CLINICAL STUDY PROTOCOL

NCT Number: NCT04465396

Study Title: A Randomized, Open-label, Two-treatment, Two-period, Single-dose, Crossover Study to Evaluate the Bioavailability of Teduglutide Administered Subcutaneously by Syringe Injection Versus Pen Injector in Healthy Adult Subjects

Study Number: TAK-633-1001

Protocol Version and Date:

Amendment 03: 09 Dec 2020

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Open-label, Two-treatment, Two-period, Single-dose, Crossover Study to Evaluate the Bioavailability of Teduglutide Administered Subcutaneously by Syringe Injection Versus Pen Injector in Healthy Adult Subjects

Study Identifier: TAK-633-1001

Compound: Teduglutide

Date: 09 Dec 2020

Version/Amendment Number: Amendment 03

Amendment History:

Date	Amendment Number	Amendment Type	Region
28 Feb 2020	Initial Version		United States
29 Apr 2020	01	Not Applicable	United States
28 Sep 2020	02	Not Applicable	United States
09 Dec 2020	03	Not Applicable	United States

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1. STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, MA 02421	Teduglutide
Study Identifier (ID): TAK-633-1001	**Phase:** I

Protocol Title: A Randomized, Open-label, Two-treatment, Two-period, Single-dose, Crossover Study to Evaluate the Bioavailability of Teduglutide Administered Subcutaneously by Syringe Injection Versus Pen Injector in Healthy Adult Subjects

Study Design:

This is a randomized, open-label, two-treatment, two-period, two-sequence, single dose, crossover bioavailability study in healthy adult subjects.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dosing.

Subjects will be enrolled into 1 of 2 cohorts based on their weight (≥40.0 kg to ≤75.0 kg [Cohort 1] and >75.0 kg to ≤120.0 kg [Cohort 2]). In each cohort, subjects will be admitted to the clinical facility the day prior to each dosing and will be confined at least 24 hours; subjects will be released following completion of the 24-hour study procedures in each period. On Day 1 of Period 1, subjects in each cohort will be randomized to 1 of 2 treatment sequences as indicated in Table 1 below. Fixed teduglutide doses (delivered by pen injector or from approved single-use vials) is 3 mg for subjects in Cohort 1 and 4 mg for subjects in Cohort 2. Each dose will be separated by a washout period of 7 days. Blood samples for teduglutide pharmacokinetics (PK) will be collected predose and for 24 hours following each teduglutide dose.

Table 1 Treatment Scheme for Each Cohort

Weightband	Cohort/ Dose level	No. of Subjects	Sequence*	Treatment Period 1 (Day 1)	Washout Period (7 days)	Treatment Period 2 Day 1)
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=16	AB	Reference (fixed dose by vial and syringe)**	→	Test (fixed dose by pen injector)**
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=16				
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=16	BA	Test (fixed dose by pen injector)**	→	Reference (fixed dose by vial and syringe)**
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=16				

* To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will be stratified by injection site within each cohort.

**Fixed teduglutide doses (delivered by pen injector or from approved single-use vials) is 3 mg for subjects in Cohort 1 (≥40.0 kg - ≤75.0 kg) and 4 mg for subjects in Cohort 2 (>75.0 kg - ≤120.0 kg).

Treatment A: Teduglutide administered by syringe injection

Treatment B: Teduglutide administered by pen injector

Safety and tolerability will be assessed by treatment-emergent adverse events (TEAEs), including injection site reaction and injection site injury assessments, clinical laboratory evaluations, physical examinations, and vital signs.

All subjects who received at least one dose of study drug (including subjects who terminate the study early) will be contacted by the Clinical Research Unit (CRU) 7 (±2) days after the last study drug administration to determine if any adverse event (AE) has occurred since the last study visit.

Study Primary Objective:

To evaluate the bioavailability of teduglutide following the administration of a single, subcutaneous (SC) fixed dose of 3 mg or 4 mg teduglutide (depending upon subjects assignment in one of two cohorts as defined by body weight) administered via manual injection or via pen injector in healthy subjects.

Study Secondary Objectives:

To evaluate the bioavailability of teduglutide, by injection site (ie, thigh, abdomen, and arm), following the administration of a single, SC fixed dose of 3 mg or 4 mg teduglutide (depending upon subjects assignment in one of two cohorts as defined by body weight) administered via manual injection or via pen injector in healthy subjects.

