Statistical Analysis Plan

NCT Number: NCT06268301

Title: A Randomized, Open-Label, Single-Dose, Two-Way Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics, Safety, and Tolerability of Budesonide Oral Suspension in Healthy Adult Participants

Study Number: TAK-721-1003

Document Version and Date: Final, 18 January 2023

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-721-1003

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Phase: 1

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ABBREVIATIONS

λ_z	terminal disposition phase rate constant
AE	adverse event
AESI	adverse event of special interest
$AUC_{0\text{-}12}$	area under the concentration-time curve from time 0 to 12 hours
AUC_{∞_obs}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{∞_pred}	area under the concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration
$AUC_{extrap\%\_obs}$	area under the curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_obs}
$AUC_{extrap\%\_pred}$	area under the curve from the last quantifiable concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred}
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BLQ	below the lower limit of quantitation
BOS	budesonide oral suspension
CI	confidence interval
$CL/F_{\_obs}$	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
$CL/F_{\_pred}$	apparent clearance after extravascular administration, calculated using the predicted value of the last quantifiable concentration
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variance
DMP	data management plan
ECG	electrocardiogram
ET	early termination
Geom	geometric
GMR	geometric least-squares mean ratio
ICF	informed consent form
LLN	lower limit of normal
LSM	least-squares mean
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
PK	pharmacokinetic

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SOC	System Organ Class
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{lag}	lag time to first quantifiable concentration
t_{max}	time to first occurrence of C_{max}
$V_z/F_{\_obs}$	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration
$V_z/F_{\_pred}$	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the predicted value of the last quantifiable concentration
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To assess the relative bioavailability of a single dose of budesonide oral suspension (BOS) administered under fasting and fed (high-fat/high-calorie meal) conditions.

1.1.2 Secondary Objectives

To assess the safety and tolerability of a single dose of BOS administered under fasting and fed (high-fat/high-calorie meal) conditions.

To evaluate other pharmacokinetic (PK) parameters of a single dose of BOS administered under fasting and fed (high-fat/high-calorie meal) conditions.

1.2 Endpoints

1.2.1 Primary Endpoints

The following primary PK parameters will be analyzed for plasma budesonide:

- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞_obs}).

1.2.2 Secondary Endpoints

Safety endpoints will include:

- Incidence of treatment-emergent adverse events (TEAEs) and their severity, seriousness, and causality.
- Incidence of clinically significant abnormal values for vital signs, and clinical laboratory evaluations.

The following secondary PK parameters will be analyzed for plasma budesonide:

- Area under the concentration-time curve from time 0 to 12 hours ($AUC_{0\text{-}12}$).
- Area under the curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_obs} ($AUC_{extrap}\%_{obs}$).
- Time to first occurrence of C_{max} (t_{max}).

- Lag time to first quantifiable concentration (t_{lag}).
- Terminal disposition phase half-life ($t_{1/2z}$).
- Terminal disposition phase rate constant (λ_z).
- Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration ($CL/F_{\_obs}$).
- Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration ($V_z/F_{\_obs}$).

1.2.3 Additional Endpoints

The following additional PK parameters will be analyzed for plasma budesonide:

- Area under the concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration (AUC_{∞_pred}).
- Area under the curve from the last quantifiable concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred} ($AUC_{extrap}\%_{\_pred}$).
- Apparent clearance after extravascular administration, calculated using the predicted value of the last quantifiable concentration ($CL/F_{\_pred}$).
- Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the predicted value of the last quantifiable concentration ($V_z/F_{\_pred}$).

