs. medium- and high-dose ICS/LABA), and absolute eosinophil count (300 to <400 cells/μL, or ≥400 cells/μL) will be summarized using descriptive statistics for the ITT, safety, mITT, and PP analysis sets. In addition, baseline characteristics including asthma history and EGC findings at screening will be summarized for the ITT and safety analysis sets using descriptive statistics. No inferential analyses will be performed.

Asthma history includes

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

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. 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 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.

Confidence/credible intervals will be provided at the two-sided 95% confidence level.

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

For the purpose of the efficacy analysis, the time point of "endpoint" will be derived and is defined as the last assessment during 16 weeks for a patient.

6.1.1. Analysis Windows and Baseline for Data Collected Daily

For data collected on e-diary and hand-held spirometry daily, the weekly analysis windows (week 1 to week 16) 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 from days 1 to 7; Week 12 is days 78 to 84, etc.

Notes: Day 1 is the IMP administration date; for patients who withdraw from the study early, the last window may be less than 7 days.

The daily average of the efficacy data with each weekly analysis window will be calculated based on non-missing e-diary as follow:

$$\frac{\sum an\ efficacy\ variable\ during\ an\ analysis\ window}{Number\ of\ days\ with\ nonmissing\ data\ in\ the\ analysis\ window} \quad [1]$$

Baseline daily average for data collected daily will be calculated using the same formula above based on non-missing data.

6.1.2. Analysis Windows for Pulmonary Function Data Collected on Site

For pulmonary function tests conducted on site at study visits, the following analysis windows will be applied to include observations in deriving the analysis visits. When multiple eligible values are available in the same analysis window, the scheduled value, if available, will be used; and if the scheduled value is not available, then the value that is closest to the target date will be used.

Table 1: Analysis Windows for On-Site Pulmonary Function Test Parameters

Analysis Visit	Target Study Day	Analysis Window
Visit 4/Day 4	4	Day 1 post-dose to Day 7
Visit 5/Week 2	15	Day 8 to Day 21
Visit 6/Week 4	29	Day 22 to Day 42
Visit 7/Week 8	57	Day 43 to Day 70
Visit 8/Week 12	85	Day 71 to Day 99
Visit 9/Week 16	113	Day 99 to Day 126

6.2. Primary Efficacy Endpoint and Analysis

6.2.1. Definition

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

6.2.2. Primary Efficacy Analysis

[redacted]

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 Section 1.3. In the primary analysis, the missing data will be handled using multiple imputations with 100 imputed datasets.

[redacted]

[redacted]

[redacted]

6.2.3. Subgroup Analysis

Sub-group analyses will be performed on the primary endpoint and selected secondary endpoints for

- gender (male vs female)
- race (white vs other races)
- age group (<65 years vs ≥65 years)
- Randomization factor per IRT: eosinophil count (<400 cells/uL vs. ≥400 cells/uL)Randomization factor per IRT: prior asthma maintenance therapy (ICS alone or low dose ICS/LABA vs. medium and high dose ICS/LABA)

The selected secondary endpoints are

- overall weekly well-controlled asthma status defined by the asthma control composite score and weekly asthma control status (Yes versus No) over 12 weeks from week 1 through 12 and over 16 weeks 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

[redacted] For continuous endpoints, the same MMRM analysis as described in Section 6.3.2 will be applied, by each subgroup variable. For the binary endpoint of weekly asthma control status, the analysis described in Section 6.3.1 will be applied, by each subgroup variable. The final estimated treatment differences will be presented together with the 2-sided 95% CI and p-values by the subgroup variables using the Forest Plot.

6.2.4. Sensitivity/Supportive Analysis for the Primary Efficacy Endpoint

6.2.4.1. Sensitivity Analyses

As sensitivity analyses, the primary efficacy analysis and supportive analysis will be repeated using the PP population and ITT population if the difference between mITT and ITT is more than 5%.

In order to assess the robustness of the results under a missing not at random (MNAR) mechanism, another sensitivity analysis using the reference-based multiple imputation method as the missing data handling method will be conducted. The reference-based multiple imputations method (Mallinckrodt et al 2017) imputes missing data based on regression models from the placebo-treated patient data, representing a missing not at random (MNAR) mechanism. A sample SAS code for the reference-based multiple imoutations is given below:

[redacted]

6.2.4.2. Supportive Analysis

The frequentist approach will be used for analyzing the primary efficacy endpoint as a supportive analysis. The primary estimand with respect to treatment condition, study population, efficacy endpoint and ICEs along with the ICE handling strategies will be applied. Both the multiple imutation method and the reference-based multiple imputations method will be used to handle

the missing data. The population-level summary statistics will be the combined least squares means in the treatment groups and the combined least squares mean treatment differences derived from analyses of the multiply imputed datasets using 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 absolute eosinophil count at screening), 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 (UN) covariance structure will first be used; however, In the case UN covariance structure does not converge, the compound symmetry (CS) covariance structure will be used.

