STATISTICAL ANALYSIS PLAN FOR FINAL ANALYSIS

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A Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study to evaluate the efficacy and safety of GB001 as maintenance therapy in adult subjects with moderate to severe asthma

SPONSORED BY

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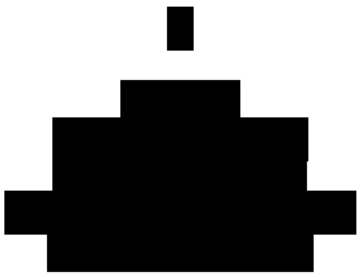

VERSION CONTROL

Version Number	Date	Comments/Changes
1.0	11 April 2020	Final

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACQ	asthma control questionnaire
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AQLQ-S	asthma quality of life questionnaire-standardized
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BLQ	below limit of quantification
BMI	body mass index
BPM	beats per minute
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
CTS	continuous
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EMA	European Medicines Agency
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GINA	Global Initiative for Asthma
GMR	geometric mean ratio
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IgE	immunoglobulin E

Abbreviation	Definition
IM	intramuscular
IP	investigational product
ITT	intent-to-treat
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic antagonist
LLOQ	lower limit of quantification
LS	least squares
LTRA	leukotriene receptor antagonist
MCID	minimal clinically important difference
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effects model with repeated measures
OR	odds ratio
PD	pharmacodynamics
PEF	peak expiratory flow
PK	pharmacokinetics
PRO	patient reported outcomes
PT	preferred term
QOL	quality of life
QTcB	Bazett’s correction formula for QT interval
QTcF	Fridericia's correction formula for QT interval
REML	restricted maximum-likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SNOT-22	Sino-Nasal Outcome Test
SoA	schedule of activities
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

Abbreviation	**Definition**
WHO	World Health Organization

1. PURPOSE OF THE ANALYSIS

This statistical analysis plan (SAP) provides a comprehensive and detailed description of the statistical methodology to be used for reporting of the study results for use in the clinical study report (CSR) and is based on protocol version 4.0. The purpose of this SAP is to describe the methodology, procedures, rules, and conventions to be used for the reporting of results. Results to be reported will include summaries of subject disposition, demographic and baseline characteristics, significant protocol deviations, prior and concomitant medications, study treatment exposure and compliance, primary, secondary, and select tertiary/exploratory efficacy endpoints, pharmacokinetic (PK) concentrations, and safety endpoints, including adverse events (AEs), serious AEs (SAEs), and laboratory, vital sign, and electrocardiogram (ECG) parameters.

If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR as post hoc.

The last "Tertiary/Exploratory" objectives and endpoints in Section 2.1 will not be addressed in this SAP.

This SAP was written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline (ICH E9, 1998) entitled Guidance for Industry E9 Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline (ICH E3, 1995) entitled Guidance for Industry Structure and Content of Clinical Study Reports and was finalized prior to study unblinding at the interim analysis.

In this document, investigational product (IP) and study treatment have the same meaning.

2. PROTOCOL SUMMARY

2.1. Objectives and Endpoints

The purpose of this Phase 2b study is to evaluate the efficacy, safety, PK, and pharmacodynamic (PD) of 3 GB001 dose levels compared with placebo in subjects with moderate to severe asthma and an eosinophilic phenotype. The study will assess the efficacy of GB001 relative to placebo in reducing asthma worsening when added to standard of care asthma maintenance therapy. The primary, secondary, and tertiary/exploratory objectives and endpoints are as follows:

Objectives	Endpoints
Primary	
• To evaluate the effect of GB001 compared to placebo on reducing asthma worsening	• The proportion of subjects who experience worsening of asthma by Week 24 as defined by at least one of the following: o On 2 consecutive days, morning (AM) peak expiratory flow (PEF) ≤ 75% of mean AM PEF measured over the last 7 days of the Run-in o Forced expiratory volume in 1 second (FEV_1) < 80% of baseline (Visit 2) o Increase in rescue medication use of ≥ 6 puffs/day on 2 consecutive days compared to mean use over the last 7 days of the Run-in o Increase in Asthma Control Questionnaire (ACQ-5) score of ≥ 0.5 compared to baseline (Visit 2) o The occurrence of a severe asthma exacerbation (asthma attack) defined as deterioration of asthma that leads to the use of systemic corticosteroids for at least 3 days, hospitalization, or an Emergency Department visit
Secondary	
• To evaluate the effects of GB001 compared with placebo on a range of clinical endpoints, including change in ACQ-5 score, change in pulmonary function, and time to first asthma worsening event	• Change from baseline to Week 24 in ACQ-5 score • Change from baseline to Week 24 in pre-bronchodilator FEV_1 • Time to first asthma worsening • Annualized rate of severe asthma exacerbations • Change from baseline to Week 24 in post-bronchodilator FEV_1 • Change from baseline to Week 24 in AM PEF

• To evaluate the safety and tolerability of GB001 compared with placebo	• Incidence of treatment-emergent adverse events (TEAEs) • Change from baseline in laboratory, vital signs, and electrocardiogram (ECG) parameters
Tertiary/Exploratory	
• To evaluate the effect of GB001 compared to placebo on patient reported outcomes (PRO)	• Proportion of subjects with a greater than or equal to 0.5 decrease in ACQ-5 score from baseline • Change from baseline in Asthma Quality of Life Questionnaire-Standardized (AQLQ-S) • Change from baseline in Sino-Nasal Outcome Test (SNOT-22) • Change from baseline in hair-loss assessment
• To evaluate the effects of GB001 on additional markers of asthma control	• Change from baseline in daily salbutamol/albuterol use • Change from baseline in daily asthma symptom scores • Change from baseline in awakening at night due to asthma symptoms requiring rescue medication use
• To evaluate the PK of GB001	• PK in plasma
• To characterize target engagement, biomarkers and PD profile of GB001	• Change from baseline in target engagement, biomarkers and other PD parameters (may include blood, urine, and airway)

2.2. Overall Study Design and Plan

This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study to evaluate the efficacy and safety of GB001 as maintenance therapy in a moderate to severe eosinophilic asthma population. GB001 will be added to the subject's standard of care asthma treatment.

The study will commence with a Screening Visit (Visit 1), at which informed consent will be obtained and inclusion and exclusion criteria will be assessed. Informed consent may be obtained prior to the day of the Screening Visit to allow for medication washouts or for other logistical reasons such as obtaining documentation of exacerbations or historical reversibility, if necessary. All other screening procedures should be completed on the day of the Screening Visit. Subjects not meeting the eligibility criteria will be deemed screen failures and will not continue participation in the study. Eligible subjects will enter a Run-in period of a minimum of 2 weeks and a maximum of 6 weeks and will remain on their standard of care regimen. The Run-in period commences with completion of all Screening Visit procedures and concludes at the Randomization Visit. After the Randomization Visit, subjects will enter the Double-Blind, Placebo-Controlled period which will be followed by a Follow-up period.

Total duration for study participation per subject is up to 34 weeks (includes a Screening Visit; followed by a 2-week to 6-week Run-in period to allow for collection of baseline eDiary data; a 24-week Double-Blind, Placebo-Controlled period; and 4-week Follow-up period).

Subjects who permanently discontinue IP will be requested to attend the Early Discontinuation of IP Visit and will be strongly encouraged to complete any remaining study visits as per the Schedule of Activities (SoA).

The first dose of double-blind IP will be administered in the clinic on Day 1. All subsequent doses will be taken orally at home at bedtime on an empty stomach. Following initiation of IP, subjects will visit the clinic for assessments at Weeks 2 and 4, followed by visits approximately every 4 weeks for an additional 5 visits. Subjects should remain on their stable current standard of care therapy (i.e., medium or high dose inhaled corticosteroid (ICS) plus additional controller therapy) through the duration of their time on study.

All subjects will be closely monitored throughout the study through daily home morning PEF and eDiary monitoring. Subjects will be provided with an eDiary which is programmed to alert the subject of potential asthma worsening:

1. On 2 consecutive days, AM PEF ≤ 75% of mean AM PEF measured over the last 7 days of the Run-in period
2. Increase in rescue medication use of ≥ 6 puffs/day (last 24 hours) on 2 consecutive days compared to mean use over the last 7 days of the Run-in period
3. Nighttime awakening due to asthma symptoms requiring rescue medication for at least 2 of 3 successive nights
4. An asthma symptom score of 4 for at least 2 of 3 successive days.

Subjects will be asked to record the following parameters daily in the eDiary from the Screening Visit through the Follow-up Visit:

- Morning peak flow (best of three efforts) before rescue medication usage (L/min)
- Puffs of rescue medication used over the previous 24 hours
- Asthma symptom score over the previous 24-hours using a 6-point scale (as defined in Protocol Section 10.7)
- Frequency of awakening due to asthma symptoms requiring rescue medication use

The protocol contains further details related to the study design and conduct.