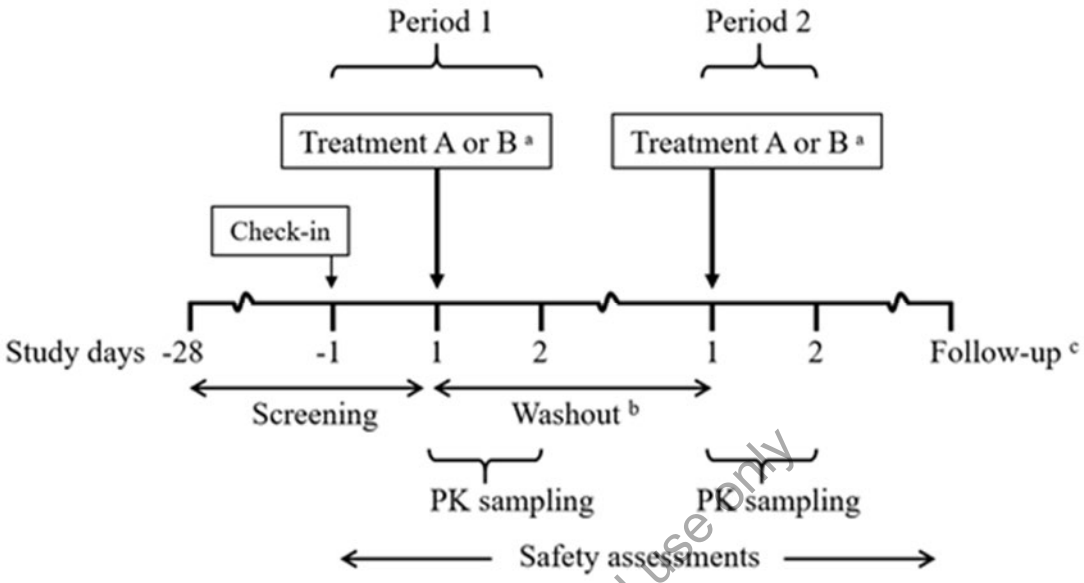
1.3 Estimands

Not applicable.

2.0 STUDY DESIGN

This is an open-label, single-dose, randomized, 2-period, 2-sequence, 2-way crossover study in healthy adult participants. A study schematic of the overall study design is shown in Figure 2.a and the dose regimens are shown in Table 2.a.

Figure 2.a Overall Study Design



AE=adverse event; BOS=budesonide oral suspension; CRU=clinical research unit; PK=pharmacokinetic
a. In each period, participants will receive a single oral dose of BOS under fasting (Treatment A) or fed (high-fat/high-calorie meal; Treatment B) conditions on Day 1, according to the randomization schedule.
b. There will be a washout of at least 2 days between doses.
c. All participants who received any BOS (including participants who terminate the study early) will return to the CRU approximately 3 days after the last dose of BOS for follow-up procedures, and to determine if any AE has occurred since the last study visit.

Table 2.a Study Treatments

Treatment	Study Drug	Dose	Dose Regimen
Treatment A	Budesonide oral suspension	2 mg (10 mL of 0.2 mg/mL)	Single dose, oral, fasting
Treatment B	Budesonide oral suspension	2 mg (10 mL of 0.2 mg/mL)	Single dose, oral, fed: following a high-fat/high-calorie meal

On Day 1 of Period 1, participants will be randomly assigned to 1 of 2 treatment sequences.

On Day 1 of each period, a single oral dose of BOS will be administered under fasting (Treatment A) or fed (high-fat/high-calorie meal; Treatment B) conditions. PK samples will be collected predose and up to 24 hours postdose in each period. There will be a washout of at least 2 days between doses.

Safety and tolerability will be assessed throughout the study by TEAEs, vital signs, and clinical laboratory evaluations. All participants who received any BOS (including participants who

terminate the study early) will return to the clinical research unit (CRU) approximately 3 days after the last dose of BOS for follow-up procedures, and to determine if any adverse event (AE) has occurred since the last study visit.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

Twenty (20) participants will be enrolled to account for possible dropouts.

A total of approximately 18 participants should complete all treatment periods of the study.

For plasma budesonide C_{max}, AUC_{∞_obs}, and AUC_{last}, assuming the true mean ratio of 1.0 with intra-participant coefficient of variance (CV) of 21.8, 21.0, and 21.8%, respectively, 18 completers will provide 80, 85, and 80% power to test for bioequivalence between dosing under fed versus fasting condition using the criteria of a 90% confidence interval (CI) within (0.80, 1.25). Considering 10% dropout rate, a total of 20 participants will be enrolled.

5.0 ANALYSIS SETS

5.1 Safety Set

All participants who received any study drug will be included in the safety evaluations.

5.2 PK Set

All participants who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements, and absence of major protocol violations) will be included in the PK analyses.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonlin® Version 8.3.4, or higher. All statistical analyses will be conducted using SAS® Version 9.4. All data recorded on the case report form (CRF) will be listed by participant and treatment. All table, figure, and listing (TFL) shells and numbering list will be included and specified in the TFL Shells document.

The number of observations (n) will be presented as an integer (no decimal places), arithmetic mean (mean), median, and geometric mean (geom mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (geom CV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the individual data. Geometric LSM ratios (GMRs) and 90% confidence intervals (CIs) for the GMRs will be reported to 2 decimal places. Intra-participant CVs will be reported to 1 decimal place.

