Clinical Study Protocol

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, 22 November 2022

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TAKEDA PHARMACEUTICALS

PROTOCOL

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 Identifier:	TAK-721-1003
Compound:	TAK-721, Budesonide Oral Suspension (BOS)
Date:	22 Nov 2022
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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. (TDCA) 95 Hayden Avenue Lexington, MA 02421 Telephone: +1 (617) 679-7000	**Compound:** TAK-721, budesonide oral suspension (BOS)
Study Identifier: TAK-721-1003	**Phase:** 1
Protocol 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 Design: This is an open-label, single-dose, randomized, 2-period, 2-sequence, 2-way crossover study in healthy adult participants. Study schematic and dose regimens are shown in Figure 2.a and Table 6.a. The schedule of assessments is shown in the Schedule of Study Procedures (Section 3.0). 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. Pharmacokinetic (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 treatment-emergent adverse events (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.	
Study Primary Objective: To assess the relative bioavailability of a single dose of BOS administered under fasting and fed (high-fat/high-calorie meal) conditions. **Study 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 PK parameters of a single dose of BOS administered under fasting and fed (high-fat/high-calorie meal) conditions.	
Study Participant Population: Healthy male and female participants aged 19 to 55 years inclusive, with a body mass index (BMI) of 18.0-32.0 kg/m^2, inclusive, at the screening visit.	
Planned Number of Participants: Twenty (20) participants will be enrolled.	**Planned Number of Sites:** 1
Dose Levels: 2 mg (10 mL of 0.2 mg/mL) BOS	**Route of Administration:** Oral

Duration of Treatment:	**Planned Study Duration:**
Single dose	Up to approximately 34 days including the screening period and the follow-up.

Criteria for Inclusion:

Participants must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female*, 19-55 years of age, inclusive, at the screening visit.

   * Females of childbearing potential are defined as all females physiologically capable of becoming pregnant.

   Females of non-childbearing potential are defined as follows:

   - Females who have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:
     - Hysteroscopic sterilization.
     - Bilateral tubal ligation or bilateral salpingectomy.
     - Hysterectomy.
     - Bilateral oophorectomy.

   or

   - Females who are postmenopausal with amenorrhea for at least 12 months prior to the first dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status at the screening visit.
2. Female of childbearing potential and male participants must follow protocol specified contraception guidance as described in Appendix D.
3. Continuous non-smoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to the first dosing based on participant self-reporting.
4. BMI $\geq$ 18.0 and $\leq$ 32.0 kg/m^2 at the screening visit.
5. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, and electrocardiograms (ECGs), as deemed by the Investigator or designee, including the following:
   - Seated blood pressure is $\geq$ 90/40 mmHg and $\leq$ 140/90 mmHg at the screening visit.
   - Seated pulse rate is $\geq$ 40 bpm and $\leq$ 99 bpm at the screening visit.
   - QTcF interval is $\leq$ 460 msec (males) and $\leq$ 470 msec (females) and has ECG findings considered normal or not clinically significant by the Investigator or designee at the screening visit.
   - Estimated creatinine clearance $\geq$ 80 mL/min at the screening visit.
   - Liver-related tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin $\leq$ upper limit of normal (ULN) at the screening visit and at check-in.
6. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

Criteria for Exclusion:

Participants must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
4. Presence of any active infection at the screening visit or check-in.
5. History or presence of alcohol or drug abuse within the past 2 years prior to the first dosing.

6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug, inactive ingredients, or related compounds.
7. Female participant with a positive pregnancy test at the screening visit or at check-in or who is lactating.
8. Positive urine drug or alcohol results at the screening visit or check-in.
9. Positive results for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) at the screening visit.
10. Unable to refrain from or anticipates the use of:
    - Any drugs, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to the first dosing. Medication listed as part of acceptable birth control methods (refer to Appendix D), hormone replacement therapy, and thyroid hormone replacement medication (refer to Section 7.3) will be allowed.
    - Any drugs known to be moderate or strong inducers of cytochrome P450 (CYP) 3A4 enzymes and/or P-glycoprotein (P-gp), including St. John's Wort, for 28 days prior to the first dosing. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with the study drug.
    - Any injectable steroid within 12 weeks prior to the first dosing or any other form of steroids (eg, inhaled, nasal, oral) within 30 days prior to the first dosing.
11. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing.
12. Is lactose intolerant.
13. Donation of blood or significant blood loss within 56 days prior to the first dosing.
14. Plasma donation within 7 days prior to the first dosing.
15. Participation in another clinical study within 30 days or 5 half-lives, whichever is later, prior to the first dosing. The 30-day (or 5 half-lives) window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

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_{∞}).

Secondary endpoints:

Safety endpoints will include:

- Incidence of 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_{0-12}).
- 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_{∞} (AUC_{extrap}%).
- Time of 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).

- 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).

Statistical Considerations:

PK analysis:

Plasma budesonide concentrations and PK parameters will be listed by participant and treatment, and summarized using appropriate descriptive statistics to be fully outlined in the statistical analysis plan (SAP).

PK parameters (C_{max}, AUC_{last}, AUC_{∞}, $AUC_{0\text{-}12}$, $AUC_{extrap\%}$, t_{max}, t_{lag}, $t_{1/2z}$, λ_z, CL/F, and V_z/F) will be computed using standard non-compartmental analysis (NCA). Individual plasma concentration/time curves will be presented in linear/linear and log/linear scale.

The appropriate PK analysis will be fully specified in the SAP.

Estimation of food-effect:

A linear mixed-effects model will be applied to log-transformed C_{max}, AUC_{last}, and AUC_{∞} with treatment, period, and sequence as fixed effects, and participant within sequence as a random effect. Point estimates and their associated 90% confidence intervals (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).

Analysis of t_{max} and t_{lag} will be performed by non-parametric Wilcoxon signed-rank test.

Safety analysis:

TEAEs will be tabulated. Summary statistics for vital signs, and clinical laboratory assessments will be computed and provided.