2.3. Study Population

This study will enroll male and female subjects with moderate to severe asthma who are currently receiving Global Initiative for Asthma (GINA) step 4 or 5 therapy and have evidence of eosinophilic inflammation, and are ≥ 18 and < 75 years of age at the time of the Screening Visit. Other key eligibility criteria include:

- A peripheral blood eosinophil count of ≥ 250 cells/μL measured at the Screening Visit. Note: In a subject with prior evidence of an eosinophilic phenotype, as assessed by the investigator, an eosinophil count < 250 may be repeated during Run-in upon approval by the medical monitor.
- Subjects with a documented requirement for regular treatment with medium or high dose ICS and at least one other controller medication for at least 12 months prior to Visit 1. Subjects must maintain a stable ICS dose regimen during the 4 weeks prior to Visit 1.
- Demonstration of uncontrolled asthma by one of the following:
  a. Previously confirmed history of 2 or more asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Screening Visit. OR
  b. Previously confirmed history of 1 asthma exacerbation requiring treatment with systemic corticosteroids in the 12 months prior to Screening Visit and ACQ-5 of ≥ 1.5 at Screening Visit.

2.4. Randomization and Treatment Regimens

This study will randomize approximately 480 subjects, with approximately 120 subjects per treatment group, randomized in a 1:1:1:1 ratio to the following treatment groups:

- GB001 60 mg daily
- GB001 40 mg daily
- GB001 20 mg daily
- Matching placebo daily

Randomization will be stratified by baseline ICS dose (medium or high, as defined in Protocol Section 10.10) and country.

2.5. Sample Size Determination

A total sample size of approximately 480 subjects (approximately 120 per treatment group, randomized in a 1:1:1:1 ratio) is estimated to provide 80% power to detect a reduction in odds of 66% between each GB001 group and placebo at an 0.050 two-sided level of significance for the primary endpoint of the proportion of subjects who experience worsening of asthma by Week 24. This assumes the proportion of subjects who experience worsening of asthma by Week 24 is 25% in the placebo group and 10.2% in each GB001 group and a dropout rate of 8%.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

All analyses will be performed using SAS® System (SAS Institute Inc., Cary, NC) version 9.4 or later.

Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the format "n (xx.x)". If a count is 0, no percentage will be shown. To ensure completeness, summaries for categorical and discrete variables may include all categories, even if no subjects had a value in a particular category. Additionally, for missing data, a category of "Missing" will be presented as needed.

Continuous (cts) variables, unless otherwise stated, will be summarized using descriptive statistics: number of subjects with non-missing data (n), mean, standard deviation (SD), median, 25^{th} and 75^{th} percentiles, minimum, and maximum. Descriptive statistics on select measures may also include the standard error (SE). Rounding rules for reporting cts descriptive summary statistics are as follows:

- If the original values have 0 or 1 decimal places: mean, median, 25th and 75th percentiles will be reported to one more decimal place than the original values, and SD and SE will be reported to 2 more decimal places than the original values
- If the original values have 2 or more decimal places: mean, median, 25th and 75th percentiles, SD, and SE will all be reported to 3 decimal places

Minimum and maximum will always be reported to the same decimal places as the original values, up to a maximum of 3 decimal places.

Efficacy results will be summarized by various measures including but not limited to odds ratios (ORs), hazard ratios, rate ratios, least squares (LS) means, differences in LS means, SEs, p-values, and two-sided confidence intervals (CIs). The ORs, hazard ratios, rate ratios, and corresponding CIs will be reported to 3 decimal places, percentage reductions and corresponding CIs will be reported to 1 decimal place, and SEs, LS means, differences in LS means and corresponding CIs will be reported per the rules above. P-values will be reported to 4 decimal places, with values less than 0.0001 displayed as < 0.0001 and values greater than 0.9999 displayed as > 0.9999. All statistical hypothesis tests will be two-sided with a significance level of 0.050.

Values with "<" or ">" signs will be analyzed without the signs in tables and figures. In by-subject data listings, values will be reported as collected with the sign.

Dates in by-subject data listings will be displayed as yyyy-mm-dd (e.g., 2015-01-24). In general, by-subject data listings will be sorted by randomized treatment group and subject number.

Disposition, demographic and baseline characteristics, significant protocol deviations, and prior medication tables will be presented by randomized treatment group and will also include an overall column combining all treatment groups. Efficacy tables will be presented by randomized treatment group only. Safety tables will be presented by actual treatment group and, in general, will also include a total GB001 column combining all GB001 treatment groups. Sorting in disposition, etc. tables will be based on decreasing incidence within the overall column. In general, AE tables that are displayed by system organ class (SOC) and/or preferred term (PT) will be sorted by the internationally agreed order for SOC, and by decreasing incidence and then

alphabetically for PT within the total GB001 column. Otherwise, safety tables when applicable, will be sorted by decreasing incidence within the total GB001 column.

Assessments at the Randomization Visit are to be performed prior to the first dose of study treatment. Therefore, for all measures, the baseline value is defined as either the last non-missing value on or before the first dose of study treatment or the mean over the last 7 days of the Run-in including the value on Day 1.

If multiple evaluations occur on the same day, the average of these evaluations will be used for analysis excluding maximum post-baseline, abnormality, and outlier analyses.

If complete dates are unavailable, July 2 (midpoint of a non-leap year) will be utilized in calculations in cases where both month and day are missing, and the 15th will be utilized in calculations in cases where only day is missing.

3.1. Visit Windowing

Subjects do not always strictly adhere to the visit schedule timing in protocols. Therefore, the designation of visits (or timepoints) will generally be based on the actual day of evaluation relative to the date of first dose of study treatment (Day 1), rather than the nominal visit, for analyses conducted by visit.

Mutually exclusive visit windows containing no gaps will generally be utilized to assign visits for by visit analysis and will correspond to post-baseline visits specified in the protocol. Visits for analysis will be assigned by using a windowing scheme as described below.

The upper bound of the baseline visit window is Day 1, and the lower bound of the first post-baseline visit window is Day 1 after the time of the first dose. For all other lower and upper bounds of visit windows, windows will end at the midpoint between scheduled visit timepoints, with the midpoint in the latter visit window with the exception of the Week 24 visit for the efficacy endpoints, which will include Day 174 as the upper bound of the visit window.

If a subject's last observation is after the date of first dose of study treatment but prior to the first scheduled visit, data from an early withdrawal visit will be assigned to the first scheduled visit. If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis. The target visit day for Week 2 and on is defined as the week number specified in the SoA of the protocol multiplied by 7 plus 1.

3.2. Standard Calculations

Standard calculations are described as follows:

Age:

Age will be calculated in years to two decimal places using the date of birth and the date of the Screening Visit (Visit 1), rounded down to the nearest integer.

Duration:

Duration between two dates date1 and date2 will be calculated as follows:

date2 – date1 + 1, when expressed in days

(date2 – date1 + 1)/7, when expressed in weeks

(date2 – date1 + 1)/365.25, when expressed in years

Change/Percent Change from Baseline:

Change from baseline will be calculated as: Value at post-baseline visit – value at baseline

Percent change from baseline will be calculated as: (Change from baseline/value at baseline) * 100%

Note: Change from baseline summaries will only include subjects with a baseline value and at least one post-baseline value. If the value at baseline is 0, percent change from baseline will be missing.

Study Day:

Study day will be calculated as follows:

assessment date – date of the first dose of study treatment, where assessment date < date of the first dose of study treatment

assessment date – date of the first dose of study treatment + 1, where assessment date ≥ date of the first dose of study treatment

3.3. Considerations Related to the COVID-19 Pandemic

Screening of subjects for this study began in October 2018, and the last subject is expected to complete their participation in the study around August-September 2020. As such, a portion of this study's conduct may be affected by the global Coronavirus Disease 2019 (COVID-19) pandemic.

At the time of finalization of this SAP in April 2020, several regulatory authorities have recently issued guidance related to trial conduct and associated methodological issues related to the effect of the COVID-19 pandemic, including Food and Drug Administration (FDA) (Reference: FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, March 2020) and European Medicines Agency (EMA) (References: Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2 (27/03/2020) and Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, 25 March 2020).

Potential anticipated effects on conduct of this ongoing study related to the COVID-19 pandemic include, but are not limited to, the following: subject discontinuation of study treatment and/or withdrawal from study; inability or reduced ability for subjects to continue on IP due to disruptions in IP dispensing; missed visits; alternative procedures (e.g., telephone visit or virtual visit) used for collection of critical efficacy and/or safety assessments; and inability for sites to complete entry of data in the electronic case report form (eCRF) and/or collect data via other sources (e.g., eDiary).

At the time of finalization of this SAP, it is acknowledged that it is not known the degree to which study conduct and subject participation may be affected by the COVID-19 pandemic, as the study is currently approximately 4-5 months from the last subject completing participation.

Given the COVID-19 pandemic is a developing and rapidly evolving situation, a determination will be made at the end of study if additional statistical analyses are warranted as part of the final analysis, should participation of subjects be affected by the COVID-19 pandemic to a substantial degree. These additional analyses would be undertaken to enable an understanding of the potential impact of the COVID-19 pandemic on study results.