Noncompartmental analyses of PK parameters will be used in this study. Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are deemed questionable (eg, BLQ value between measurable values), in which case they will be treated as missing and excluded from the concentration summary statistics and the PK analysis. Values of 0 are not included in the calculation of geom mean and geom CV%.

A participant's PK parameter data will be included in the listings but may be excluded from the descriptive and inferential statistics if one or more of the following criteria are met:

- A predose (0 hour) concentration is greater than 5% of that participant's C_{max} value for the same treatment
- A participant did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A participant deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A participant may be excluded due to vomiting $\geq$2 times within the median t_{max} of budesonide (2 × 1.5 hours = 3 hours)

The details on PK parameter calculations and TFLs will be outlined in the clinical pharmacology and analysis plan (CPAP) and TFL Shells document including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other λ_z-dependent parameters
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter Phoenix® WinNonlin® output file used to generate the TFLs
- PK parameter ratios for C_{max}, AUC_{last}, AUC_{∞_obs}, and AUC_{∞_pred} presented in end-of-text tables.
- Linear mixed-effect model and non-parametric statistical analysis results presented in in-text and end-of-text tables
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures
- Listings of concentration data for individual participants in Appendix 16.2.5.
- Individual concentration-time figures presented in Appendix 16.2.6.

Continuous demographic and safety data will be summarized descriptively. For categorical variables, the count and percentages of each reported value will be tabulated, where applicable. The denominator for the percent calculation will be the number of participants in the safety set for overall summaries, and the number of participants dosed with each treatment in by-treatment summaries. For continuous variables, n, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers. Baseline is defined as the last observation prior to dosing.

6.1.1 Handling of Treatment Misallocations

Participants with any treatment misallocations will be analyzed based on the treatment the participants actually received.

6.2 Study Information

A study information table will be generated including the following items: date of first participant's signed informed consent form (ICF), date of first dose of BOS, date of last dose of BOS, date of last participant's last visit/contact, date of last participant's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory

Activities (MedDRA®), the version of World Health Organization (WHO) Drug Dictionary, and SAS version used for creating the datasets.

6.3 Disposition of Participants

Disposition of all randomized participants (number of participants dosed, completed the study, discontinued from the study and/or BOS, and reason(s) for discontinuation(s)) will be summarized by randomized treatment sequence and overall. Treatment sequence, study completion status, date of completion, and whether BOS was discontinued will be listed by participant. Reasons for discontinuation of BOS and/or study and dates of discontinuation will be listed, if applicable.

A listing of participants with major protocol deviations will also be provided by the clinic.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized by randomized treatment sequence and overall based on the safety set. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age, weight, height, and body mass index [BMI]) and the number and percentages of participants within each category will be presented for categorical variables (sex, race, and ethnicity). The last height, weight, and BMI measured prior to dosing will be used in the summaries. All demographic data will be listed by participant as recorded on the CRF, including date of informed consent and protocol version.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history will include determining whether the participant has any significant conditions or diseases that resolved at or before signing the ICF. All medical history reported by the participant will be recorded regardless of when it may have occurred. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Medical history and concurrent medical conditions will be listed based on safety set.

Any medical condition starting or worsening after taking the first dose of BOS will be classified as a TEAE. All medical history will be coded using MedDRA® version specified in the data management plan (DMP). If available, the medical history and concurrent medical condition listings will include the coded term (preferred term and system organ class [SOC]), start date (if known) and end date (if known) or whether the condition was ongoing, and a description of the condition or event. No summaries or statistical analysis will be performed for these data.

6.5 Medication History and Concomitant Medications

Medication history includes any relevant medication stopped at or within 28 days before signing the ICF. Concomitant medication includes any medication other than BOS taken at any time between screening and the end of the study (including follow-up contact). All medication history

and concomitant medications recorded during the study will be coded with the WHO Drug Dictionary version specified in the DMP and listed based on the safety set. If available, the listings will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time (if known), or whether it continued after study completion, and indication for use. No summaries or statistical analysis will be performed for these data.

6.6 Efficacy Analysis

Not applicable.

6.7 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and relationship(s) of TEAEs, and changes from baseline in the participants' clinical laboratory results, vital signs, and 12-lead ECGs using the safety set. Clinically significant laboratory values and vital signs will be reported as AEs, as applicable. All safety data will be listed by participant, treatment, and assessment time points, including rechecks, unscheduled assessments, and early termination (ET), chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators. Postdose recheck, unscheduled, or ET results will not be used in summaries.