Sample Size Justification:

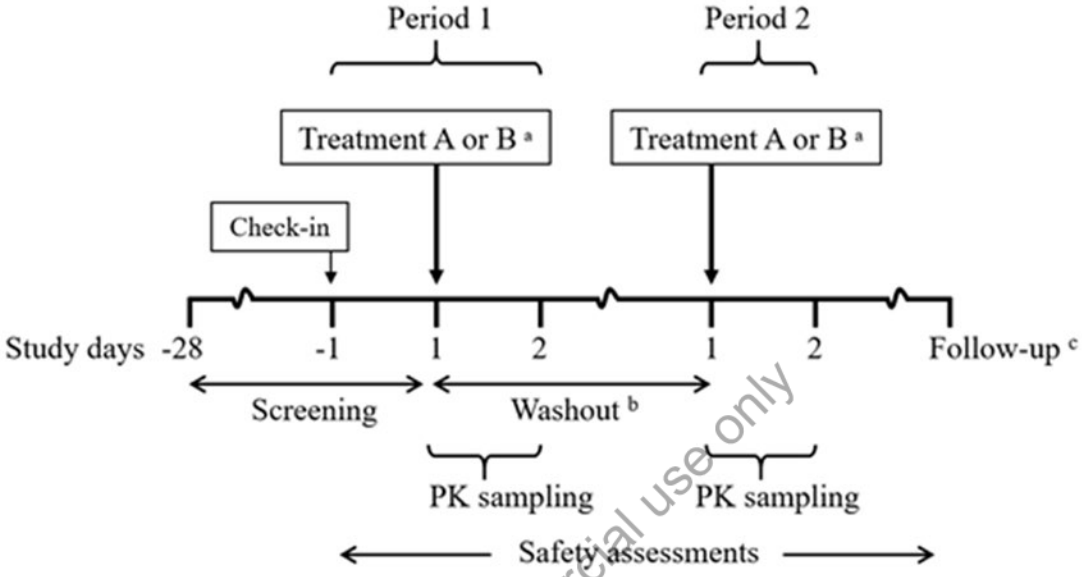
Twenty (20) participants will be enrolled to account for possible dropouts.

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

For plasma budesonide C_{max}, AUC_{∞}, 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% CI within (0.80, 1.25). Considering 10% dropout rate, a total of 20 participants will be enrolled.

2.0 STUDY SCHEMATIC

Figure 2.a Overall Study Design



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.

Abbreviations: CRU = clinical research unit, PK = pharmacokinetic.

3.0 SCHEDULE OF STUDY PROCEDURES

Table 3.a Daily Schedule of Study Procedures

Study Procedures [a]	S [b]		Study Days in Each Treatment Period [c]																Follow-up [d]
Days →		-1	1															2	
Hours →		C-I [e]	0	0.25	0.5	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12	24	
Administrative Procedures																			
Informed Consent	X																		
Demographics	X																		
Inclusion/Exclusion Criteria	X	X																	
Medical History	X																		
Safety Evaluations																			
Full Physical Examination	X	X																	X
Height	X																		
Weight	X	X																	
Vital Signs (pulse rate and blood pressure)	X		X [f]					X				X			X			X [g]	X
Vital Signs (respiratory rate and temperature)	X		X [f]																X
12-Lead ECG	X																		
Hematology, Serum Chemistry [h], and Urinalysis	X	X	X [i]															X [j]	X
Serum Pregnancy Test (females only)	X	X																	
Serum FSH (PMP females only)	X																		
Urine Drug and Alcohol Screen	X	X																	
HIV/Hepatitis Screen	X																		
AE Monitoring	X	X																	X
Concomitant Medication Monitoring	X	X																	X
Study Drug Dosing / PK																			
BOS Dosing			X																
Blood for Budesonide PK			X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 3.a Daily Schedule of Study Procedures

Study Procedures [a]			**Study Days in Each Treatment Period** [c]															**Follow-up** [d]
Days →	**S** [b]	**-1**	**1**														**2**	
Hours →		C-I [e]	0	0.25	0.5	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12	24	
Other Procedures																		
Confinement in the CRU		X																
Visit and Return Visit	X																	X
Mouth Rinse					X [k]													

a For details on study procedures, refer to Section 9.0.

b Within 28 days prior to the first dosing.

c There will be a washout of at least 2 days between doses.

d 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.

e Participants will be admitted to the CRU on Day -1 of Period 1, at the time indicated by the CRU, until after the 24-hour blood draw and/or study procedures on Day 2 of Period 2. Procedures scheduled on Day -1 will be performed in Period 1 only. Participants may be admitted earlier than Day -1 of Period 1 for COVID-19 testing not related to study protocol as per CRU requirements.

f To be performed prior to dosing.

g To be performed at the end of each period or prior to early termination from the study.

h Samples for serum chemistry will be obtained after a fast of at least 8 hours, however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

i To be performed in Period 2 only, prior to dosing.

j To be performed at the end of Period 2 or prior to early termination from the study.

k All participants must rinse their mouths and spit (see Section 9.2.6 for details).

Abbreviations: AE = Adverse event(s), BOS = Budesonide oral suspension, C-I = Check-in, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, FSH = Follicle-stimulating hormone, HIV = Human immunodeficiency virus, PK = Pharmacokinetics, PMP = Postmenopausal, S = Screening.

4.0 INTRODUCTION

4.1 Background

Budesonide is an anti-inflammatory corticosteroid that has potent glucocorticoid activity, weak mineralocorticoid activity, and potent local anti-inflammatory effects. Takeda is currently developing budesonide oral suspension (BOS), through the TAK-721 (previously SHP621) clinical development program, for the treatment of eosinophilic esophagitis (EoE). BOS is designed to increase the residence time of budesonide on the surface of the esophagus after swallowing, as compared with other budesonide formulations. Four different formulations of BOS (MB-7, MB-8, MB-9, and SB-10) have been evaluated in nonclinical and/or clinical studies to date. In this study, the effect of food will be evaluated using the BOS SB-10 formulation.