A non-exhaustive list of examples of such additional analyses is as follows:

- Analysis of compliance:
  - By subgroup of subjects who received direct IP shipment due to the COVID-19 pandemic versus those that did not
- Analyses of primary and select secondary efficacy endpoints:
  - By subgroup of subjects whose study participation was affected by the COVID-19 pandemic versus was not affected;
  - Excluding only data that is missing for reasons related to the COVID-19 pandemic (but including imputation of data missing for other reasons); and
  - By subgroup of subjects who had an alternative method of collection for an assessment contributing to a particular endpoint (e.g., ACQ-5 completed by subject at home via virtual visit) versus subjects who did not have an alternative method of collection
- Analysis of AEs:
  - Incidence of AEs by subgroup of subjects whose study participation was affected by the COVID-19 pandemic versus was not affected;
  - Incidence of AEs that were collected via an alternative method versus incidence of AEs that were not collected via an alternative method
- Analysis of laboratory values:
  - By subgroup of subjects whose study participation was affected by the COVID-19 pandemic versus was not affected;
  - Excluding values resulting from local collection due to reasons related to the COVID-19 pandemic; and
  - Including only values resulting from local collection due to reasons related to the COVID-19 pandemic

In addition, by-subject listings indicating subjects whose study participation was affected by the COVID-19 pandemic, subjects with missing data related to the COVID-19 pandemic, and/or subjects with an alternative method of collection for specific assessments may be provided.

4. ANALYSIS POPULATIONS

4.1. All Enrolled Population

The all enrolled population will include all subjects with a non-missing date of informed consent. The all enrolled population will be utilized for disposition summaries.

4.2. Run-in Period Population

The run-in period population will include all enrolled subjects who are not screen failures and enter the Run-in period. The run-in period population will be presented in disposition summaries.

4.3. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who are randomized and receive at least 1 dose of study treatment, with subjects grouped according to randomized treatment. The ITT population will be utilized for efficacy analyses.

4.4. Per Protocol Population

The per protocol population will include all subjects in the ITT population who do not violate terms of the protocol that may affect primary or secondary efficacy outcomes. The criteria for the per protocol population will be determined and documented prior to unblinding based on review of study data in a blinded manner.

Programmatically-derived and/or manually reviewed criteria for exclusion from the per protocol population include, but are not limited to:

- Subjects who do not meet the following eligibility criteria:
  - Inclusion Criteria 5, 6, 7, or 9
  - Exclusion Criteria 12
  - Randomization Criteria 1, 2, 4, 5, or 11
- Poor study treatment compliance up to the last dose of study treatment defined as < 80.0% compliance
- Subjects at any site with good clinical practice (GCP) compliance issues identified, if applicable

4.5. Safety Population

The safety population will include all subjects who receive at least 1 dose of study treatment, with subjects grouped according to their actual treatment. If GB001 was taken, subjects will be grouped according to the highest dose of GB001 actually taken (20 mg, 40 mg, or 60 mg) based on kit and study treatment accountability data. The safety population will be utilized for safety and PK analyses.

5. STUDY PATIENTS

5.1. Disposition of Patients

The disposition of subjects will be summarized for the all enrolled population. The number and percent of subjects who are screened, screen failures, run-in participants, completed run-in, and run-in failures, along with screen failure reasons, run-in failure reasons, and reasons not randomized will be summarized overall. In addition, the number and percent of subjects who are randomized, treated, completed study treatment, discontinued study treatment, completed the study, and withdrew from the study, along with associated reasons, and in each analysis population, will be summarized by treatment group and overall.

Disposition data will also be presented in a by-subject data listing. In addition, a listing of the randomization scheme will be presented.

5.2. Protocol Deviations

Protocol deviations will be identified and reviewed on an ongoing basis by the study team and entered into a Clinical Trial Management System. Significant protocol deviations are defined as those that can affect efficacy and/or safety assessments, the safety or mental integrity of a subject, or the scientific value of the study. Protocol deviations will be classified as significant or non-significant and will be assigned a protocol deviation type prior to unblinding. The number and percent of subjects with at least 1 significant protocol deviation overall and for each protocol deviation type will be summarized for the ITT population.

Protocol deviations will also be presented in a by-subject data listing. In addition, subjects who were randomized in error and subjects who were mis-stratified for ICS dose (medium or high) at randomization may be presented in a by-subject data listing.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1. Demographic Characteristics

Demographic characteristics will be summarized for the ITT and per protocol populations for the following parameters:

- Age (years; cts; ≥ 18-< 50, ≥ 50-< 65, ≥ 65)
- Sex (male, female)
- Race (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Height (cm; cts)
- Weight (kg; cts)
- Body mass index (BMI [kg/m^2; cts; < 18.5, ≥ 18.5-< 25, ≥ 25-< 30, ≥ 30])
- Country (Austria, Belgium, Canada, Czech Republic, France, Germany, Poland, Spain, Ukraine, United Kingdom, United States)
- Region (North America [United States, Canada], Eastern Europe [Czech Republic, Poland, Ukraine], Western Europe [Austria, Belgium, France, Germany, Spain, United Kingdom])

Demographic characteristics will also be presented in a by-subject data listing.

6.2. Baseline Disease Characteristics

Baseline disease characteristics will be summarized for the ITT and per protocol populations for the following parameters:

- ICS dose at Randomization and actual (medium, high)
- Asthma duration (years; cts)
- Triggers of exacerbations (air pollution, allergy, aspirin, etc.)
- Total number of exacerbations in the past 12 months (cts; 0, 1, 2, 3, ≥ 4; overall and by exacerbation categories [treated with systemic corticosteroids, resulted in an emergency department visit, resulted in a hospitalization])
- Uncontrolled asthma demonstrated by the following:
  - 2 or more asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Screening Visit
  - Previously confirmed history of 1 asthma exacerbation requiring treatment with systemic corticosteroids in the 12 months prior to Screening Visit and ACQ-5 score of ≥ 1.5 at Screening Visit

- Chronic Rhinosinusitis and Nasal Polyps (neither, chronic rhinosinusitis and nasal polys, chronic rhinosinusitis without nasal polys, nasal polys without chronic rhinosinusitis)
- Smoking history (former smoker [yes, no]; cigarette pack-years)
- Alcohol history (never, former, current)

Baseline disease characteristics will also be presented in by-subject data listings.

6.3. Atopic/Allergic Conditions

Atopic/allergic conditions will be summarized for the ITT and per protocol populations for the following parameters:

- Allergic Rhinitis, Anaphylactic Reaction, Aspirin-exacerbated Respiratory Disease, Atopic Dermatitis, Chronic Rhinosinusitis, Food Allergy, Nasal Polyps, Urticaria (none, ongoing, past)

Atopic/allergic conditions will also be presented in a by-subject data listing.

6.4. Efficacy-Related Baseline Characteristics

Efficacy-related baseline characteristics will be summarized for the ITT and per protocol populations for the following parameters:

- Pre-bronchodilator FEV_1 at Screening and Baseline (L; cts)
- Post-bronchodilator FEV_1 at Screening (L; cts)
- Pre-bronchodilator percent predicted FEV_1 at Screening (%; cts; < 60, ≥ 60)
- Post-bronchodilator percent predicted FEV_1 at Screening (%; cts)
- Pre-bronchodilator FEV_1/forced vital capacity (FVC) at Screening and Baseline (ratio; cts; < 0.7, ≥ 0.7)
- FEV_1 reversibility at Screening (%; cts)
- AM PEF over last 7 days of the Run-in (L/min; cts)
- Rescue medication usage over last 7 days of the Run-in (puffs/day; cts)
- ACQ-5 score at Baseline (cts; < 1.5, ≥ 1.5)

Efficacy-related baseline characteristics will also be presented in a by-subject data listing.

6.5. Biomarker Baseline Characteristics

Biomarker baseline characteristics will be summarized for the ITT and per protocol populations for the following parameters:

- Qualifying blood eosinophils (GI/L; cts; ≥ 0.25, ≥ 0.30, ≥ 1.50)
- Blood eosinophils at Baseline (GI/L; cts; < 0.20, ≥ 0.20; < 0.25, ≥ 0.25; < 0.30, ≥ 0.30; < 1.50, ≥ 1.50)
- Qualifying and Baseline blood eosinophils (GI/L; ≥ 0.25 and < 0.25; ≥ 0.30 and < 0.30)
- Fractional exhaled nitric oxide (FeNO) at Screening (ppb; cts; < 25, ≥ 25; < 30, ≥ 30; < 35, ≥ 35; < 50, ≥ 50)
- FeNO at Baseline (ppb; cts; < 25, ≥ 25; < 30, ≥ 30; < 35, ≥ 35; < 50, ≥ 50)
- Screening and Baseline FeNO (ppb; ≥ 25 and < 25; ≥ 30 and < 30; ≥ 35 and < 35; ≥ 50 and < 50)
- Baseline blood eosinophils and Baseline FeNO categories (all combinations for 0.25 and 25; 0.25 and 30; 0.25 and 35; 0.25 and 50; repeat for 0.30)
- Immunoglobulin E (IgE) at Baseline (IU/mL; cts; normal [≤ 158], high [> 158])
- 25-Hydroxyvitamin D at Baseline (ng/mL; cts; ≤ 20, > 20)
- Chloride at Baseline (mmol/L; cts; ≤ Quartile 1, > Quartile 1-≤ Quartile 2, > Quartile 2-≤ Quartile 3, > Quartile 3, where quartiles are based on the ITT population)

Biomarker baseline characteristics will also be presented in a by-subject data listing.

6.6. Prior Medications

Verbatim prior medication terms will be coded to a drug class (anatomical therapeutic chemical [ATC2]) and PT using World Health Organization (WHO)Drug Global B3 March 2018 or later. Prior medications are defined as all medications that started prior to the date of first dose of study treatment. In general, if it is not clear whether a medication is prior due to missing or incomplete medication start date, the medication will be considered to be prior unless the non-missing portions of the start date indicate otherwise. Counting will be by subject and at each level of summarization (e.g., any medication, ATC2, and PT), subjects receiving more than one medication will be counted only once.