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.

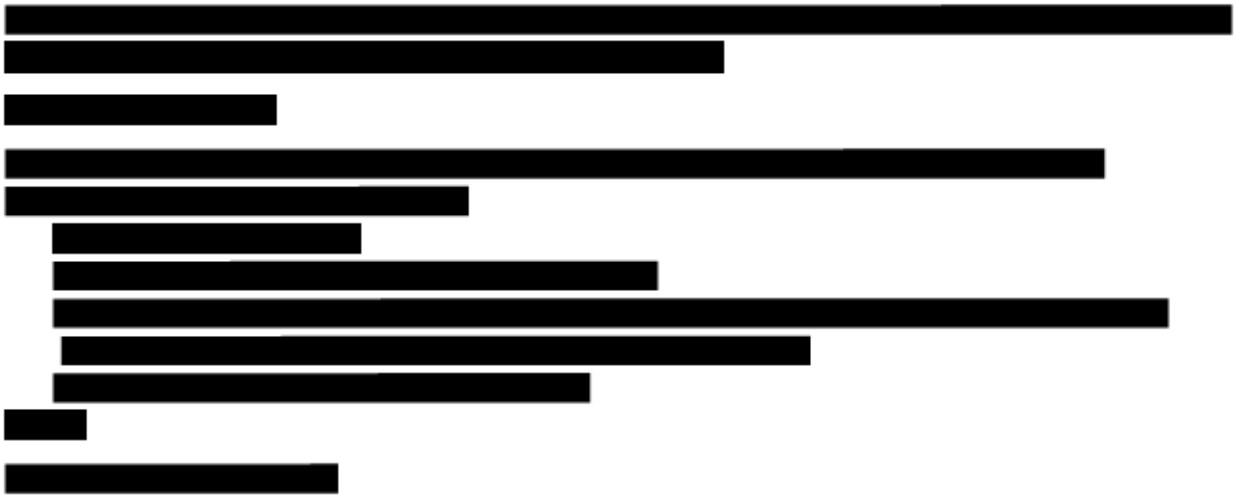
MI steps and SAS example codes are as follows:

Step 1: Following observations will be considered as "analysis dropouts" and be excluded from the analysis (set to missing)

- observations after the use of asthma maintenance medications (regardless of availability of data obtained afterwards);
- observations that occurred after the diagnosis of COVID-19 infections.

For all early dropouts and "analysis dropouts", regardless of assigned treatment arm, missing imputation will be based on data from the placebo-treated patients (eg, reference-based imputation).

Step 2: Missing data will be imputed with 100 imputations using multiple imputation and reference-based multiple imputations. The same sample codes for imputations for the Bayesian analysis will be used (see Section 6.2.2 and Section 6.2.4.1, respectively).



Where TRTP denotes the planned treatment group; AVISIT denotes visit/week; RSTRATA the randomization stratification; BASE denotes the baseline FEV_1; CHG_i denotes the change from baseline at each visit based on imputed data.

Step 4:The results from the 100 analyses from Step 3 will be combined using Rubin's formulae. The least square (LS) mean estimates for the mean change from baseline to each time point, as well as the difference of the estimates between the active and placebo group, with the corresponding SE, p-value and associated 95% CI will be provided.

[redacted]

6.2.4.3. Supplementary Analysis

A supplementary analysis using all data, including retrieved observations following alternative asthma medication use will be run to assess the robustness of study results to the secondary estimand, defined in Section 1.3. The primary Bayesian analysis and the frequentist supportive analysis will be used.

6.3. Secondary Efficacy Endpoints and Analyses

The key secondary efficacy endpoints are listed in Section 1.1. Analyses will be based on the mITT analysis set.

6.3.1. 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

The weekly asthma control status (Yes or No) is the derived asthma control composite score based on the following criteria (also see Section 6.1.7 of the study protocol):

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

For the analysis purpose, weekly analysis windows (weeks 1 to 16) will be derived as described in Section 6.1.1. The asthma control status in each weekly analysis window will be Yes if the conditions 1 and 2 above met, No otherwise.

The overall weekly asthma control status from week 1 through 12 or week 1 through 16 will be analyzed using the repeated measures logistic regression with treatment group, baseline status, and the randomization stratification factor, week, and week-by-treatment group interactions in the model and with the unstructured (UN) covariance structure. In the case UN covariance structure does not converge, the compound symmetry covariance structure (CS) will be used. All weekly asthma control statuses from weeks 1 to 16 will be included in the repeated measures model.