To evaluate other PK parameters of teduglutide, as appropriate, following the administration of a single dose of teduglutide administered via manual injection or pen injector in healthy subjects.

To assess the safety and tolerability of SC injections of teduglutide in healthy subjects.

To assess the safety and performance of the pen injector for SC drug administration in healthy subjects.

Study Subject Population: Healthy male and female subjects aged 18 – 45 years inclusive, at time of consent. Each subject in Cohort 1 will weigh ≥40.0 kg to ≤75.0 kg at screening and confirmed on Day -1 of Period 1 and each subject in Cohort 2 will weigh >75.0 kg to ≤120.0 kg at screening and confirmed on Day -1 of Period 1.

Planned Number of Subjects: The planned total sample size for this study is 64 randomized subjects.	**Planned Number of Sites:** 1
Dose Levels: Cohort 1 (body weight ≥40.0 kg to ≤75.0 kg): 3 mg Cohort 2 (body weight >75.0 kg to ≤120.0 kg): 4 mg	**Route of Administration:** SC
Duration of Treatment: Single dose	**Planned Study Duration:** Up to 6 weeks from screening to end of study (follow up)

Criteria for Inclusion:

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

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent and assent as applicable to participate in the study.
3. Aged 18 - 45 inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential, refer to Appendix D.
5. Considered "healthy" by the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a full physical examination including vital signs, 12-lead ECG, hematology, coagulation (as appropriate), serum chemistry, and urinalysis.
6. Body mass index (BMI) ≥18.0 and ≤32.0 kg/m^2 at screening. Body weight for a subject in Cohort 1 will be ≥40.0 kg to ≤75.0 kg, and body weight for a subject in Cohort 2 will be >75.0 kg to ≤120.0 kg, inclusive. This inclusion criterion will be assessed at the screening visit and confirmed at first check-in.

Criteria for Exclusion:

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

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments.

2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Positive PCR (polymerase chain reaction) test for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), either with the absence or presence of the clinical symptoms of Coronavirus disease 2019 (COVID-19).
4. Known or suspected intolerance or hypersensitivity to teduglutide, closely-related compounds, or any of the stated ingredients.
5. Significant illness, as judged by the investigator, within 2 weeks of the first dose of teduglutide.
6. Known history of alcohol or other substance abuse within the last year prior to screening.
7. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of teduglutide.
8. Pregnant or lactating female.
9. Within 30 days prior to the first dose of teduglutide:
    - Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
    - Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's (or designee's) opinion, may impact this study.
    - Have had any substantial changes in eating habits, as assessed by the investigator (or designee).
10. Use of dipeptidyl peptidase 4 inhibitors within 30 days or 5 half-lives, whichever is greater, prior to administration of the first dose of teduglutide.
11. Confirmed systolic blood pressure >140 mmHg or <90 mmHg, and diastolic blood pressure >90 mmHg or <40 mmHg at screening.
12. Twelve (12)-lead ECG demonstrating QTcF >450 msec at screening. If the QTcF exceeds the aforementioned limits, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
13. Positive screen for drugs of abuse or alcohol at screening and at each check-in.
14. Male subjects who consume more than 21 units of alcohol per week or regularly consume more than 3 units per day. Female subjects who consume more than 14 units of alcohol per week or regularly consume more than 2 units per day. (1 alcohol unit=150 mL of wine, or 360 mL of beer, or 45 mL of 45% alcohol).
15. Positive HIV, HBsAg, or HCV antibody screen at screening.
16. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch) based on subject self-reporting. Ex-users must report that they have stopped using tobacco for at least 3 months prior to receiving the first dose of teduglutide.
17. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. One caffeine unit is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz (360 mL) cup of tea, three 1 oz (85 g) chocolate bars.
18. Prior screen failure, randomization, participation, or enrollment in this study, or prior exposure to any GLP-2 analogs.
19. Presence of lesions, rashes, tattoos, and moles etc. on administration sites not allowing adequate conduct of injection site reaction and injection site injury assessments.
20. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of occasional use of ibuprofen [1.2 g per 24 hour period] or acetaminophen [2 g per 24 hour period]). Current use is defined as use within 14 days of the first dose of teduglutide and throughout the study.