Prior medications will be summarized for the safety population.

6.6.1. Prior Asthma Medications

Prior asthma controller medications will be summarized for the ITT population.

Prior asthma biologic medications will be summarized and include, but are not limited to, those with a PT in the following list: mepolizumab, benralizumab, omalizumab, and dupilumab.

In addition, prior leukotriene receptor antagonist (LTRA) (e.g., montelukast) use will be summarized.

Lastly, the number and percent of subjects who received an ICS plus a long-acting beta-agonist (LABA), who received an ICS plus a LABA plus a long-acting muscarinic antagonist (LAMA), and who received an ICS plus a LABA plus a LTRA will be summarized.

6.7. Concomitant Medications

Verbatim concomitant medication terms will be coded to a drug class (ATC2) and PT using WHODrug Global B3 March 2018 or later.

Concomitant medications are defined as all medications that started on or after the date of first dose of study treatment or that started prior to the date of first dose of study treatment and stopped on or after the date of first dose of study treatment or were ongoing. In general, if it is not clear whether a medication is concomitant due to missing or incomplete medication start and/or end dates, the medication will be considered to be concomitant unless the non-missing portions of the start and end dates indicate otherwise.

A medication may be considered as both prior and concomitant i.e. prior and concomitant medications are not mutually exclusive. Counting will be by subject and at each level of summarization (e.g., any medication, ATC2, and PT), subjects receiving more than one medication will be counted only once.

Concomitant medications will be summarized for the safety population. Prior and concomitant medications will also be presented in a by-subject data listing and will include an indicator, identifying each medication as prior and/or concomitant.

6.7.1. Concomitant Asthma Medications

Concomitant asthma controller medications will be summarized for the ITT population. In addition, concomitant LTRA (e.g., montelukast) will be summarized for the ITT population.

Lastly, the number and percent of subjects who received an ICS plus a LABA, who received an ICS plus a LABA plus a LAMA, and who received an ICS plus a LABA plus a LTRA will be summarized for the ITT population.

7. EXTENT OF EXPOSURE, COMPLIANCE, AND TIME ON STUDY

7.1. Extent of Exposure

Duration of study treatment (days, weeks, and subject-years) will be summarized for the safety population using descriptive statistics and categorically (every 4 weeks). Duration of study treatment will also be presented in a by-subject data listing.

7.2. Compliance

Compliance with study treatment will be assessed using the following formula:

Treatment compliance (%) = (# of actual tablets taken/# of expected tablets) x 100,

where # of actual tablets taken = (# of tablets dispensed - # of tablets returned) and # of expected tablets is based on actual duration of study treatment

Compliance will be summarized for the safety population using descriptive statistics and categorically (< 80, ≥ 80-100, > 100-< 120, ≥ 120).

Compliance with study treatment will also be presented in a by-subject data listing. In addition, IP accountability including kit information will be presented in a by-subject data listing.

7.3. Time on Study

Time on study (days, weeks, and subject-years) will be summarized for the safety population using descriptive statistics and categorically (every 4 weeks). The latest assessment date for each subject will be used in the calculation of time on study. Time on study will also be presented in a by-subject data listing.

8. EFFICACY EVALUATION

8.1. Overview of Efficacy Analysis Issues

8.1.1. Handling of Dropouts or Missing Data

A variety of methodological approaches will be applied for handling subjects with missing data; full details are provided in Section 8.3.

8.1.2. Multicenter Studies

Data from all countries and sites will be pooled for the purpose of analyses.

8.1.3. Multiple Comparisons/Multiplicity

In general, statistical testing of efficacy endpoints will be made without any adjustments for multiplicity, and all statistical hypothesis tests will be two-sided with a significance level of 0.050.

8.2. Efficacy Endpoints

Table 1 provides a summary of the statistical models/methods of primary and sensitivity analyses to be used for the primary, secondary, and select tertiary/exploratory endpoints. For all efficacy analyses, ICS dose stratification factor values used for randomization will be used as a covariate and results will be summarized for the ITT population, unless otherwise stated.

Table 1: Efficacy Endpoints and Analysis Methods

Efficacy Endpoints	Missing Data Threshold[a]	Logistic Regression		ANCOVA		MMRM		Cox Proportional Hazards	Negative Binomial Regression[b]
		without MI	with MI	with MI	without MI	with MI	without MI		
Primary Proportion of subjects who experience worsening of asthma by Week 24		P, S	S						
Secondary									
Change from baseline to Week 24 in ACQ-5 score	< 5%				P		S		
	≥ 5%			P	S	S	S		
Change from baseline to Week 24 in pre-bronchodilator FEV_1	< 5%				P		S		
	≥ 5%			P	S	S	S		
Time to first asthma worsening								P	
Annualized rate of severe asthma exacerbations									P, S
Change from baseline to Week 24 in post-bronchodilator FEV_1	< 5%				P				
	≥ 5%			P	S				
Change from baseline to Week 24 in AM PEF	< 5%				P		S		
	≥ 5%			P	S	S	S		
Tertiary/Exploratory									
PROs									
Proportion of subjects with a greater than or equal to 0.5 decrease in ACQ-5 score at any time post-baseline		P							
Change from baseline to Week 24 in AQLQ-S					P				
Change from baseline to Week 24 in SNOT-22					P				
Change from baseline to Week 24 in hair-loss assessment[c]									
Additional Markers of Asthma Control									
Change from baseline to Week 24 in rescue medication use					P				

Efficacy Endpoints	Missing Data Threshold[a]	Logistic Regression		ANCOVA		MMRM		Cox Proportional Hazards	Negative Binomial Regression[b]
		without MI	with MI	with MI	without MI	with MI	without MI		
Change from baseline to Week 24 in daily asthma symptom scores					P				
Change from baseline to Week 24 in awakening at night due to asthma symptoms requiring rescue medication use					P				
Biomarkers									
Change from baseline to Week 24 in FeNO					P				
Percentage change from baseline to Week 24 in FeNO					P				
Change from baseline to Week 24 in sputum eosinophils and neutrophils					P				

ANCOVA = analysis of covariance; MMRM = mixed-effects model with repeated measures; MI = multiple imputation; P = primary; S = sensitivity

[a] The analysis approach depends on the amount of missing data for the endpoint in the ITT population.

[b] If the distribution of severe exacerbation data is underdispersed, or if the negative binomial regression model fails to converge, a Poisson regression model will be used instead.

[c] Cross tabulations of the Baseline assessment versus the Week 24 assessment for Norwood classification (males) and Savin classification (females) separately.

8.3. Analysis Methods

8.3.1. Primary Efficacy Analyses

The primary endpoint is the proportion of subjects who experience worsening of asthma by Week 24 as defined by at least one of the following:

- On 2 consecutive days, AM PEF ≤ 75% of mean AM PEF measured over the last 7 days of the Run-in
- FEV_1 < 80% of baseline (Visit 2)
- Increase in rescue medication use of ≥ 6 puffs/day on 2 consecutive days compared to mean use over the last 7 days of the Run-in
- Increase in ACQ-5 score of ≥ 0.5 compared to baseline (Visit 2)
- The occurrence of a severe asthma exacerbation (asthma attack) defined as deterioration of asthma that leads to the use of systemic corticosteroids for at least 3 days, hospitalization, or an Emergency Department visit

Logistic regression modeling will be used to compare each GB001 group with placebo. The model will include covariates for treatment group, ICS dose (medium or high) at randomization, region (North America, Eastern Europe, Western Europe), baseline pre-bronchodilator FEV_1, and baseline ACQ-5 score. If the full model does not converge, a model with treatment group, ICS dose at randomization, and region as covariates will be utilized. If this reduced model does not converge, a model with treatment group and ICS dose at randomization will be used. In the rare case that convergence issues remain, only treatment group will be included in the model.

The number and proportion of subjects meeting the primary endpoint and corresponding 95% Wilson (Score) CIs (Wilson, 1927) will be summarized by treatment group. ORs, corresponding asymptotic 95% CIs along with the absolute differences and corresponding 95% CIs, and p-values will be summarized for each GB001 group versus placebo. The 95% CIs for the absolute difference will be Newcombe continuity-corrected CIs (Newcombe, 1998). Percentage reductions and corresponding 95% CIs will also be summarized. Lastly, the number and proportion of subjects meeting each component of the primary endpoint, with observed worsening of asthma, and with an assigned status of asthma worsening will also be summarized by treatment group. Subjects can meet more than one component of the primary endpoint.

A subject who prematurely withdraws from the study without experiencing asthma worsening will be assigned asthma worsening status by Week 24 (yes/no) based on their discontinuation of study treatment and withdrawal from study reasons as summarized below in Table 2. If a subject's reason for discontinuation of study treatment or withdrawal from study is indicative of lack of efficacy or is an AE indicative of asthma worsening, a determination will be made prior to study unblinding for the interim analysis regarding whether the subject should be considered to have had asthma worsening for the primary endpoint. Otherwise, subjects who prematurely withdraw from the study will be considered to have not experienced asthma worsening for the primary endpoint.