To estimate the probability of overall asthma control over 12 weeks in each treatment group, or to conduct a comparison between the treatment groups, appropriate contrast statements need to be used.

[redacted]

[redacted]

6.3.2. 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

The FEV_1 is measured by a handheld device daily. The weekly analysis window will be derived as described in Section 6.1.1. The daily average within each weekly analysis window will be

derived using formula [1] in Section 6.1.1. Measurement values taken within 4 hours of a rescue bronchodilator use will be set to missing.

The endpoints will be analyzed using a MMRM including baseline FEV_1, randomization stratification factors, week, treatment group, and week-by-treatment group interactions in the model with UN covariance structure. In the case UN covariance structure does not converge, the compound symmetry (CS) covariance structure will be used.

One MMRM model will be run including all 16-week data. The overall and by-week results will be derived using appropriate contrast statements and presented. The endpoint will be measured by the overall results. LS mean and SE for each treatment group, LS means and corresponding 95% confidence intervals for the treatment differences (active - placebo), and the associated p-values from the overall results for treatment comparisons.

Descriptive statistics from each week will be provided.

[redacted]

6.3.3. 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

The number of times asthma rescue medication (number of inhalations/puffs) used will be recorded on e-diary.

The post-baseline analysis window for over 12 weeks will be from the first day of IMP up to the day 84. The post-baseline analysis window for over 16 weeks will be from the first day of IMP up to the day 112. Baseline window will include days up to the first dose of IMP. Data in each analysis window will be normalized to 7 days as

> (∑ rescue medication uses during an analysis window / number of non-missing e-dairy days during the analysis window) *7

The changes from baseline in weekly average of rescue medication over week 12 and over week-16 will be calculated and analyzed using Wilcoxon rank-sum test stratified on randomization stratification factors, respectively. The Hodges-Lehmann estimator of the treatment differences (TEV43275 treatment groups vs placebo) will be presented.

[redacted]

6.3.4. 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

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.

The post-baseline analysis window for over 12 weeks will be from the first day of IMP up to the day 84. The post-baseline analysis window for over 16 weeks will be from the first day of IMP up to the day 112. Baseline window will include days up to the first dose of IMP.

Percentage of asthma control days in each analysis window will be calculated as

> (∑ asthma control days in an analysis window / number of non-missing e-dairy days during the analysis window) * 100

The changes from baseline in percentage of asthma control days over 12 weeks (up to day 84) and over 16 weeks (up to day 112) will be analyzed, respectively, using analysis of covariance (ANCOVA) including baseline percentage of asthma control days, randomization stratification factors, and treatment group in the model.

[redacted]

6.3.5. Change From Baseline in Clinic-Based Standardized Baseline-Adjusted Morning Trough FEV_1 at Week 16

The analysis will be based on data collected at site visits. FEV_1 measures at visit 1/screening, visit 3/DoR, visit 4/week 1, visit 5/week 2, visit 6/week 4, visit 7/week 8, visit 8/week12, and visit 9/week 16 or the early withdrawal visit. The analysis will include post-baseline data up to the visit 6/week 16. Baseline will be the last measure before the first dose of IMP.

The change from baseline in clinic-based morning trough FEV_1 at week 16 will be analyzed using MMRM method in a manner analogous to the analysis as described in Section 6.3.2. Baseline clinic-based morning trough FEV_1 will be used in model. WEEK will denote to the visit.

For model-based results, only week 16 results will be displayed. Summary statistics will be provided by visit/week.

6.3.6. Proportions of Patients Who Achieve Clinic-Based FEV_1 ≥80% Predicted at Weeks 12, 16, and at Endpoint

The percent of predicted FEV_1 will be measured by handheld device. The analysis will be based on data collected at site visits and will be applied in patients with baseline FEV_1 <80% Predicted.

For analysis purposes, a dichotomous scale of 'Yes' (FEV_1 ≥80% Predicted) or 'No' (FEV_1<80% Predicted) will be derived and analyzed using the repeated measures logistic regression model. Baseline percent of predicted FEV_1 will be used in the model. Weeks/visits include site visits visit 8/week 12 , visit 9/week 16 , and "endpoint". Summary statistics will be provided.

[redacted]

[redacted]

6.3.7. 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

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 and will be measured by handheld device.