Tables summarizing safety data by assessment time point will only include summaries for baseline and post-baseline time points.

6.7.1 Adverse Events

All AEs captured in the database will be listed in by-participant data listings including verbatim term, coded term, severity (mild, moderate, severe), relationship to BOS (related or not related), relationship to COVID-19 and COVID-19 vaccine, frequency, and action relative to the AE as recorded in the CRF. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA® version specified in the DMP. Only TEAEs will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after the first dose of BOS administered in the study, and until the follow up visit approximately 3 days after the last dose of BOS. Each TEAE will be attributed to the treatment prior to and the closest to the AE based on the AE onset date and time.

If the onset time of an AE is missing and the onset date is the same as a treatment dosing date, then the AE will be counted under the treatment given on the same day. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered

treatment emergent for the most recent treatment administered. If the onset date of an AE is missing, then the AE will be considered treatment emergent and attributed to the first treatment received. If severity is missing, the AE will be counted as severe, and if relationship is missing, the AE will be counted as related.

TEAEs will be tabulated by treatment (including overall), SOC, and preferred term. Summary tables will include number of participants reporting the TEAE as percent of safety set by treatment and overall. The most commonly reported non-serious TEAEs (i.e., those events reported by >1 participant in any treatment, excluding serious adverse events (SAEs) will also be summarized. The denominators for percent calculations will be the number of participants dosed for each treatment. In addition, TEAEs will be summarized as number of TEAEs and percentage of TEAEs for each treatment and overall.

Additional TEAE summary tables will be presented by severity and relationship to BOS. If a participant has multiple TEAEs with different severity levels within the same preferred term, the participant will be counted in the most severe category only. For relationship to BOS, if a participant has both related and unrelated TEAEs with the same preferred term, the participant will be counted as having related TEAEs.

An overview summary of TEAEs table, including number of participants with TEAEs, treatment-emergent SAEs, treatment-related TEAEs, treatment-related SAEs, TEAEs by severity, and AEs leading to discontinuation will be provided.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAEs. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the clinical study report (CSR).

6.7.2 Adverse Events of Special Interest

Since BOS is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed:

- Hypercortisolism and adrenal suppression.
- Increased risk of infection.
- Other glucocorticoid effects including fractures, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, or cataracts.
- Gastrointestinal symptoms related to corticosteroid use.

However, identification of AESI is not mandatory for the purposes of this study.

6.7.3 Clinical Laboratory Evaluation

Clinical laboratory tests will be measured as described in Table 6.a:

Table 6.a Collection of Laboratory Samples

Clinical Laboratory Panels	Time Point		
	Period	CRF/Listing Day and Hour	Table
Serum Chemistry, Hematology, Urinalysis	Screening		NA
	1	Day -1 PRE-DOSE	Baseline
	2	Day 1 PRE-DOSE Day 2 Hour 24	Period 2 Predose Period 2 Day 2
	Follow-up	Follow-up	Follow-up

NA=Not Applicable
Time points in the CRF/Listing column are based on the protocol, and it should be noted that the data listings will reflect the data found in the final participant CRFs.
If applicable, an early termination assessment will be performed.

For all numeric values of laboratory test results, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented by randomized sequence at each scheduled visit using the units found in the source data. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment including rechecks taken prior to the first dose in Period 1. The mean value calculated for each assessment time point will be compared to the reference range and flagged if outside of the reference range (* if above the reference range and ^ if below the reference range). In the event there is more than one reference range for a laboratory test, the comparison will be made against the lowest of the lower ranges and the highest of the higher ranges. Postdose unscheduled, recheck, or ET assessments will not be used in summaries. Only baseline and post-baseline time points will be summarized All clinical laboratory data will be listed by participant. Urine drug screen will be performed at screening and check-in, and results will be listed by participant.

Out-of-normal range flags will be recorded as high (H) and low (L) for numerical results and did-not-match (*) for categorical results. For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Any clinically significant laboratory results, as determined by the Investigator, will be recorded and summarized as AEs.