The nonclinical pharmacology, toxicology, clinical pharmacology, and safety of budesonide are well studied as budesonide is present in several United States (US) Food and Drug Administration (FDA)-approved drug products. Budesonide has been shown to be tolerated and effective in numerous well-controlled clinical studies for other indications. Various approved formulations of budesonide are currently marketed for the management of Crohn's disease, for asthma maintenance, for the treatment of allergic rhinitis, and for induction of remission in patients with active, mild to moderate ulcerative colitis.

Recently, budesonide oral disintegrating tablet was approved for use in adults with EoE in a number of countries in Europe. There is a large safety database in humans with budesonide in a variety of formulations given by multiple routes of administration (oral, inhalation, rectal, and nasal sprays), which forms the primary basis of support for the safety assessment of BOS and the proposed clinical studies.

Refer to the Investigator's Brochure (IB) for detailed background information on BOS.

4.1.1 Clinical Pharmacology

The current clinical program for the development of BOS for the treatment of EoE in adolescents and adults includes one completed Phase 1 study (SHP621-101), two completed Phase 2 studies (MPI 101-01 and MPI 101-06), and three completed Phase 3 studies (SHP621-301, SHP621-302, SHP621-303).

Study SHP621-101 utilized the SB-10 formulation and demonstrated that budesonide is readily absorbed from the BOS SB-10 formulation with a median t_{max} observed at 1.5 hours while a delayed absorption of budesonide is demonstrated for ENTOCORT EC (budesonide delayed-release capsules) with a median t_{max} observed at 4 hours. The oral bioavailability of budesonide from the BOS SB-10 formulation is estimated at 14.2% in healthy participants, consistent with high first-pass metabolism as observed with ENTOCORT EC; however, estimated oral bioavailability was approximately 57.5% higher than that from ENTOCORT EC (estimated at 9%). The reason for higher oral bioavailability of budesonide from the BOS SB-10 formulation as compared to the ENTOCORT EC formulation is unknown, but likely related to reduced first-pass metabolism, not related to the extent of absorption.

Although budesonide is a poorly soluble, highly permeable Biopharmaceutics Classification System Class II compound, absorption from ENTOCORT EC following oral dosing appears to be complete. The absorption of budesonide from the BOS formulation is expected to be complete as well given the BOS formulation is an immediate release formulation targeting drug release in the esophagus.

Budesonide PK is dose-proportional following repeated administration in the dose range of 0.5 to 2 mg based on the population PK analysis which demonstrated dose was not a significant covariate in the model. This is supported by complete absorption and is also consistent with what is seen with ENTOCORT EC whose PK were dose-proportional following repeated administration in the dose range of 3 to 15 mg.

A small accumulation (≤15%) of budesonide is estimated following twice daily (BID) dosing by the method of superposition using PK data from Study SHP621-101. This is consistent with the observed $t_{1/2}$ of 5.05 hours.

Following oral administration, budesonide is subject to high first-pass metabolism (80-90%) primarily via CYP3A4 isozymes. Budesonide is a substrate for CYP3A4; therefore, concomitant use with CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, cyclosporine, grapefruit juice) should be avoided as they can increase systemic budesonide concentrations. Co-administration of ketoconazole results in an 8-fold increase in the AUC of oral budesonide. Grapefruit juice, an inhibitor of gut mucosal CYP3A4, approximately doubles the systemic exposure of oral budesonide. Oral contraceptives containing ethinyl estradiol, which is also metabolized by CYP3A4, do not affect the PK of budesonide. Budesonide does not affect the plasma levels of oral contraceptives (ie, ethinyl estradiol).

4.1.2 Clinical Safety

In Study SHP621-101 with healthy adult participants, no notable differences were apparent with respect to TEAEs or related TEAEs across treatments, including a comparison among all BOS treatment arms and ENTOCORT EC. Overall, 15 (68.2%) participants in the safety analysis set had 19 TEAEs. Of these, 13 (59.1%) participants had 17 TEAEs that were considered by the Investigator to be related to the study drug. The system organ class with the most participants reporting TEAEs in the safety analysis set was nervous system disorders with 8 (36.4%) participants reporting 9 events, followed by gastrointestinal disorders with 7 (31.8%) participants reporting 8 events. By preferred term, the most commonly reported TEAE was headache (7 [31.8%] participants reporting 8 events) followed by dry mouth (4 [18.2%] participants reporting 4 events). All TEAEs were mild in severity. There were no severe TEAEs, deaths, or TEAEs resulting in discontinuation reported during the study. No notable differences in TEAEs were apparent across treatments.

4.2 Rationale for the Proposed Study

The purpose of this study is to determine if the systemic exposure to the proposed to-be-marketed BOS SB-10 product will be altered if dosed with food.

Co-administration of a high-fat meal delayed the t_{max} of budesonide capsule (ENTOCORT EC delayed-release capsules) by 2.3 hours but did not significantly affect the AUC in healthy participants. A food-effect study involving administration of budesonide tablets to healthy participants under fasting conditions and with a high-fat meal indicated that the C_{max} decreased by 27% while there was no significant decrease in AUC. Additionally, a mean delay in absorption lag time of 2.4 hours is observed under fed conditions.

As the PK difference between ENTOCORT EC and BOS is primarily related to the rate and extent of absorption of budesonide and no significant differences are expected in the distribution, metabolism, and excretion of budesonide, a similar effect by food is anticipated for the BOS formulation.

In addition to a food effect assessment, results of this study will provide an important safety and tolerability comparison of product performance under fed and fasting conditions in healthy adult participants.

4.3 Benefit/Risk Profile

The dose of BOS administered in this study is not anticipated to induce any potential risk to participants, as it is a single dose administered according to the dosing recommendations found in the IB.

There will be no direct health benefit for study participants from the receipt of BOS. An indirect health benefit to the healthy participants enrolled in this study is the free medical tests received at screening and during the study.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, vital signs, clinical laboratory tests, AE questioning, and physical examinations) are adequate to protect the participant's safety and should detect all TEAEs.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable.