For analysis purpose, a dichotomous score of 'Yes' (FEF_{25-75} ≥70%) or 'No' (FEF_{25-75} <70%) will be derived and analyzed using the repeated measures logistic regression model in a manner analogous to the analysis as described Section 6.3.1. Baseline FEF_{25-75} will be used in the model. Weeks/visits include all post-baseline site visits up to visit 8/week 12 (for Week 12 analysis) or up to visit 9/week 16 (for Week 16 analysis). Summary statistics will be provided by visit/week.

6.3.8. Time to First Clinical Asthma Exacerbation (CAE) Throughout the Study

The time (days) to the first CAE is the interval from the randomization to the occurrence of the first CAE.

The observation for each patient is the interval from randomization to the occurrence of the first CAE, or censoring, whichever occurs earlier. It is derived as:

the date of censoring or the date CAE - the date of randomization + 1.

Patients who early terminated from the study without CAE due to lack of efficacy or an asthma-related AE will be also treated as experiencing CAE at the time of early withdraw visit.

Patients who complete the week 16 visit without CAE will be right-censored at the time of Week 16 visit. Patients without CAE and early withdrawn from the study before the week 16 with reasons other than lack of efficacy or asthma-related AEs will be right-censored at the time of early withdrawal visit.

The Kaplan-Meier (KM) 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]

[redacted]

6.3.9. Changes From Baseline in Asthma Control Questionnaire (ACQ-6) at Weeks 12 and 16

The ACQ-6 is a validated asthma assessment tool that has been widely used. 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. ACQ-6 will be administered at visit 2/run-in, visit 3/DoR, visit 5/week 2, visit 6/week 4, visit 7/week 8, visit 8/week 12, and visit 9/week 16 or early withdrawn visit.

The mean total score of the ACQ-6 is derived as the average of the individual item scores. For incomplete data, the following rules will apply:

1. Mean total score for a visit will not be calculated if Question 1 is left blank, irrespective of the completion of the remaining questions.
2. A missing score on post-baseline questionnaire for Questions 2-6 will be imputed based on the total scores from the previous visit, as long as at least 3 out of the 5 questions have responses for the current visit (ie, at least half of the remaining questions are answered).

   The formula is: (total sum of non-missing scores for the current visit / total sum of scores for the previous visit for questions answered for the current visit) * (score for the missing question on the previous visit)
3. Mean total score at baseline will not be calculated if Question 1 or two or more among Questions 2-6 is left blank. A missing score for Questions 2-6 at baseline will be replaced by an average of the available scores.

The changes from baseline in ACQ-6 mean total score at Weeks 12 and 16 will be analyzed using MMRM method in a manner analogous to the analysis as described in Section 6.3.2. Baseline ACQ-6 total score will be used in the model.

The analysis includes data up to visit 9/week 16.

6.3.10. Changes From Baseline in Asthma Control Test (ACT) at Weeks 12 and 16

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). 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. ACT will be measured at visit 3/DoR, visit 6/week 4, visit 7/week 8, visit 8/week 12, and visit 9/week 16 or early withdrawn visit.

The total score will be calculated based on the available data and will be set to missing if any questions are incomplete.

The changes from baseline in ACT total score at Weeks 12 and 16 will be analyzed using MMRM method in a manner analogous to the analysis as described in Section 6.3.2. Baseline ACT total score will be used in the model.

The analysis includes data up to visit 9/week 16.

6.3.11. Changes From Baseline in Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) at Weeks 12 and 16

The Standardized Asthma Quality of Life Questionnaire AQLQ[S]) 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 questionnaire contains 32 items with a 2-week recall period and uses a 7-point Likert scale (7=not impairment at all to 1=severely impairment). Scores range from 1 to 7, with higher scores indicating better quality of life. The 32 questions (items) in the AQLQ(S) are divided in to 4 domains and the corresponding questions are:

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

AQLQ(S) will be measured at visit 3/DoR, visit 8/week 12, and visit 9/week 16 or early withdrawn visit.

The overall and domain mean scores of the AQLQ will be derived as the average of the corresponding items. For incomplete data, the overall mean score for a particular visit will not be calculated if 3 or more responses are missing with no more than 1 per domain. For the symptom and activity domain mean scores, calculation will require no more than 1 missing item. The mean domain score for the other 2 domains will be regarded as missing if 1 or more item is missing.

The changes from baseline in AQLQ(S) at week 12 and week 16 will be analyzed, respectively, using ANCOVA in a manner analogous to the analysis as described Section 6.3.4. The analyses will be for the overall mean score and mean score of each domain. The baseline in the model will be baseline overall mean score of AQLQ(S) or baseline mean score of AQLQ(S) for the domain, respectively.