Table 2: Criteria for determination of asthma worsening status for subjects who prematurely withdraw from the study without experiencing asthma worsening

Reason for Discontinuation of Study Treatment and/or Withdrawal from Study	**Asthma Worsening Status Assigned (Yes/No)**
Lack of Efficacy	Yes
AE where the corresponding AE PT reflects asthma worsening including 'asthma'	Yes
Death where death is due to an SAE where the corresponding SAE PT reflects asthma worsening including 'asthma'	Yes
Lost to follow-up, Non-compliance with study drug, Physician decision, Protocol deviation, Withdrawal by Subject, or Other, where further details indicate asthma, asthma worsening, lack of efficacy or prescription of or switch to a new asthma treatment	Yes
AE where the corresponding AE PT does not reflect asthma worsening	No
Death where death is due to an SAE where the corresponding PT does not reflect asthma worsening	No
Lost to follow-up, Non-compliance with study drug, Physician decision, Protocol deviation, Withdrawal by Subject, or Other, where further details do not indicate asthma, asthma worsening, lack of efficacy or prescription of or switch to a new asthma treatment	No

A bar graph of the proportion of subjects meeting the primary endpoint by treatment group and a bar graph of the proportion of subjects meeting each component of the primary endpoint by treatment group will be provided.

The primary endpoint and components will also be presented in a by-subject data listing.

8.3.1.1. Sensitivity Analyses

Table 3 provides an overview of the primary and sensitivity analyses of the primary endpoint.

Table 3: Summary of Primary and Sensitivity Analyses of the Primary Endpoint

Analysis	Description
Primary analysis	Logistic regression where subjects with missing values are assigned asthma worsening status by Week 24 based on discontinuation of study treatment /withdrawal from study reasons
Sensitivity analysis #1: Missing Status Imputed as Asthma Worsening	Logistic regression where subjects with missing values are considered to have asthma worsening by Week 24
Sensitivity analysis #2: Worse Case Imputation	Logistic regression where placebo subjects with missing values are considered to NOT have asthma worsening by Week 24 and GB001 subjects with missing values are considered to have asthma worsening by Week 24
Sensitivity analysis #3: As Observed Analysis	Logistic regression using only those subjects with an observed status for asthma worsening by Week 24
Sensitivity analysis #4: MI	Logistic regression using MI
Sensitivity analysis #5: Per Protocol Population	Logistic regression in per protocol population using the same approach as primary analysis

MI = multiple imputation

Sensitivity analyses of the primary endpoint will be conducted to evaluate the robustness of treatment effect under different assumptions and imputation algorithms. Sensitivity analyses will utilize the same logistic regression model as the primary analysis.

In general, for all sensitivity analyses, the number and proportion of subjects meeting each component of the primary endpoint, with observed worsening of asthma, and with an assigned status of asthma worsening will be summarized. The exceptions are Sensitivity Analysis #3 where the number of subjects with an assigned status will not be presented given that the analysis is among subjects with an observed status, and Sensitivity Analysis #4 where the number for each component will not be presented as multiple imputation (MI) will be performed for the overall asthma worsening status (yes/no).

8.3.1.1.1. Sensitivity Analysis #1: Missing Status Imputed as Asthma Worsening

A sensitivity analysis will be conducted with all subjects who prematurely withdraw from the study without experiencing asthma worsening by Week 24 considered as having experienced asthma worsening by Week 24.

8.3.1.1.2. Sensitivity Analysis #2: Worst Case Imputation

A worst case sensitivity analysis will be conducted where all placebo subjects who withdraw from study without experiencing asthma worsening are considered as not having asthma

worsening by Week 24 and all GB001 subjects who withdraw from study without experiencing asthma worsening are considered as having asthma worsening by Week 24.

8.3.1.1.3. Sensitivity Analysis #3: As Observed Analysis

An as observed sensitivity analysis will be conducted where only subjects with an observed status for asthma worsening by Week 24 are included.

8.3.1.1.4. Sensitivity Analysis #4: Multiple Imputation

If the number of subjects overall with a missing observed status for asthma worsening by Week 24 is ≥ 5%, then the following MI approach will be conducted as a sensitivity analysis.

The dichotomous outcome of asthma worsening by Week 24 will be imputed for subjects who have withdrawn from study without having experienced asthma worsening using a MI approach assuming that these subjects with a missing dichotomous outcome would have similar outcomes to subjects who had an observed status of asthma worsening by Week 24. The dichotomous outcome will be imputed directly as opposed to imputing the individual components of the primary endpoint and then deriving the composite outcome.

The following steps will be performed:

- Intermittent missing values will first be imputed using the Fully Conditional Specification method, which is appropriate for non-monotonic missing data for binary data.
- The monotone missing values will then be multiply imputed using the monotone logistic regression imputation method (Allison, 2005). A monotone missing pattern is such that in the event that a variable is missing it is implied that all subsequent variables are also missing (i.e. once a subject withdraws from study, no additional data is expected for that subject).
- For each stage, MI will be performed within treatment group with covariate adjustment the same as the primary analysis of the primary endpoint and non-missing outcomes for asthma worsening. Should convergence issues occur due to small cell size for the categorical covariates at either stage, they will be removed from the model.
- The primary analysis of the primary endpoint as described in Section 8.3.1 will be performed for each complete, imputed dataset.
- Fifty imputations will be performed.
- Results of the logistic regression on the multiple imputed data sets will be combined to generate an overall estimate and associated variance using Rubin's rules (Rubin, 1987).

The imputed data logistic regression model-based estimates of the proportion of subjects with asthma worsening, ORs, corresponding 95% CIs, and p-values will be reported. Percentage reductions and corresponding 95% CIs will also be provided.

8.3.1.1.5. Sensitivity Analysis #5: Per Protocol Population

If ≥ 5% of subjects in the ITT population are excluded from the per protocol population, then a sensitivity analysis will be conducted in which the primary analysis of the primary endpoint will be repeated in the per protocol population.

8.3.1.2. Evaluation of Dose Response for the Primary Endpoint

A dose response analysis will be conducted to evaluate the relationship between increasing dose and the effect of GB001, using the primary analysis method of the primary endpoint.

A one-sided, asymptotic, Cochran-Armitage test for trend (Cochran, 1954; Armitage, 1955) will be used to test if the response proportion with asthma worsening decreases linearly with increasing dose level (placebo, 20 mg, 40 mg, 60 mg). The p-value from the test will be reported.

For this test, the null hypothesis, H0 ($\Pi_0 = \Pi_{20} = \Pi_{40} = \Pi_{60}$) is: There is no linear trend in binomial proportions of response across increasing levels of dosage.

The alternative hypothesis, (H1) ($\Pi_0 \geq \Pi_{20} \geq \Pi_{40} \geq \Pi_{60}$) is: There is a decreasing trend in binomial proportions of response across increasing levels of dosage.

To further evaluate the dose response relationship, the ORs and corresponding 95% CIs for the 3 pairwise comparisons among each of the GB001 treatment groups will be provided (60 mg vs 20 mg, 60 mg vs 40 mg, 40 mg vs 20 mg). Percentage reductions and corresponding 95% CIs will also be provided.

8.3.1.3. Additional Analyses of the Primary Endpoint

Logistic regression modeling based on an as observed analysis using the same logistic regression model as Sensitivity Analysis #3 will be used to compare each GB001 group with placebo for the following:

- Each individual component of the primary endpoint separately. An individual component will not be analyzed if < 5 total subjects meet the criterion in the ITT population.
- The AM PEF and FEV_1 components only, as they represent worsening of asthma related to lung function.
- The rescue medication, ACQ-5 score, and severe asthma exacerbation components only, as they represent worsening of asthma related to asthma control.

Lastly, the primary endpoint will be analyzed in a manner similar to the primary analysis, but for the timeframe of by the Follow-up Visit (Week 28) rather than by Week 24.

8.3.2. Secondary Efficacy Analyses

The secondary efficacy endpoints are listed in Table 1 and will be analyzed as described below.

8.3.2.1. Change from Baseline to Week 24 Endpoints

Change from baseline to Week 24 in ACQ-5 score, pre-bronchodilator FEV_1, post-bronchodilator FEV_1, and AM PEF will be analyzed as described below.

The ACQ-5 is a five-item questionnaire which has been developed as a measure of the subject's asthma control that can be quickly and easily completed (Juniper E. F., 2005). The response options for each of these questions consists of a zero (no impairment/limitation) to 6 (total impairment/limitation) scale with the total score ranging from 0 to 30. ACQ-5 score is the average of the 5 non-missing items and will be calculated at each visit for each subject. The minimal clinically important difference (MCID) is 0.5 points.

For AM PEF, the baseline value is defined as the mean over the last 7 days of the Run-in including the value on Day 1 and Week 24 is defined as the mean over the last 7 days prior to Week 24 including the value on the day of the Week 24 visit. For the other endpoints, the baseline value is defined as the last non-missing value on or before the date of the first dose of study treatment.

If the number of subjects overall with a missing change from baseline value is < 5% for a particular endpoint:

- The primary analysis will be analysis of covariance (ANCOVA) without MI.
- As a sensitivity analysis, mixed-effects model with repeated measures (MMRM) without MI will also be performed.