5.2 Study Objectives

5.2.1 Study Primary Objective

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

5.2.2 Study 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 PK parameters of a single dose of BOS administered under fasting and fed (high-fat/high-calorie meal) conditions.

5.3 Endpoints

5.3.1 Primary Endpoint

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_{∞}).

5.3.2 Secondary Endpoints

Safety endpoints will include:

- Incidence of 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_{0-12}).
- 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_{∞} ($AUC_{extrap\%}$).
- 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).
- 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).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, single-dose, randomized, 2-period, 2-sequence, 2-way crossover study in healthy adult participants.

Study schematic and dose regimens are shown in Figure 2.a and Table 6.a. The schedule of assessments is shown in the Schedule of Study Procedures (Section 3.0).

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 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 6.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

6.2 Dose Escalation

Not applicable.

6.3 Stopping Rules

An urgent safety review will be conducted by the Sponsor if one or more of the following criteria are met:

- Death that is considered related to the study drug.
- Two SAEs of similar type (defined as same or similar Medical Dictionary for Regulatory Activities® (MedDRA®) higher level group code), and considered related to the study drug.

The urgent review will be performed by a Sponsor safety review group, which will include the study Global Safety Lead, Global Clinical Lead, and Global Safety Therapeutic Area Head.

Following the Sponsor's review of safety data, one of the following actions will be taken with respect to study status:

- Continue study with protocol unchanged.
- Continue study with modifications to the protocol.
- Terminate study.

Participant safety will be monitored on a continuous basis during this study until the last participant completes his or her last scheduled study visit/assessment.

6.4 Rationale for Study Design, Dose, and Endpoints

6.4.1 Rationale of Study Design

This study is being conducted to assess the effect of food on the PK profile of budesonide after a single oral dose.

The current study is designed in accordance with the FDA guidance [FDA 2022] as a definitive food-effect study in healthy participants and will utilize a high-fat and high-calorie test meal in Treatment B.

Participants will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to reduce the residual variability as every participant acts as their own control.

The washout period of at least 2 days between doses is more than 7x the budesonide $t_{1/2z}$, which is also in accordance with FDA recommendations [FDA 2022] and is considered sufficient to prevent carryover effects of the preceding treatment.

6.4.2 Rationale for Dose

The 2 mg single oral dose of BOS was selected as it is the recommended clinical dose and is expected to provide a safety margin should a food effect occur.

Participants in the completed Phase 3 studies received oral BID administration of BOS at 10 mL of 0.2 mg/mL (daily dose of 2 mg BID) for a total of 12 weeks during the completed induction study (SHP621-301), for an additional 36 weeks in the extension study (Study SHP621-302), and for up to an additional 4.5 years at doses up to 2 mg BID in the SHP621-303 open-label continuation study.

The highest total dose of budesonide in the Phase 3 studies is 4 mg/day (given as 2 mg BID), which is lower than the chronically administered oral dose of budesonide labeled for the treatment of Crohn's disease. The approved daily dosage of oral budesonide capsules is 9 mg/day for the treatment of Crohn's disease (ENTOCORT EC) or oral budesonide tablets for ulcerative colitis (UCERIS) followed by long-term maintenance with 6 mg/day oral budesonide tablets for the treatment of Crohn's disease. The systemic exposure of budesonide, AUC, after ingestion of 2 mg BID of BOS is predicted to be 67% of that from ENTOCORT EC 9 mg once a day and similar to that from ENTOCORT 6 mg once a day.

6.4.3 Rationale for Endpoints

6.4.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of study.

6.4.3.2 Safety Endpoints

The key safety endpoints are typical for Phase 1 studies and will be assessed through monitoring of AEs, vital signs, clinical laboratory assessments, and physical examinations.

6.4.4 Future Biomedical Research

No additional analysis is planned to be performed on the PK blood samples for possible future research. Any additional research on these samples unspecified by this protocol will require approval from the participants.

6.4.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is the blood collection for plasma concentrations of budesonide, and is to be collected as close to the scheduled times defined in this protocol as possible.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of BOS to any participant may not be modified. If necessary, a participant may be discontinued for the reasons described in Section 7.5 and Section 7.6.

6.6 Study Beginning and End/Completion

6.6.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the ICF) of the first participant.

6.6.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled procedure ie, the follow-up visit, as outlined in the Schedule of Study Procedures (Section 3.0).

A participant is considered to have completed the study if the participant has completed the last scheduled procedure ie, the follow-up visit shown in the Schedule of Study Procedures (Section 3.0).

6.6.3 Definition of Study Discontinuation

Celerion reserves the right to terminate the study in the interest of participant welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.6.4 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for participants participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

6.6.5 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

7.1 Inclusion Criteria

Participants must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female*, 19-55 years of age, inclusive, at the screening visit.

   * Females of childbearing potential are defined as all females physiologically capable of becoming pregnant.

     Females of non-childbearing potential are defined as follows:

     - Females who have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:
       - Hysteroscopic sterilization.
       - Bilateral tubal ligation or bilateral salpingectomy.
       - Hysterectomy.
       - Bilateral oophorectomy.

     or

     - Females who are postmenopausal with amenorrhea for at least 12 months prior to the first dosing and FSH serum levels consistent with postmenopausal status at the screening visit.

2. Female of childbearing potential and male participants must follow protocol specified contraception guidance as described in Appendix D.
3. Continuous non-smoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to the first dosing based on participant self-reporting.