6.3.12. Proportions of Patients Who Achieve FEV_1:FVC (Forced Vital Capacity) Ratio ≥0.80 at Weeks 12, 16, And at Endpoint

The proportions of patients who achieve FEV_1: FVC ratio ≥80% will be analyzed using the repeated measures logistic regression model in a manner analogous to the analysis as described Section 6.3.1. Baseline FEV_1: FVC ratio will be used in the model. The analysis will be applied those with baseline FEV_1: FVC ratio < 0.80.

The analysis will include data up to visit 9/week 16.

6.4. [redacted]

[redacted]

[redacted]

6.4.1. [redacted]

[redacted]

[redacted]

[redacted]

6.4.2. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

7. MULTIPLE COMPARISONS AND MULTIPLICITY

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

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

Patients will be administered the study drug at visit 3 and receive a total of 4 sc injections in the abdomen.

The number of patients who received the study drug, the number of injection received, and reasons for IMP not administrated (adverse event or other) will be summarized using descriptive statistics.

IMP administration and IMP accountability 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), serious adverse events, adverse events causing drug withdrawal or discontinuation from the study, protocol-defined adverse events of special interest (PDAESI), and PDAESI require completion of suspected anaphylaxis. 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.

Listings for deaths, serious adverse events, adverse events leading to drug withdrawn or the study discontinuation, PDAESI, and PDAESI require completion of suspected anaphylaxis. 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.

8.4. Injection Site Assessments

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'?".

Table 2: 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

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.

In order to account for both placebo and TEV-53275 injections in the 600 mg dose, the summaries will be split into three columns: placebo injections, TEV-53275 injections and total.

The data will be listed using safety analysis set, sorted by treatment group, subject ID, visit, and injection. The study medication administered for each injection will also be listed.

8.5. 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.

8.6. Deaths

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

8.7. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 2 of the study protocol. Clinical laboratory tests will be performed using the central laboratory.

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 of the study protocol. (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.)

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 seeSection 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.

Note that: The ULN for some test parameters may depend on demographic parameters such as gender (e.g. creatine phosphokinase).

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
Creatine phosphokinase		≥3x ULN
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L

Test	Criterion value
Hemoglobin Men	≤115 g/L
Women	≤95 g/L
WBC counts	≤3 x 10^9/L ≥20 x 10^9/L
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

8.7.1. 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.

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.

Beta human chorionic gonadotropin (β-HCG) tests in urine will be performed for women of childbearing potential as detailed in Table 2 of the study protocol.

Testing of patients asymptomatic for COVID-19 active infection may be conducted at the discretion of the investigator within 72 hours of any visit. COVID-19 testing may be conducted by the central laboratory or locally.

Other clinical laboratory tests results will be listed.

8.8. Physical Examinations

Physical examinations will be performed at the time points detailed in Table 2 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 the source document, and monitored as described in Section 7.1.2 of the study protocol.

Abnormal physical examination findings will be listed and summarized descriptively.

8.9. 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 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.

Height and weight will be obtained at the at the time points detailed in Table 2 of the study protocol.

Vital signs (including weight and BMI) 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
Temperature	≥38.3°C	Change of ≥1.1°C
Respiratory rate	>24 breaths/min	Increase >=10
	<6 breaths/min	Not applicable

Bpm=beats per minute

8.10. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 2 of the study protocol. ECGs should be performed in a supine position. 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 of the study protocol.

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

At DoR visit ECG will be performed in triplicate, 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. For ECG findings, the last measurement before the first dose of IMP will be used for analysis.

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.

In addition, the incidence of patients meeting the following potentially clinically significant thresholds will be presented using descriptive statistics:

- Combined absolute QTc Bazett and Fridericia interval prolongations plus change from baseline in QTc Bazett and Fridericia interval to week 52 and endpoint
  - QTc interval >450 msec and QTc interval increases from baseline >30 msec
  - QTc interval >450 msec and QTc interval increases from baseline >60 msec
  - QTc interval >500 msec and QTc interval increases from baseline >30 msec
  - QTc interval >500 msec and QTc interval increases from baseline >60 msec
- QRS duration >110 msec and a 25% increase from baseline
- PR interval >200 msec and a 25% increase from baseline

8.11. 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.

[redacted]

[redacted]

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

The final primary efficacy analyses will be performed when all patients have completed V9 (week 16) or withdrawn from 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. These analyses will be described in details in Section 13.1.

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]

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. However, the feability of stopping the trial earlier with a smaller sample size is evaluated based on the week 12 efficacy endpoint, ie, change from baseline at week 12 in morning trough FEV_1.

The same Bayesian analysis for the final primary efficacy analysis will be applied to the week 8 and week 12 endpoints, as applicable, to derive the posterior probability of the TEV-53275 dose group performing better than the placebo group in terms of the week 8 endpoint and the posterior probability of the TEV-53275 dose group performing better than the placebo group in terms of the week 12 endpoint using the interim analysis data.