If the number of subjects overall with a missing change from baseline value is ≥ 5% for a particular endpoint:

- The primary analysis will be ANCOVA with MI.
- As sensitivity analyses, MMRM with MI, ANCOVA without MI, and MMRM without MI will also be performed.

Post-bronchodilator FEV_1 will not be analyzed using MMRM as it is collected at only one post-baseline timepoint.

Each secondary endpoint of change from baseline to Week 24 will be analyzed using ANCOVA models. For this analysis, the MI procedure analogous to that described in Section 8.3.1.1.4 will be performed if the number of subjects overall with a missing change from baseline value is ≥ 5% with the following modifications for cts data: (1) intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) method (Schafer, 1997), and (2) monotone missing values will be imputed using a regression model. Covariate adjustment will be the same as for the primary endpoint for ACQ-5 score and pre-bronchodilator FEV_1. For post-bronchodilator FEV_1 and AM PEF, the covariates used in the model will be the same as for the primary endpoint except that baseline pre-bronchodilator FEV_1 will be replaced with baseline post-bronchodilator FEV_1 or baseline AM PEF, depending on the endpoint of interest. ANCOVA without MI will be performed similarly as described above without the imputation of values.

Descriptive statistics for change from baseline to Week 24 along with the LS means, SEs, and corresponding 95% CIs for each treatment group will be presented. Differences in LS means, SEs, corresponding 95% CIs, and p-values for each GB001 group versus placebo will also be constructed from the ANCOVA models.

In addition, each secondary endpoint of change from baseline to Week 24 will be analyzed by MMRM except for change from baseline to Week 24 in post-bronchodilator FEV_1. MMRM will

be performed using a restricted maximum-likelihood (REML)-based approach and an unstructured covariance structure to model within-subject error. The MMRM model will include change from baseline values up to Week 24 as the response variable; the fixed, categorical effects of treatment group, ICS dose (medium or high) at randomization, region, visit, and treatment group by visit interaction; and the cts, fixed covariates of baseline value and baseline value by visit interaction.

Parameters will be estimated using REML with the Newton-Raphson algorithm. Treatment comparisons will be derived from the MMRM. Differences in LS mean changes from baseline, the corresponding 95% CIs, and p-values with Kenward-Roger adjustment (Kenward, 1997) will be provided for comparison for each GB001 group versus placebo. LS means will be reported along with SEs and corresponding 95% CIs, and differences between treatment groups reported with LS means, SEs, corresponding 95% CIs, and p-values.

If a given analysis fails to converge due to the complexity of model specification, the following will be considered to enable model convergence: 1) use of maximum likelihood estimation instead of REML; and/or 2) a compound symmetric or first-order autoregressive covariance structure will be utilized, based on the covariance structure converging to better fit as determined based on Akaike's information criterion (Akaike, 1973).

Actual values and change from baseline values for ACQ-5 score, pre-bronchodilator FEV_1, post-bronchodilator FEV_1, and AM PEF will be summarized by visit. Differences in means, SEs, and corresponding 95% CIs constructed from analysis of variance (ANOVA) models adjusting for treatment group only will also be presented. In addition, figures of mean actual values and mean change from baseline values, including SE bars, for ACQ-5 score and pre-bronchodilator FEV_1 by visit will be provided. Lastly, bar graphs of the LS means and CIs for Week 24 for ACQ-5 score and pre-bronchodilator FEV_1 will be provided.

Lastly, a sensitivity analysis with a different method of handling pre-bronchodilator FEV_1 measurements confounded by systemic corticosteroid use will be performed. Pre-bronchodilator FEV_1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date + 14 days will be excluded in order to reduce the confounding effect of systemic corticosteroids. If the number of subjects overall with a missing change from baseline is < 5%, then only ANCOVA without MI will be performed. If the number of subjects overall with a missing change from baseline value is ≥ 5%, ANCOVA with MI and MMRM with MI will be performed.

ACQ-5 score, pre-bronchodilator FEV_1, post- bronchodilator FEV_1, and AM PEF data will also be presented in by-subject data listings.

8.3.2.1.1. Evaluation of Dose Response for ACQ-5 and Pre-Bronchodilator FEV_1

A dose response analysis for change from baseline to Week 24 in ACQ-5 score and pre-bronchodilator FEV_1 will be conducted to evaluate the relationship between increasing dose and the effect of GB001, using the primary analysis method of these secondary efficacy endpoints. Differences in LS means and SEs for all pairwise comparisons will be provided. In addition, Tukey's multiple comparisons test (i.e. Tukey's honest significance difference) will be used to compare all possible pairwise means to test which pairwise means differ while adjusting nominal

type 1 error at 5%. The simultaneous 95% CIs and p-values from Tukey's test will be reported. Box plots for mean change from baseline to Week 24 by treatment group will be presented.

8.3.2.2. Time to First Asthma Worsening

Time to first asthma worsening is defined as the time from the date of the first dose of study treatment to the first date that any of the components of the asthma worsening endpoint is met. Subjects who do not experience asthma worsening will be censored on the date of their last assessment for any of the components of asthma worsening. For the primary analysis of time to first asthma worsening, all data up to Week 24 will be utilized; a sensitivity analysis of time to first asthma worsening will be performed utilizing all data up to the Follow-up Visit (Week 28).

For subjects who experience asthma worsening, the date of the event is defined for each component as:

- AM PEF and rescue medication use – date of event is considered to be on the first of 2 consecutive days where the respective criterion is met
- FEV_1 and ACQ-5 score – date of event is considered to be on the date of the qualifying assessment
- Severe exacerbation – date of event is considered to be on the date of onset of exacerbation as captured on the Severe Asthma Exacerbations eCRF

The number and proportion of subjects with asthma worsening will be summarized. The number and proportion of subjects meeting each component will also be summarized with subjects counted only once for the component first met.

Time to asthma worsening will be compared between treatment groups using a Cox proportional hazards model. The exact method will be used to handle ties in event times. Covariate adjustment will be the same as for the primary endpoint. Estimates of the hazard ratio for each GB001 group versus placebo, corresponding 95% CIs, and p-values will be provided from the model. Percentage reductions and corresponding 95% CIs will also be provided. Kaplan-Meier summaries of the proportion of subjects with asthma worsening over time will also be presented and displayed graphically. The median event time (and other quartiles), if estimable, and corresponding 95% CI based on the Brookmeyer and Crowley method (Brookmeyer, 1982) will be provided for each treatment arm.

Time to asthma worsening data will also be presented in a by-subject data listing.

8.3.2.3. Annualized Rate of Severe Asthma Exacerbations

A severe asthma exacerbation is defined as deterioration of asthma that leads to the use of systemic corticosteroids for at least 3 days, hospitalization, or an Emergency Department visit. Exacerbations for which the courses of systemic corticosteroids are separated by 7 or more days will be counted as separate severe asthma exacerbations.

The number and proportion of subjects with 0, 1, and ≥ 2 severe exacerbations and the annualized rate of severe asthma exacerbations will be summarized. The unadjusted annualized rate of severe exacerbations will be calculated as the total number of severe exacerbations divided by the total number of subject-years of follow-up and will also be summarized.

The total number of severe exacerbations will be analyzed using a negative binomial regression model, with the logarithmic transformation of follow-up time as the offset parameter. The follow-up time is defined as the subject's time on study up to and including Day 174. The model will include terms for treatment group, ICS dose (medium or high) at randomization, region, age at screening, and the number of exacerbations in the past 12 months. If the distribution of severe exacerbation data is under dispersed, or if the negative binomial regression model fails to converge, a Poisson regression model will be used instead of the negative binomial regression model. Exacerbations for which the courses of systemic corticosteroids are separated by 7 or more days will be counted as separate exacerbations.

Rate ratios for each GB001 group versus placebo, corresponding 95% CIs, and p-values will be provided from the model. In addition, the rate ratios and corresponding 95% CIs for the 3 pairwise comparisons among each of the GB001 treatment groups will be provided (60 mg vs 20 mg, 60 mg vs 40 mg, 40 mg vs 20 mg). Lastly, percentage reductions and corresponding 95% CIs will also be provided.

A sensitivity analysis will be performed to include asthma exacerbations that were treated with an intramuscular (IM) injection of systemic corticosteroids for less than 3 days. In this analysis, a severe asthma exacerbation will be defined as deterioration of asthma that leads to the use of oral or intravenous systemic corticosteroids for at least 3 days, the use of IM systemic corticosteroids for at least 1 day, hospitalization, or an Emergency Department visit.

Lastly, analyses of annualized rate of severe exacerbations will also be presented for the primary definition of severe asthma exacerbation by various time periods (Baseline to Week 12, Week 12 to Week 24, and Baseline through the Follow-up Visit [Week 28]) in order to elucidate onset and durability of effect over time.

This data will also be presented in a by-subject data listing.

8.3.3. Tertiary/Exploratory Analyses

The tertiary/exploratory endpoints are listed in Table 1 and will be analyzed as described below.

8.3.3.1. PRO Endpoints

8.3.3.1.1. Proportion of Subjects with a ≥ 0.5 Decrease in ACQ-5 Score from Baseline

The proportion of subjects with a ≥ 0.5 decrease from baseline in ACQ-5 score at any time post-baseline by Week 24 will be analyzed in the subset of the ITT population who have a non-missing baseline value and at least one post-baseline value. Logistic regression modeling will be used to compare each GB001 group with placebo as for the primary endpoint. ORs, corresponding asymptotic 95% CIs along with the absolute differences and corresponding 95% CIs, and p-values will be summarized for each GB001 group versus placebo. Percentage reductions and corresponding 95% CIs will also be provided.