4. BMI ≥ 18.0 and ≤ 32.0 kg/m^2 at the screening visit.
5. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, and ECGs, as deemed by the Investigator or designee, including the following:
   - Seated blood pressure is ≥ 90/40 mmHg and ≤ 140/90 mmHg at the screening visit.
   - Seated pulse rate is ≥ 40 bpm and ≤ 99 bpm at the screening visit.
   - QTcF interval is ≤ 460 msec (males) and ≤ 470 msec (females) and has ECG findings considered normal or not clinically significant by the Investigator or designee at the screening visit.
   - Estimated creatinine clearance ≥ 80 mL/min at the screening visit.
   - Liver-related tests including ALT, AST, ALP, and total bilirubin ≤ ULN at the screening visit and at check-in.
6. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

Participants must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
4. Presence of any active infection at the screening visit or check-in.
5. History or presence of alcohol or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug, inactive ingredients, or related compounds.
7. Female participant with a positive pregnancy test at the screening visit or at check-in or who is lactating.
8. Positive urine drug or alcohol results at the screening visit or check-in.
9. Positive results for HIV, HBsAg, or HCV at the screening visit.
10. Unable to refrain from or anticipates the use of:
    - Any drugs, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to the first dosing. Medication listed as part

of acceptable birth control methods (refer to Appendix D), hormone replacement therapy, and thyroid hormone replacement medication (refer to Section 7.3) will be allowed.

- Any drugs known to be moderate or strong inducers of CYP3A4 enzymes and/or P-gp, including St. John's Wort, for 28 days prior to the first dosing. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with the study drug.
- Any injectable steroid within 12 weeks prior to the first dosing or any other form of steroids (eg, inhaled, nasal, oral) within 30 days prior to the first dosing.

11. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing.
12. Is lactose intolerant.
13. Donation of blood or significant blood loss within 56 days prior to the first dosing.
14. Plasma donation within 7 days prior to the first dosing.
15. Participation in another clinical study within 30 days or 5 half-lives, whichever is later, prior to the first dosing. The 30-day (or 5 half-lives) window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

Prior concomitant medications (including prescription and non-prescription medications, herbal remedies, or vitamin supplements) will be prohibited as listed in the exclusion criteria in Section 7.2 and throughout the study (ie, until the follow-up visit) with the exception of acceptable birth control methods as described in Appendix D. Hormone replacement therapy will be allowed. Thyroid hormone replacement medication, if the participant has been on the same stable dose for at least the immediate 3 months prior to the first dosing, will also be allowed.

After the first dose, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case-by-case basis whether the participant may continue participation in the study.

All medications taken by participants during the course of the study will be recorded.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and First Dosing (Days -28 to predose [Day 1])	After First Dosing (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from first dosing until the last PK sample collection on Day 2 of Period 2.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing [a]	Prohibited from first dosing until the last PK sample collection on Day 2 of Period 2. [a]
Medications	See Sections 7.1 and 7.2.	See Sections 7.1 and 7.2.
Nicotine- and tobacco-containing and/or cannabis products	Prohibited from 3 months prior to first dosing	Prohibited from first dosing until the follow-up visit.
Food substance		
Grapefruit/Seville orange	Prohibited from 14 days prior to first dosing	Prohibited from first dosing until the follow-up visit.

(a) small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each dosing, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

For Treatment A, participants will be required to fast overnight for at least 10 hours prior to dosing and will continue to fast for at least 4 hours postdose.

For Treatment B, participants will be required to fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat breakfast (800-1000 calories and approximately 50% fat) [FDA 2022] which will be entirely consumed within 30 minutes. An example of a high-fat breakfast would be 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 8 ounces (approximately 240 mL) of whole milk [FDA 2022]. Participants will fast for at least 4 hours postdose.

Each meal and/or snack served at the CRU will be standardized and will be similar in caloric content and composition (except for the meal served as part of Treatment B) and will be taken at approximately the same time in each period.

When confined, standard meals and snacks will be provided at appropriate times, except when participants are required to fast. When confined in the CRU, participants will be required to fast from all food and drink except water between meals and snacks.

7.4.2 Activity

Participants will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

Should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side.

Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from the screening visit until completion of the study.

Activities such as brushing teeth or other rinsing of the mouth (except for the scheduled mouth rinse approximately 30 minutes after each dosing) will not be allowed for 1 hour prior to and 1 hour after each dosing.

7.5 Criteria for Discontinuation or Withdrawal of a Participant

The primary reason for discontinuation or withdrawal of the participant from the study or study drug should be recorded in the case report form (CRF) using the following categories:

1. AE: The participant has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the participant's health or the participant is unwilling to continue because of the AE.

   Liver Function Test (LFT) Abnormalities:

   Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status, see Section 9.2.8), if the following circumstances occur at any time during study drug treatment:

   - ALT or AST >8 × ULN, or
   - ALT or AST >5 × ULN and persists for more than 2 weeks, or
   - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN, or
   - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

2. Significant protocol deviation: The discovery post-enrollment that the participant failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the participant's health.
3. Lost to follow-up: Attempts to contact the participants were unsuccessful. Attempts to contact the participant must be documented in the participant's source documents.

4. Voluntary withdrawal: The participant (or participant's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category). If a participant chooses to withdraw from study participation due to personal concerns related to the Coronavirus disease 2019 (COVID-19) pandemic (other than a COVID-19-related AE), this should be specified as the reason for participant withdrawal in the CRF.

5. Study termination: The Sponsor, institutional review board (IRB)/independent ethics committee (IEC), or regulatory agency terminates the study.
6. Pregnancy: as described in Appendix D.
7. Participants may be withdrawn from the study by the Investigator or designee for the following reasons:
   - Difficulties in blood collection.
   - Positive urine drug or alcohol test.
8. Other. The specific reasons for discontinuation should be entered into the CRF including unavoidable circumstances such as the COVID-19 pandemic. Participants may be withdrawn from the study at any time at the discretion of the Investigator or Sponsor for safety reasons which should be entered into the CRFs.

7.6 Procedures for Discontinuation or Withdrawal of a Participant

The Investigator may discontinue a participant's study participation at any time during the study when the participant meets the study termination criteria described in Section 7.5. In addition, a participant may discontinue his or her participation without giving a reason at any time during the study. Should a participant's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.7 Participant Replacement

Replacement of discontinued or withdrawn participants due to any reason will be assessed on a case-by-case basis by the Sponsor and Investigator.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Product Name:	Budesonide oral suspension (BOS)
Strength:	0.2 mg/mL
Dose:	2 mg
Dosage Form/Formulation:	Oral suspension
Dosing regimen:	Single dose
Route of Administration:	Oral

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of the study drug to allow completion of this study.