13.1.1. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.1.2. [redacted]

[redacted]

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

[redacted]

13.1.3. Early Stopping with a Smaller Sample Size

Due to challenges in patient enrollment in the face of COVID-19 pandemic, the feasibility of an early stopping of the trial with smaller sample sizes will also be evaluated during the interim analysis. The unblinded assessment is based on

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

for the primary efficacy endpoint (12-week endpoint).

The final trial sample size would be reduced to a smaller number according to the following criteria:

1. Reduce to 80 per arm in case of "Very good" efficacy signal:

$$Posterior\ probability \geq 0.95;$$

2. Reduce to 90 per arm in case of "Good" efficacy signal:

$$0.95 > Posterior\ probability \geq 0.9;$$

3. Keep 100 per arm when the efficacy signal is not as good, but not futile:

$$Posterior\ probability < 0.9.$$

Simulations were conducted to assess the operating characteristics of the early stopping rules. The simulations took into account the non-binding futility stopping specified in Section 13.1.2. When the futility criterion is met, a simulated trial is stopped due to futility with a probability of 50% or 30%. For the purpose of estimating type 1 error rates and study powers using simulations, the posterior distributions for the mean responses were derived using the conjugate priors for the means with a known standard deviation of 0.35 L in the Bayesian analysis. The priors follow normal distributions with mean 0 for all treatment groups. The simulations assumed a 10% dropout rate and 5000 simulations run were used in each scenario.

Table 6 below summarizes the simulation results for a range of treatment effects, including the overall study power under the study design, the probability of meeting the "Very good" and "Good" efficacy criteria at the interim analysis, as well as the conditional power given that the sample size reduction criteria are met at the interim analysis. The results showed that the early stopping rules didn't compromise the type 1 error control (controlled at 15% under the null hypothesis). The overall study power is maintained at approximately the same level (approximately 80% when the high-dose treatment effect=0.1L). In addition, it is reassuring that, when the early stopping criteria are met and the sample size is reduced, the conditional power is high (>94% in all scenarios). It ensures that the decision to stop early with a smaller sample size is made with high assurance of final success, despite a smaller sample size to be used. It's also worth noting that there is a 44% to 68% of chance to meet the early stopping criteria due to "Very good" and "Good" efficacy results under the alternative hypotheses, but an approximately 10% chance under the null hypothesis.

[redacted]

From a practical standpoint, if the site personnel learned about the plan for the early stopping with reduced sample size using the unblinded assessmsnet of interim data, there can be a potential unblinding and biasing risk. When the decision is made to early stop the trial with a smaller sample size, the site personnel can guess about the treatment efficacy and it can bias their views. Therefore, favorable actions may be taken towards the active treatment subconsciously or consciously. In order to alleviate this concern, the early stopping plan is concealed in the protocol amendment 1, but is only described in the SAP. When a decision on early stopping is made, it will be documented and the reduced sample size (240 or 270) will be communicated to the study team. However, in order to minimize the potential risk of biasing the site personnel, the decision will not be revealed to sites until the enrolment is close to reaching the reduced sample size goal.

13.2. The Execution of the 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. The charter will specify the processes for properly unblinding, storing and analyzing the interim data, and the communication plan to disseminate the unblinded study results in a secure fashion. The processes will be followed to ensure that the study blind 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.

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

In the protocol, it is proposed to estimate the posteriors of the Bayesian longitudinal linear model, together with the Bayesian dose-response model, by using a multiple imputation with chained equations (MICE) procedure. This method imputes missing week 12 data, by using the longitudinal model in the case of complete observations of prior visit data and covariates in the model, or by the dose-response model in the case of missing prior visit data or covariates in the longitudinal model. The two model parameters are updated in loops and the imputation of missing data uses the most updated model parameters at each step. This algorithm is difficult to implement and can have convergence issues.

It is replaced by a multiple imputation method described in Section 6.2.2 of the statistical analysis plan. The replacement method is expected to be to produce reliable estimates (Zhou et al, 2010) and is easy to implement. Simulation studies were performed to compare the method with a comparable frequentist analysis using multiple imputations and showed comparable results (Section 16.2).