6.7.4 Vital Signs

Vital signs will be measured as described in Table 6.b:

Table 6.b Collection of Vital Signs

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
Blood Pressure, Heart Rate	Screening		NA
	1, 2	Day 1 PRE-DOSE Day 1 Hour 2 Day 1 Hour 4 Day 1 Hour 8 Day 2 Hour 24	Baseline Hour 2 Hour 4 Hour 8 Hour 24
	Follow-Up	Follow-Up	Follow-Up
Respiration, Temperature	Screening		NA
	1, 2	Day 1 PRE-DOSE	NA
	Follow-up	Follow-up	NA

NA=Not applicable
Time points in the CRF/Listing column are based on the protocol, and it should be noted that the data listing will reflect the data found in the final participant CRFs.
If applicable, an early termination assessment will be performed.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for blood pressure and heart rate results by treatment and time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment including rechecks taken prior to dosing in each treatment. Postdose unscheduled or recheck assessments, or ET results, will not be used in analysis. Only baseline and post-dose results will be summarized. Vital sign data will be listed by participant.

6.7.5 12-Lead ECG

Single 12-lead ECGs will be measured at screening. ECG data will be listed by participant.

Any clinically significant ECG results, as determined by the Investigator, will be recorded and summarized as AEs.

6.7.6 Physical Examinations

Full physical examinations will be performed at screening, check-in, and at the follow-up visit. Additional physical examinations may be performed at other times at the discretion of the Investigator. Physical examination findings will be presented in the data listings by participant.

6.7.7 Overdose

All cases of overdose will be presented in a data listing by participant. Any AEs associated with overdose will be documented.

6.7.8 Extent of Exposure and Compliance

The dates, times, and doses of BOS will be listed by participant and study period.

6.8 Pharmacokinetic Analysis

Blood samples for assessment of plasma budesonide concentrations will be collected as outlined in Table 6.c below:

Table 6.c Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Scheduled Time (Hours)*
Budesonide	Plasma	Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 hours postdose.

*The actual date and time of sample collection will be recorded on the source document in the case report form.

Plasma concentrations of budesonide will be listed and summarized descriptively by PK sampling time and treatment using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, and maximum. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive statistics.

Individual participant concentration-time curves will be plotted by treatment on linear and semi-log scales. The arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales. For summary statistics and arithmetic mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

The PK parameters will be calculated from plasma budesonide concentration-time profiles using non-compartmental analysis methods where all calculations will be based on actual sampling times after dosing. The PK parameters will be summarized by treatment using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, geom mean, and geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

Estimation of Food-Effect

A linear mixed-effects model will be applied to natural log-transformed C_{max}, AUC_{last}, AUC_{∞_obs}, and AUC_{∞_pred} with treatment, period, and sequence as fixed effects, and participant within sequence as a random effect. Point estimates and their associated 90% CIs will be constructed for the difference between Treatment B (fed) minus Treatment A (fasting). The point estimates and their associated 90% CIs will be then back transformed to provide point estimates and 90% CIs for the ratios of Treatment B (fed) versus Treatment A (fasting).

The following SAS code will be used to perform the food-effect analysis:

```
PROC MIXED;
CLASS TREAT PERIOD SEQUENCE PARTICIPANT;
MODEL LN<Parameter> = TREAT PERIOD SEQUENCE / DDFM = KR;
RANDOM PARTICIPANT(SEQUENCE);
ESTIMATE "Treatment B (Fed) vs Treatment A (Fasted)" TREAT -1 1 / CL ALPHA=0.1 E;
RUN;
```

Non-Parametric Analysis

Analysis of t_{max} and t_{lag} will be performed by non-parametric Wilcoxon signed-rank test. The median difference (fed versus fasted) and 90% CI will be estimated using the Hodges-Lehmann method and Walsh averages. The t_{max} and t_{lag} parameters will not be ln-transformed. The comparison of interest is the same as in the linear mixed-effects model.

6.9 Patient Reported Outcomes and Health Care Utilization Endpoints Analysis

Not applicable.

6.10 Interim Analysis

Not applicable.

6.11 Preliminary Analysis

Two preliminary PK analyses, the first based on quality-controlled data and the second based on quality-assured data, will be completed as described in the CPAP and Section 6.8 of the statistical analysis plan (SAP), with the following changes: 1) nominal times (not actual sampling times) will be used to calculate PK parameters; 2) tables and figures will be created using Phoenix® WinNonlin® Version 8.3.4 or higher.

6.12 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The following PK parameters not specified in the protocol will also be calculated for plasma budesonide: AUC_{∞_pred}, $AUC_{extrap}\%_{\_pred}$, $CL/F_{\_pred}$, and $V_z/F_{\_pred}$.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

Not applicable.

9.3 Analysis Software

SAS® Version 9.4 or higher will be used for all statistical analysis provided in the CSR.