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drug supplied will be recorded in the final report. Study drug will be stored according to the product labels provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drug supplied.

8.1.3 Clinical Study Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage

A computerized randomization scheme will be created by a Celerion statistician.

Treatments A and B will be randomized to 1 of 2 sequences as indicated in Table 8.a.

Table 8.a Randomization Sequence

Sequences	Number of participants (N)	Period 1	Period 2
1	10	A	B
2	10	B	A

Treatment A = 2 mg BOS (10 mL of 0.2 mg/mL), fasting
Treatment B = 2 mg BOS (10 mL of 0.2 mg/mL), fed, following a high-fat/high-calorie meal.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the study drug supplied. At the conclusion of the study, any unused study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Any remaining supplies that were purchased by Celerion will be destroyed, if appropriate. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the participants in non-technical terms. Participants will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Participants will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each participant will be assigned a unique identification number upon the screening visit. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the study drug.

The sequences to be used in the randomization will be AB and BA.

If replacement participants are used, the replacement participant number will be 100 more than the original (eg, Participant No. 101 will replace Participant No. 1).

9.1.1.2 Study Drug Assignment

All participants will receive the treatments as detailed in Section 9.2.6.

9.1.2 Inclusion and Exclusion

Please refer to Section 7.1 and Section 7.2.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.3. All medications taken by participants during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to participant safety.

For this study, collection of blood for budesonide PK is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time.

Any non-scheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Full Physical Examination

Full physical examinations will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at the screening visit.

9.2.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and pulse rate will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary by the Investigator or designee.

Blood pressure and pulse rate measurements will be performed with participants in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

Vital signs will be measured within 2 hours prior to dosing in each period. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with participants in a supine position. All ECG tracings will be reviewed by the Investigator or designee.

9.2.6 Study Drug Administration

BOS will be provided as described in Section 8.1.

Treatments are described in Table 6.a.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each participant and for each study period, as per the randomization schedule.

Each dose of BOS will be administered orally with approximately 240 mL of water.

The exact clock time of dosing will be recorded. Hour 0 will be set as the dosing time.

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the participants have swallowed the study drug. Once a participant has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth.

Approximately 30 minutes after each dosing, all participants must rinse their mouths with approximately 60 mL of room temperature water and spit (participants are not to swallow this rinsing water).

9.2.7 AE Monitoring

Participants will be monitored throughout the study for adverse reactions to the study drug and/or procedures as described in Section 10.0.

9.2.8 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample being taken.

Serum chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Sodium
Blood Urea Nitrogen	Potassium
Bilirubin (total and direct)	Chloride
ALP	Glucose (fasting)
AST	Creatinine *
ALT	

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is abnormal for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen
HBsAg	Opiates (includes morphine, heroin [diacetylmorphine], codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone)
HCV	Amphetamines
Urine alcohol screen	Barbiturates
Serum pregnancy test (for females only)	Benzodiazepines
FSH (for postmenopausal females only)	Cocaine
COVID-19 (severe acute respiratory syndrome-coronavirus-2 polymerase chain reaction test or equivalent), to be performed as per CRU requirements	Cannabinoids

9.3 PK Samples

Samples for budesonide PK assessment will be collected as outlined in the Schedule of Study Procedures (Section 3.0).

Instructions for sample collection, processing, and shipping will be provided separately.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory

9.3.1 PK Measurements

Samples from all participants will be assayed even if the participants do not complete the study. Samples for determination of plasma budesonide will be analyzed using validated bioanalytical methods.

Pharmacokinetic parameters of budesonide will be calculated from the individual concentration-time profiles from all evaluable participants using NCA methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

9.3.1.1 Plasma for PK Measurements

The following PK parameters will be calculated from plasma concentrations of budesonide, unless otherwise specified:

AUC_{last}:	Area under the concentration-time curve, from time 0 to the last quantifiable concentration.
AUC_{∞}:	Area under the concentration-time curve, from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
AUC_{0-12}:	Area under the concentration-time curve from time 0 to 12 hours.
AUC_{extrap}%:	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_{∞}.
CL/F:	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
C_{max}:	Maximum observed concentration.
t_{max}:	Time of first occurrence of C_{max}.
t_{lag}:	Lag time to first quantifiable concentration.
$t_{1/2z}$:	Terminal disposition phase half-life.
λ_z:	Terminal disposition phase rate constant.
V_z/F:	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.

No value for λ_z, AUC_{∞}, AUC_{extrap}%, CL/F, V_z/F, or $t_{1/2z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

PK parameters will not be calculated for participants with less than 3 consecutive postdose time points with quantifiable concentrations.

Individual and mean plasma concentration curves (both linear and log-linear) will be included in the final report.

9.3.2 Biomarker Measurements

Not applicable.

9.3.3 PGx Measurements

Not applicable.

9.3.4 Confinement

Participants will be housed on Day -1 of Period 1, at the time indicated by the CRU, until after the 24-hour blood draw and/or study procedures on Day 2 of Period 2. Participants may be admitted earlier than Day -1 of Period 1 for COVID-19 testing not related to study protocol as per CRU requirements.

At all times, a participant may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation participant who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional non-invasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, X-ray, etc.) should NOT be recorded as an AE unless related to a study procedure. However, if the participant experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a participant has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, Investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a participant has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the participant experiences a worsening or complication of an AE after the first administration of study drug or after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the participant experiences a change in the severity of an AE that is not associated with a change in study drug, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the participant's medical condition should not be recorded as AEs but should be documented in the participant's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study participant, at a dose above that which is assigned to that individual participant according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the participant should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
COVID-19-related disease	Spontaneous abortion / stillbirth and fetal death
COVID-19 pneumonia	

Abbreviations: COVID-19 = Coronavirus disease 2019.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Adverse Events of Special Interest

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

Important identified risks include:

- 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.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate:	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

In addition, relationship (causality) to COVID-19 should be determined for all AEs. The relationship should be assessed as related if the Investigator considers that there is reasonable possibility that an event is due to COVID-19. Otherwise, the relationship should be assessed as not related.