The number and proportion of subjects with a ≥ 0.5 decrease from baseline in ACQ-5 score and corresponding 95% CIs will also be summarized by visit.

8.3.3.1.2. Change from Baseline in AQLQ-S

The AQLQ-S is a disease-specific, self-administered quality of life (QOL) questionnaire developed to evaluate the impact of asthma on the subject's QOL (Juniper, 1993). The questionnaire contains 32 items in 4 domains with a 2-week recall period: activity limitations (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). Additionally, each of the 32 responses are averaged to produce an overall QOL score. Responses are scored on a seven-point scale with a value of 1 indicating total impairment and 7 indicating no impairment. The MCID is 0.5 points (Juniper, 1994).

Overall and domain scores will be derived by taking the average of the item responses at each visit. The activity limitations and symptoms domain scores will only be derived if there is ≤ 1 missing item response per domain. The emotional function and environmental stimuli domain scores will only be derived if there are no missing item responses per domain. Overall score will only be derived if all 4 domain scores are non-missing. Overall and domain scores will be summarized by visit.

Change from baseline to Week 24 in AQLQ-S will be analyzed using an ANCOVA model without MI. Covariate adjustment will be the same as for the primary endpoint except that baseline pre-bronchodilator FEV_1 will be replaced with baseline AQLQ-S. LS means will be reported along with SEs and corresponding 95% CIs, and differences between treatment groups reported with LS means, SEs, corresponding 95% CIs, and p-values. Results will be presented for the overall score only.

AQLQ-S overall and domain scores will also be presented in a by-subject data listing.

8.3.3.1.3. Change from Baseline in SNOT-22

SNOT-22 is a QOL instrument to assess the impact of chronic rhinosinusitis and utilizes a 2-week recall period (Hopkins, 2009). The questionnaire will only be completed by subjects with a prior history of sinusitis, nasal polyps, or allergic rhinitis to assess whether GB001 has an impact on this common comorbidity in patients with asthma. The questionnaire consists of 22 items across 5 domains: Nasal, Ear, Sleep, General and Practical, and Emotional. A scale ranging from 0 (no problem) to 5 (problem as bad as it can be) is used to respond to each item in the questionnaire with the total global score ranging from 0 to 110. The global MCID is 8.9.

Overall and domain scores will be derived by taking the sum of the non-missing item responses at each visit. Overall and domain scores will be summarized by visit.

Change from baseline to Week 24 in SNOT-22 will be analyzed using an ANCOVA model without MI. Covariate adjustment will be the same as for the primary endpoint except that baseline pre-bronchodilator FEV_1 will be replaced with baseline SNOT-22. LS means will be reported along with SEs and corresponding 95% CIs, and differences between treatment groups reported with LS means, SEs, corresponding 95% CIs, and p-values. Results will be presented for the overall score only.

Subgroup analyses will be performed for the following:

- Subjects with sinusitis (regardless of nasal polyps)
- Subjects with sinusitis and nasal polyps

- Subjects with sinusitis and without nasal polyps

SNOT-22 overall and domain scores will also be presented in a by-subject data listing.

8.3.3.1.4. Change from Baseline in Hair-Loss Assessment

A visual scale (Norwood classification for male subjects and Savin classification for female subjects) to characterize the degree of scalp hair loss at baseline and at the end of the study will be used (Gupta, 2016). This information will be complemented with a modified questionnaire to assess patient perceptions of scalp hair growth at the end of the study. This questionnaire includes 2 simple questions to describe possible scalp hair growth changes during the study period.

Cross tabulations of the Baseline assessment versus the Week 24 assessment will be presented for the Norwood classification for males and Savin classification for females separately.

Hair-loss assessment data will also be presented in a by-subject data listing.

8.3.3.2. Additional Markers of Asthma Control

8.3.3.2.1. Change from Baseline in Daily Rescue Medication Use, Daily Asthma Symptom Scores, and Awakening at Night Due to Asthma Symptoms Requiring Rescue Medication Use

Rescue medications include the study-provided salbutamol/albuterol or any other short-acting bronchodilator. All rescue medication use is to be captured in an eDiary.

Change from baseline to Week 24 in daily rescue medication use, daily asthma symptoms scores, and awakening at night due to asthma symptoms requiring rescue medication use will be analyzed using an ANCOVA model without MI. Covariate adjustment is the same as the primary endpoint except that baseline pre-bronchodilator FEV_1 will be replaced with baseline rescue medication use, baseline daily symptom score, or baseline awakening at night due to asthma symptoms requiring rescue medication use, depending on the endpoint of interest.

Daily rescue medication use is collected as the number of puffs during the past 24 hours. The baseline rescue medication value is defined as the mean number of puffs over the last 7 days of the Run-in including the value on Day 1 and Week 24 is defined as the mean number of puffs over the last 7 days prior to Week 24 including the value on the day of the Week 24 visit. Similarly, the value at all other post-baseline visits is defined as the mean number of puffs over the last 7 days prior to that visit including the day of the visit.

Daily asthma symptom score over the previous 24 hours is assessed by subjects using a 6-point scale, with higher values indicating greater symptom severity, and is captured in the same eDiary as rescue medication use. Subjects also record the number of times they had awakening at night due to asthma symptoms requiring rescue medication use in this same eDiary.

Baseline and post-baseline visit values for daily symptom scores and awakening at night are defined as for daily rescue medication use. In order for the mean to be calculated at a visit, 4 out of the 7 days must have non-missing values. If < 4 of 7 days are available, the mean is considered missing.

Actual values and change from baseline values will be summarized by visit. Differences in means, SEs, and corresponding 95% CIs constructed from ANOVA models adjusting for treatment group only will also be presented. These data will also be presented in by-subject data listings.

8.3.3.3. Biomarkers

8.3.3.3.1. FeNO

Actual values, change from baseline values, and percent change from baseline values will be summarized by visit. LS means, SEs, and corresponding 95% CIs for each treatment group and differences in LS means, SEs, and corresponding 95% CIs for each GB001 group versus placebo will be constructed from ANCOVA models without MI for both change and percent change from baseline to Week 24. The models will include covariates for treatment group and baseline FeNO.

FeNO data will also be presented in a by-subject data listing.

8.3.3.3.2. Sputum Eosinophils and Neutrophils

As sputum eosinophils and neutrophils are known to follow a log-normal distribution, analyses will be based on a log10-transformed scale, with results back-transformed to obtain the following statistics:

- Baseline geometric means and % coefficients of variation (CV), and corresponding 95% CIs by treatment group
- Week 24 geometric means, % CV, and corresponding 95% CIs by treatment group
- Within-treatment group geometric mean ratios (GMRs) for LS means for change from baseline to Week 24, using an ANCOVA model adjusting for log of baseline value, SEs, and corresponding 95% CIs
- Percent reduction in the above within-treatment group GMRs for LS means for change from baseline to Week 24 for each GB001 group versus placebo, corresponding 95% CIs, and p-values from the ANCOVA model

Sputum eosinophils and neutrophils will also be presented in a by-subject data listing.

8.3.3.4. PK Concentrations

GB001 plasma concentrations will be summarized by visit/timepoint using the following descriptive statistics: number of subjects with non-missing data, arithmetic mean, SD, arithmetic % CV, geometric mean, geometric % CV, median, minimum, and maximum.

For calculation of mean concentrations, all below limit of quantification (BLQ) values will be set to zero. If the number of values that are BLQ at a nominal timepoint exceed 50% of the observations collected at that nominal timepoint, summary statistics for the timepoint will not be calculated. If the mean concentration value is less than the lower limit of quantification (LLOQ) value, then the mean, median, minimum, and maximum concentration values will be set to BLQ.

PK concentrations will also be presented in a by-subject data listing.

8.4. Examination of Subgroups

Subgroup analyses of the primary and two secondary (ACQ-5 score and pre-bronchodilator FEV_1) efficacy endpoints will be performed for all of the subgroups specified below. In addition, subgroup analyses of the secondary efficacy endpoint of annualized rate of severe asthma exacerbations will also be performed for select subgroups as specified below. For any subgroup level that does not comprise ≥ 10% of the ITT population, the analyses based on the models will not be performed. The subgroups of interest are described below.