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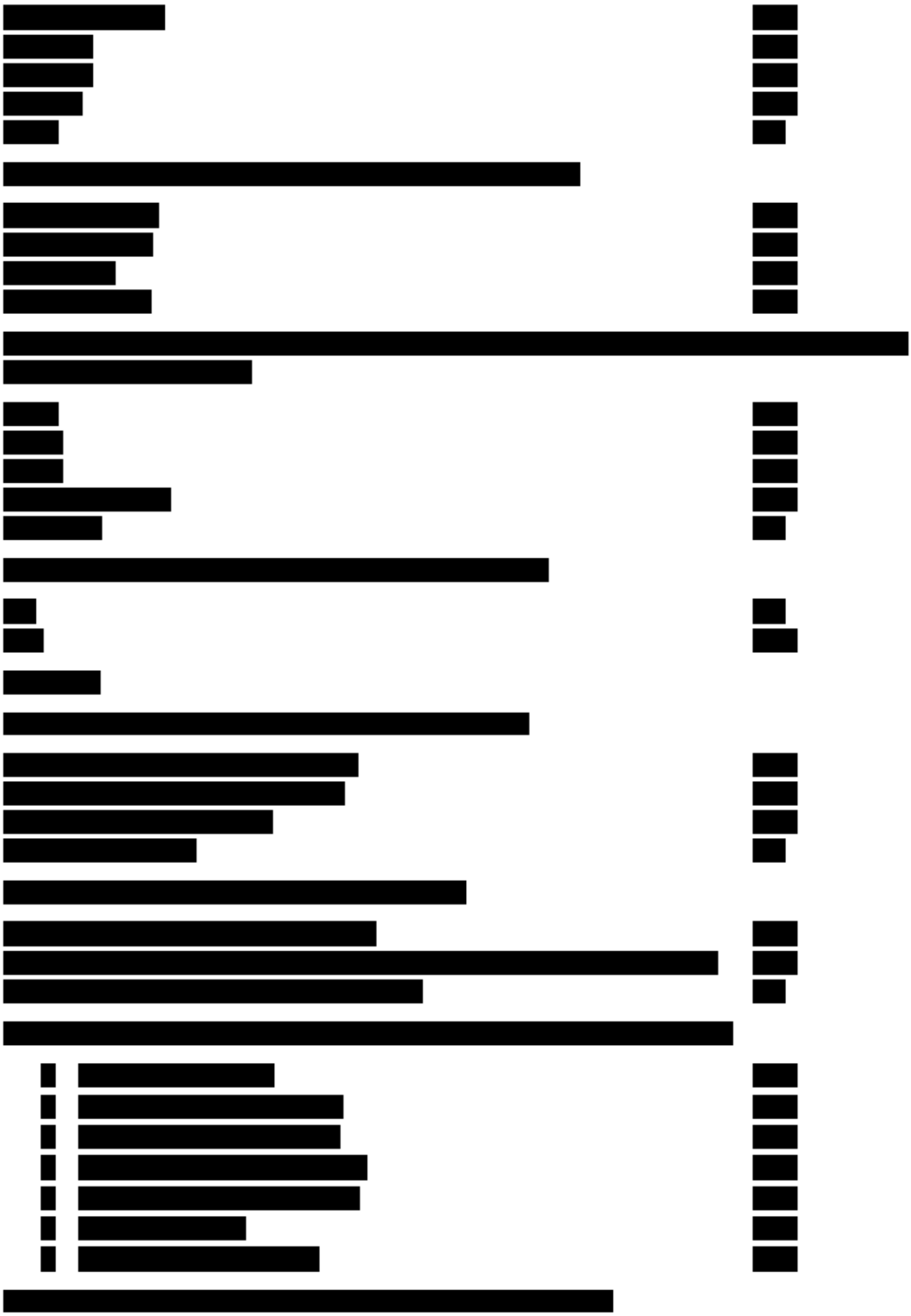
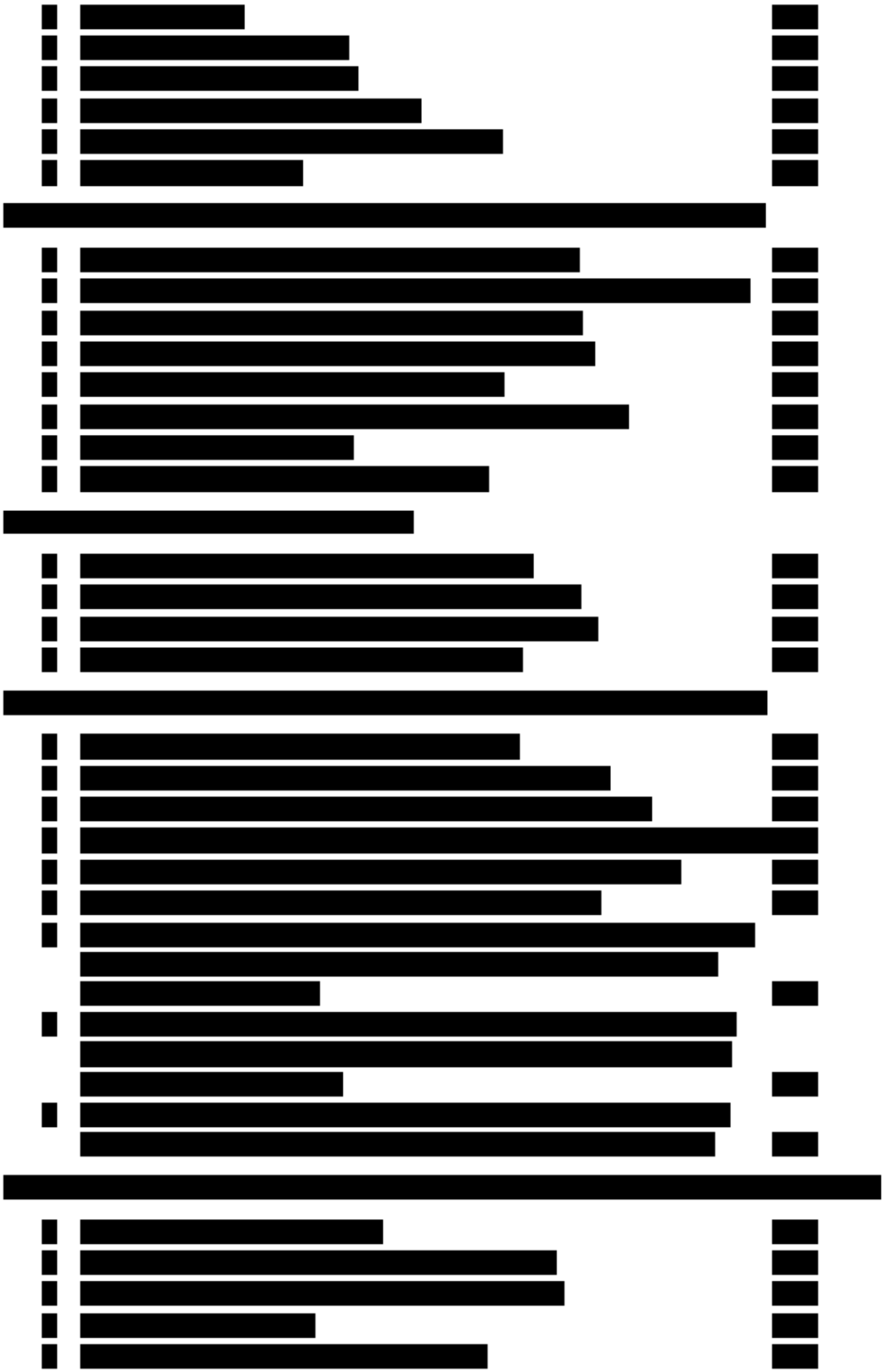
16. APPENDIX