Similarly, relationship (causality) to COVID-19 vaccines should be determined for all AEs. The relationship should be assessed as related if the Investigator considers that there is reasonable possibility that an event is due to COVID-19 vaccines. Otherwise, the relationship should be assessed as not related. If the AE has relationship to vaccination, specific verbatim term should be used, eg, post-vaccination fever, vaccination site burning.

In addition, if the causality assessment done by the Investigator determines that the event or events (AEs) are related or possible related to COVID-19 or the COVID-19 vaccine, the events should be assessed as not related to the study drug. If the AE is related to COVID-19 vaccination, specific verbatim term(s) should be used, eg, post-vaccination fever, vaccination site burning.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the participant and/or Investigator.

10.2.4 End Date

The end date of the AE is the date at which the participant recovered, the event resolved but with sequelae or the participant died.

10.2.5 Pattern of AE (Frequency)

Single AEs (eg, vomit) are those which occur instantaneously. Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. Continuous AEs (eg, sinus congestion) occur without interruption over a specified period.

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the participant died, dosing with study drug had not yet started or dosing with study drug was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

- Recovered/resolved – participant returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the participant died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the participant died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/resolved with sequelae – the participant recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and abnormal LFTs) will commence at the time the participant signs the informed consent. Routine collection of AEs will continue until the follow-up visit, approximately 3 days after the last dose of study drug. For participants who discontinue prior to the administration of study drug, AEs will be followed until the participant discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Participants may report AEs occurring at any other time during the study. Participants experiencing an SAE prior to the first exposure to the study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious AEs that begin prior to the first exposure to the study drug, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All participants experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the Investigator concludes that the event is related to the study drug. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug).
- Relationship to COVID-19.
- Relationship to COVID-19 vaccine.
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Participant identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of study drug will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Reporting Special Interest AEs

Routine collection of AEs of special interest is not mandatory for the purposes of this study.

10.2.8.5 Reporting of Abnormal LFTs

If a participant is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a participant is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported

as per Section 10.2.8.3. The Investigator must contact the Medical Monitor for discussion of the relevant participant details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.8 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

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

11.1.1.2 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.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, sex, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

Statistical analysis of PK data will be based on the PK Set.

Plasma budesonide concentrations and PK parameters will be listed by participant and treatment, and summarized using appropriate descriptive statistics to be fully outlined in the SAP.

PK parameters (C_{max}, AUC_{last}, AUC_{∞}, $AUC_{0\text{-}12}$, $AUC_{extrap\%}$, t_{max}, t_{lag}, $t_{1/2z}$, λ_z, CL/F, and V_z/F) will be computed using standard NCA. Individual plasma concentration/time curves will be presented in linear/linear and log/linear scale.

The appropriate PK analysis will be fully specified in the SAP.

11.1.3.1 Estimation of Food-Effect

A linear mixed-effects model will be applied to log-transformed C_{max}, AUC_{last}, and AUC_{∞} 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).

11.1.3.2 Non-Parametric Analysis

Analysis of t_{max} and t_{lag} will be performed by non-parametric Wilcoxon signed-rank test.

11.1.4 PD Analysis

Not applicable.

11.1.5 Safety Analysis

All safety data will be listed.

TEAEs will be tabulated. The remaining quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.5.1 AEs

AEs will be coded using the most current version of MedDRA® available at Celerion and summarized by treatment for the number of participants reporting the TEAE and the number of TEAEs reported.

An AE will be considered treatment-emergent (ie, a TEAE) if the onset date and time is at the time of or after first administration of study drug.

A by-participant AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

11.1.5.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of time of collection and a shift table describing out of normal range shifts will be provided.

More detail will be provided in the SAP.

11.1.5.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

More detail will be provided in the SAP.

11.1.5.4 Other Safety Parameters

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be listed by participant.

More detail will be provided in the SAP.

11.2 Interim Analysis and Criteria for Early Termination

Not applicable.

11.3 Determination of Sample Size

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_{∞}, and AUC_{last}, assuming the true mean ratio of 1.0 with intra-participant 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% CI within (0.80, 1.25). Considering 10% dropout rate, a total of 20 participants will be enrolled.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Due to COVID-19, monitoring visits may also be conducted remotely. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee (clinical research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, study drug, participant medical records, informed consent documentation, and review of CRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

For COVID-19-related protocol deviations, the specific protocol deviation, the reason for the deviation, and the relationship to COVID-19 should be documented using CRU standard processes.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and participant informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by participants, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRB or IEC and Sponsor.

13.2 Participant Information, Informed Consent, and Participant Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study. The ICF and the participant information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact

that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the participant authorization form. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be written in a language fully comprehensible to the prospective participant. It is the responsibility of the Investigator to explain the detailed elements of the ICF, participant authorization form (if applicable), and participant information sheet (if applicable) to the participant. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the participant is not capable of rendering adequate written informed consent, then the participant's legally acceptable representative may provide such consent for the participant in accordance with applicable laws and regulations.

The participant, or the participant's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the participant, or the participant's legally acceptable representative, determines he or she will participate in the study, then the ICF and participant authorization form (if applicable) must be signed and dated by the participant, or the participant's legally acceptable representative, at the time of consent and prior to the participant entering into the study. The participant or the participant's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the ICF and participant authorization (if applicable) at the time of consent and prior to participant entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, participant authorization form (if applicable), and participant information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed ICF, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

All revised ICFs must be reviewed and signed by relevant participants or the relevant participant's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the participant's medical record, and the participant should receive a copy of the revised ICF.

13.3 Participant Confidentiality

The Sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age,

or date of birth, and participant initials may be used to verify the participant and accuracy of the participant's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the participant's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process (see Section 13.2).

Copies of any participant source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, participant name, address, and other identifier fields not collected on the participant's CRF).

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it Sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with Investigator's city, state (for Americas Investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting study information. Once participants receive Investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established participant screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the Sponsor.