Demographic and general baseline characteristic subgroups:

- Age (years; < 65, ≥ 65)
- Sex (male, female)
- BMI (kg/m^2; < 30, ≥ 30)
- Baseline ICS dose ([per randomization and per actual value]; medium, high, including comparison of GB001 medium to Placebo high)
- Region (North America, Eastern Europe, Western Europe)
- Total number of exacerbations in the past 12 months (1, > 1)

Efficacy-related baseline characteristic subgroups:

- Pre-bronchodilator percent predicted FEV_1 at Screening (%; < 60, ≥ 60)
- ACQ-5 score at Baseline (< 1.5, ≥ 1.5)

Biomarker baseline characteristic subgroups:

- Blood eosinophils at Baseline (GI/L; < 0.20, ≥ 0.20; < 0.25, ≥ 0.25 [including for annualized rate of severe asthma exacerbations]; < 0.30, ≥ 0.30)
- FeNO at Baseline (ppb; < 25, ≥ 25 [including for annualized rate of severe asthma exacerbations]; < 30, ≥ 30; < 35, ≥ 35; < 50, ≥ 50)
- Blood eosinophils and FeNO at Baseline ([blood eosinophils < 0.25 GI/L and FeNO < 25 FeNO ppb] vs [blood eosinophils ≥ 0.25 GI/L and/or FeNO ≥ 25 ppb] {including for annualized rate of severe asthma exacerbations}; repeat for 0.25 vs 30, 0.25 vs 35, and 0.25 vs 50)
- Blood eosinophils and FeNO at Baseline ([blood eosinophils < 0.25 GI/L and FeNO < 25 FeNO ppb] vs [blood eosinophils < 0.25 GI/L and FeNO ≥ 25 ppb] vs [blood eosinophils ≥ 0.25 GI/L and FeNO < 25 ppb] vs [blood eosinophils ≥ 0.25 GI/L and FeNO ≥ 25 ppb]; including for annualized rate of severe asthma exacerbations)
- IgE (IU/mL; normal [≤ 158], high [> 158])
- 25-Hydroxyvitamin D at Baseline (ng/mL; ≤ 20, > 20)
- Chloride at Baseline (mmol/L; ≤ Quartile 1, > Quartile 1-≤ Quartile 2, > Quartile 3-≤ Quartile 3, > Quartile 3, where quartiles are based on the ITT population)

Models used for the subgroup analyses will be the same as those used for the primary and secondary efficacy endpoints as specified in Section 8.3.1 and Section 8.3.2.1 with covariates for the subgroup (if different than the aforementioned covariates i.e. baseline ICS dose (medium or high) at randomization and region; for the efficacy-related baseline characteristic subgroups, baseline pre-bronchodilator FEV_1 or baseline ACQ-5 score will be replaced with a categorical subgroup variable) and treatment group by subgroup interaction added. If the model does not converge, a reduced model including only treatment group, ICS dose at randomization, and region will be used.

Heterogeneity of treatment effect across different levels of each subgroup will be evaluated by presenting p-values for the treatment by subgroup interaction. The interaction term tests whether the treatment effect is significantly different across different levels of the subgroup, between males and females, for example. If a subgroup variable has more than two levels then the least severe level (where applicable) will be used as the reference subgroup, and the test will assess whether the treatment effect in the more severe levels differs from that in the reference subgroup.

Forest plots of the treatment effect estimates and corresponding 95% CIs from the subgroup analyses will be provided.

9. SAFETY EVALUATION

9.1. Adverse Events

Verbatim AE terms will be coded to a SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or later.

All analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment-emergent if it has a start date on or after the date of the first dose of study treatment. In general, if the treatment emergence of an AE is not clear due to a missing or incomplete AE start date, the AE will be considered to be treatment-emergent unless the non-missing portions of the start date and the end date indicate otherwise.

In general, whenever a tabular summary of AEs is mentioned in this document, it is intended that the tabular summary is in reference to TEAEs, even though "treatment-emergent" may not be explicitly mentioned. By-subject data listings of AEs will include all events regardless of treatment emergence and TEAEs will be identified.

Counting will be by subject, not event, and at each level of summarization (e.g., any AE, SOC, and PT), with subjects experiencing more than one AE counted only once. In the summary of AEs by severity (mild, moderate, severe), subjects will be counted once at the highest severity reported at each level of summarization. AEs that are missing severity will be presented in summary tables as "Missing". AEs that are missing relationship to study treatment will be presented in summary tables as "Related".

The following summaries will be presented for the safety population:

- Overall Summary of AEs - showing the number and percent of subjects with an AE; a moderate or severe AE; a severe AE; a SAE including asthma worsening-related terms; a SAE excluding asthma worsening-related terms; a treatment-related AE; a treatment-related SAE; an AE leading to discontinuation of study treatment; an AE leading to withdrawal from study; an AE resulting in death; and an AE of interest (as defined in Protocol Section 10.3.3).
- Incidence of AEs by SOC and PT
- AEs with Incidence ≥ 5% in Any Treatment Group by PT
- Incidence of SAEs by SOC and PT Including Asthma Worsening-Related Terms
- Incidence of SAEs by SOC and PT Excluding Asthma Worsening-Related Terms
- Incidence of AEs by SOC, PT, and Maximum Severity
- Incidence of Treatment-Related AEs by SOC and PT
- Incidence of AEs Leading to Discontinuation of Study Treatment by SOC and PT
- Incidence of AEs Leading to Withdrawal from Study by SOC and PT
- Summary of Pruritus AEs
- Incidence of Liver Chemistry AEs by PT

- Incidence of Liver Chemistry AEs Leading to Discontinuation of Study Treatment by PT
- Incidence of AEs of Interest by SOC and PT

All AEs, AEs leading to discontinuation of study treatment and/or withdrawal from study, AEs of interest, SAEs, and AEs resulting in death will be presented in by-subject data listings.

9.2. Clinical Laboratory Evaluation

Actual values and change from baseline values for quantitative laboratory parameters (clinical and liver chemistry, hematology, and urinalysis) will be summarized by visit for the safety population.

Shift tables will be presented for clinical and liver chemistry and hematology parameters summarizing shifts from baseline to high and low at any time post-baseline based on laboratory normal ranges. A shift table will also be presented for urinalysis parameters summarizing shifts from baseline to positive at any time post-baseline based on laboratory normal ranges.

A summary of maximum post-baseline values > 1.0, > 1.5, and > 3.0 GI/L for blood eosinophils will be presented.

Summaries of maximum post-baseline values for liver chemistry parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], concurrent ALT/AST and total bilirubin, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, and gamma-glutamyl transferase [GGT]) according to categories based on multiples of upper limit of normal (ULN) will be presented. Liver chemistry parameters according to categories based on multiples of ULN will also be presented by visit.

For laboratory shift tables and summaries of maximum post-baseline values, only subjects with at least one post-baseline value will be included.

The time to first elevation for ALT will be presented for subjects with an elevation in ALT. An elevation for ALT will be defined as the first post-baseline value ≥ 1.5 x ULN for subjects with a baseline value ≤ ULN, and the first post-baseline value with a > 50% increase from baseline for subjects with a baseline value > ULN. This analysis will also be repeated using a threshold of > 1.0 x ULN. In addition, the time to first elevation of AST will be summarized in the same manner as described above for time to first elevation of ALT.

In addition, the following figures/plots will be provided:

- Mean change from baseline values, including SE bars, by visit figures for liver chemistry parameters
- Mean ratio of actual values to ULN, including SE bars, by visit figures for liver chemistry parameters
- Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) (Merz, 2014) plots
- Mean actual values and mean change from baseline values, including SE bars, by visit figures for blood eosinophils
- Maximum post-baseline values versus baseline values plot for blood eosinophils

Laboratory parameters will also be presented in by-subject data listings.

9.3. Vital Signs and Other Observations Related to Safety

9.3.1. Vital Signs

Actual values and change from baseline values for vital sign parameters (systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and weight) will be summarized by visit for the safety population.

A summary table of the incidence of abnormalities in vital sign parameters will be presented according to the following abnormality criteria.

Table 4: Vital Sign Parameter Abnormality Criteria

Vital Sign Parameter	Abnormality Criteria
Systolic Blood Pressure	High or Increased: > 180 mmHg post-baseline if ≤ 180 mmHg at baseline, or an increase from baseline of > 40 mmHg. Low or Decreased: < 90 mmHg post-baseline if ≥ 90 mmHg at baseline, or a decrease from baseline of > 30 mmHg.
Diastolic Blood Pressure	High or Increased: > 105 mmHg post-baseline if ≤ 105 mmHg at baseline, or an increase from baseline of > 30 mmHg. Low or Decreased: < 50 mmHg post-baseline if ≥ 50 mmHg at baseline, or a decrease from baseline of > 20 mmHg.
Pulse Rate	High or Increased: > 120 bpm post-baseline if ≤ 120 bpm at baseline, or an increase from baseline of > 20 bpm. Low or Decreased: < 50 bpm post-baseline if ≥ 50 bpm at baseline, or a decrease from baseline of > 20 bpm.
Temperature	> 38 degrees C and an increase from baseline of at least 1 degree C.

bpm= beats per minute

Vital sign parameters will also be presented in a by-subject data listing and abnormalities will be flagged.

9.3.2. Other Safety Measures

9.3.2.1. Electrocardiograms

Actual values and change from baseline values will be summarized by visit for the safety population for the following quantitative ECG parameters: heart rate, PR interval, QRS duration, QT interval (uncorrected), Fridericia's correction formula for QT interval (QTcF), Bazett's correction formula for QT interval (QTcB), and RR interval.

Outlier analyses for QTcF intervals will be performed. This will consist of a summary of the number and percent of subjects with a post-baseline QTcF interval greater than 450 msec, 480 msec, and 500 msec and the number and percent of subjects with an increase from baseline in QTcF interval of greater than 30 msec and 60 msec.

Each ECG will be assessed with an overall interpretation of normal, abnormal, or unable to evaluate. Shift tables for overall interpretation will be presented, summarizing shifts from baseline to abnormal at any time post-baseline.

ECG parameters will also be presented in a by-subject data listing and outliers will be flagged.

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