16.1. [redacted]

[redacted]





[redacted]

16.2. Appendix B: Simulation Results to Assess the Bayesian Analysis using Multiple Imputations for Missing Data Handling

A random sample is taken from a previous study (CEP38072-AS-3082) comparing the safety and efficacy of another aIL5 product with placebo. The sample included 100 subjects in each treatment group for a total of 200 subjects with the following data: two stratification variables, baseline FEV_1 value, changes from baseline in morning trough FEV_1 at week 4, week 8, week 12 and week 16. The week 16 endpoint was used as the primary endpoint in this simulation.

The missing/observed data patterns from this sample are shown in Table 7, which may be indicative of the missing data pattern in the current study. The patterns summarized include three categories: the complete cases, subjects with intermittent missing data, and subjects who had observations available prior to dropping out from study without further observations.

[redacted]

The results from the Bayesian analysis with multiple imputations for missing data handling, described in Section 6.2.2 , are compared with the analysis of covariance with multiple imputations. Two multiple imputation methods are used: 1) by treatment group (TRT-based); 2) using the control group data for both treatment groups (Control-based). Table 8 below show the analysis results.

The results show that the Bayesian analysis and ANCOVA with multiple imputations produced similar results. This is expected because the Bayesian analysis uses non-informative priors for the mean and variance parameters. In addition, the treatment difference estimates using the control-based multiple imputations produced a smaller treatment effect, but it was similar to the result obtained with multiple imputations by treatment group. The control-based multiple imputation method is expected to be conservative for estimating the treatment effect. Since the overall percentage of missing data is small (<10% overall), the difference was small. As a result, the same conclusions can be made based on the posterior probability or the p-value.

In conclusion, the simulation study shows that the Bayesian analysis with multiple imputations method generates reliable estimates.

[redacted]

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