Any Investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each participant in the study must be insured in accordance with the regulations applicable to the site where the participant is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to study participants. Refer to the study site agreement regarding the Sponsor's policy on participant compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: +1 224-554-1052

14.1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the IB, package insert, and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6[R2] Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{∞}	Area under the concentration-time curve, from time 0 to infinity
$AUC_{extrap}\%$	Area under the curve from the last quantifiable concentration to infinity
AUC_{0-12}	Area under the concentration-time curve from time 0 to 12 hours
AUC_{last}	Area under the concentration-time curve from time 0 to the last quantifiable concentration
BID	Twice daily
BMI	Body mass index
BOS	Budesonide oral suspension
bpm	Beats per minute
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent clearance after extravascular administration
cm	Centimeter
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRU	Clinical research unit
CV	Coefficient of variance
CYP	Cytochrome P450
ECG	Electrocardiogram
EoE	Eosinophilic esophagitis
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent ethics committee
IRB	Institutional review board
IU	International unit
kg	Kilogram
L	Liter
LFT	Liver function test
λ_z	Terminal disposition phase rate constant
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NCA	Non-compartmental analysis
P-gp	P-glycoprotein
PGx	Pharmacogenomics(s)
PK	Pharmacokinetic(s)
QTcF	QT interval corrected for pulse rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2z}$	Terminal disposition phase half-life
TDCA	Takeda Development Center Americas, Inc.
TEAE	Treatment-emergent adverse event
t_{lag}	Lag time to first quantifiable concentration
t_{max}	Time of first occurrence of C_{max}
ULN	Upper limit of normal
US	United States
USA	United States of America
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration
WHO	World Health Organization

15.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA®. Drugs will be coded using the WHO Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Celerion standard CRFs will be supplied. Each CRF will be reviewed and signed by the Investigator. The final signed CRFs will be archived electronically at the end of study in a document repository system. Final CRFs will be provided to the Sponsor in the format and transfer method as decided between Celerion and the Sponsor.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The Investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the Investigator with use of change and modification records of the CRFs. The Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the participant's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, participant authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the participant's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5

requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The Investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

1. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry: Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations. Jun 2022. Available at: https://www.fda.gov/media/121313/download.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the Investigator may participate in this study.

The Investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential participants, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each participant who participates in the study, and document the date of consent in the participant's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a participant authorization, then the Investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of

2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Participant Informed Consent

In seeking informed consent, the following information shall be provided to each participant:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the participant's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of participants involved in the study.
7. A description of the participant's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the participant may receive.
11. A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the participant or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the participant will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the participant or the participant's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the participant for participating in the study.
17. The anticipated expenses, if any, to the participant for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), participant's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the participant.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant otherwise is entitled, and that the participant or the

participant's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

20. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
21. A statement that the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the participant's participation in the study may be terminated.
23. A written participant authorization (either contained within the ICF or provided as a separate document) describing to the participant the contemplated and permissible uses and disclosures of the participant's personal information (including personal health information) for purposes of conducting the study. The participant authorization must contain the following statements regarding the uses and disclosures of the participant's personal information:

    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer participants the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

    d) that participants agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

    e) that the participant's identity will remain confidential in the event that study results are published.

24. Female participants of childbearing potential (eg, non-sterilized, pre-menopausal female participants) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the

study, and for at least 28 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female participants of childbearing potential. If a participant is found to be pregnant during study, study drug will be discontinued and the Investigator will offer the participant the choice to receive treatment information.

25. Male participants must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for at least 90 days after the last dose of study drug. If the partner of the participant is found to be pregnant during the study, the Investigator will offer the participant the choice to receive treatment information.
26. A statement that clinical trial information from this study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of Investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting Investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in Investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Participants

From signing of informed consent, throughout the duration of the study, and for at least 90 days after the last dose of study drug, non-sterilized** male participants who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

Female Participants and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 28 days after the last dose of study drug, female participants of childbearing potential* who are sexually active with a non-sterilized male partner** must use a highly effective method of contraception (from the list below).

In addition they must be advised not to donate ova during this period.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysteroscopic sterilization, bilateral tubal ligation, bilateral salpingectomy, hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
    - Non-Hormonal Methods:
        - Intrauterine device.
        - Bilateral tubal occlusion.

- Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success).
- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the participant. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from at least 28 days prior to the first dose until at least 28 days after the last dose.

- Hormonal Methods:
  - Combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug and combined with a physical (eg, male condom, female condom, diaphragm) or a chemical (eg, spermicide) barrier method from the screening visit until at least 28 days after the last dose;
    - Oral.
    - Intravaginal (eg, ring).
    - Transdermal.
  - Depot/implantable hormone (eg, Depo-Provera®, Implanon®) for at least 3 months prior to the first dose until at least 28 days after the last dose.
    - Oral.
    - Injectable.
    - Implantable.

9. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception, unless it is true sexual abstinence as described above.
2. Participants will be provided with information on highly effective methods of contraception as part of the participant informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

3. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all participants (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study.
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c) assessment of participant compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
4. In addition to a negative serum hCG pregnancy test at the screening visit, female participants of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses; with the exception of female participants using a protocol acceptable contraception method that has a known side effect of delayed or irregular menses). In addition, participants must also have a negative serum hCG pregnancy test with 24 hours prior to receiving first dose of study drug as close as possible and prior to first dose of study drug, preferably on the same day.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- assessment of participant compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

Pregnancy

If any female participant is found to be pregnant during the study she should be withdrawn and any Sponsor-supplied study drug should be immediately discontinued. In addition, any pregnancies in the partner of a male participant during the study or for at least 90 days after the last dose, should also be recorded following authorization from the participant's partner.

If the female participant and/or female partner of a male participant agrees to the primary care physician being informed, the Investigator should notify the primary care physician of her or her male partner (ie, male participant) participation in a clinical study at the time she became pregnant and provide details of the study drug the female participant or her male partner (ie, male participant) received.

All pregnancies, including female partners of male participants, in participants on active study drug (including comparator, if applicable) will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after the birth of the child will also be conducted.