Criteria for Evaluation and Analyses:

The primary endpoints of the study are the PK metrics* and will include:

- $AUC_{0\text{-}tlast}$: Area under the concentration curve from time zero to the time of last measurable concentration
- C_{max}: Maximum concentration
- $AUC_{0\text{-}\infty}$: Area under the concentration curve extrapolated to infinite time

*Beginning on Day 1 of each period, PK parameters will be calculated from reliable teduglutide concentration-time profiles using non-compartmental methods where all calculations will be based on actual sampling times.

The secondary endpoints will be assessed through evaluation of the following parameters:

PK metrics* by injection site (ie, thigh, abdomen, and arm) including:

- $AUC_{0\text{-}tlast}$: Area under the concentration curve from time zero to the time of last measurable concentration
- C_{max}: Maximum concentration
- $AUC_{0\text{-}\infty}$: Area under the concentration curve extrapolated to infinite time

*Beginning on Day 1 of each period, PK parameters will be calculated from reliable teduglutide concentration-time profiles using non-compartmental methods where all calculations will be based on actual sampling times.

- Other secondary PK parameters will include:

  t_{max}: Time of first occurrence of C_{max}

  λ_z: Terminal disposition phase rate constant

  $t_{1/2}$: Terminal disposition phase half-life

  CL/F: Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed

  Vz/F: Apparent volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
- Occurrence of TEAEs, including injection site reactions and injection site injury assessments.
- Routine clinical safety monitoring that includes: vital signs, clinical laboratory test results (hematology, serum chemistry, coagulation (as appropriate), and urinalysis) and physical examinations.
- Occurrence of device malfunctions.

The safety endpoint and safety variables will be captured for both test and reference.

A list of potential device malfunctions will be provided to the study site as a reference list for data capture.

Statistical Considerations:

Statistical Methodology for Pharmacokinetic Endpoints

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

All individual concentration data and PK metrics will be listed for each subject and treatment together with summary statistics such as geometric mean, median, arithmetic mean, standard deviation (SD), coefficient of variation, geometric coefficient of variation, and minimum and maximum grouped by treatment and cohort. The time until first occurrence of C_{max} is reached (t_{max}) will be also listed for each subject and treatment and summarized by medians, minimum and maximum grouped by treatment and cohort. The number of time points of the terminal log-linear phase used to estimate the terminal rate constant (λ_z) and the residual area will be also provided for each subject and treatment.

Individual concentration-time curves will be presented in linear/linear and log/linear scale. Figures showing the mean (with ±SD as error bars) as well as the median (with 25^{th} to 75^{th} quantiles as error bars) concentration time profiles grouped by treatment and cohort will be also presented in linear/linear and log/linear scale.

The PK endpoints will also be analyzed by injection site (ie, thigh, abdomen, and arm).

PK metrics $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} will be analyzed using an analysis of variance (ANOVA) model for each cohort separately.

PK metrics will be transformed prior to analysis using a logarithmic transformation. The difference in means and the corresponding two-sided 90% confidence interval (CI) on the log-transformed scale will be obtained from that model. The difference in means and the corresponding CI will be back-transformed to obtain the ratio of geometric means and the corresponding two-sided 90% CI for the ratio on the original scale. The terms used in the ANOVA model will be sequence, subject within sequence, period, and treatment. According to EMA guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) (EMA 2010), subjects who will not provide evaluable data for both periods will be not included and fixed effects will be used for all terms.

To assess bioavailability between test and reference, the 90% CI for the ratio of geometric means for PK metrics, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} will be derived and compared (and would be contained within the acceptance interval of 80.00 to 125.00% if bioequivalent).

Statistical Methodology for Safety Endpoints:

Statistical analysis of safety data will be based on the safety analysis data set.

Safety data will be listed by subject and summarized by cohort and treatment using descriptive statistics. Continuous variables will be summarized by sample size, mean, SD, median, minimum, and maximum. Categorical variables will be summarized by number of subjects and the percent of subjects in each category.

TEAEs will be analyzed using the number and percentage of subjects reporting events, as well as the number of events, by system organ class and preferred term, severity, and causal relationship to the study treatment and device. Among TEAEs, injection site reactions and injection site injuries will be analyzed using the number and percentage of subjects reporting events, by preferred term, severity, and causal relationship to study treatment and device. Laboratory tests, vital signs, physical examinations, and corresponding changes from baseline will be summarized by study visit where baseline will be defined as the last non-missing assessment on or before Day 1 prior to the first dose.

Device malfunctions will be listed for each subject and summarized by cohort using the number and percentage of events.

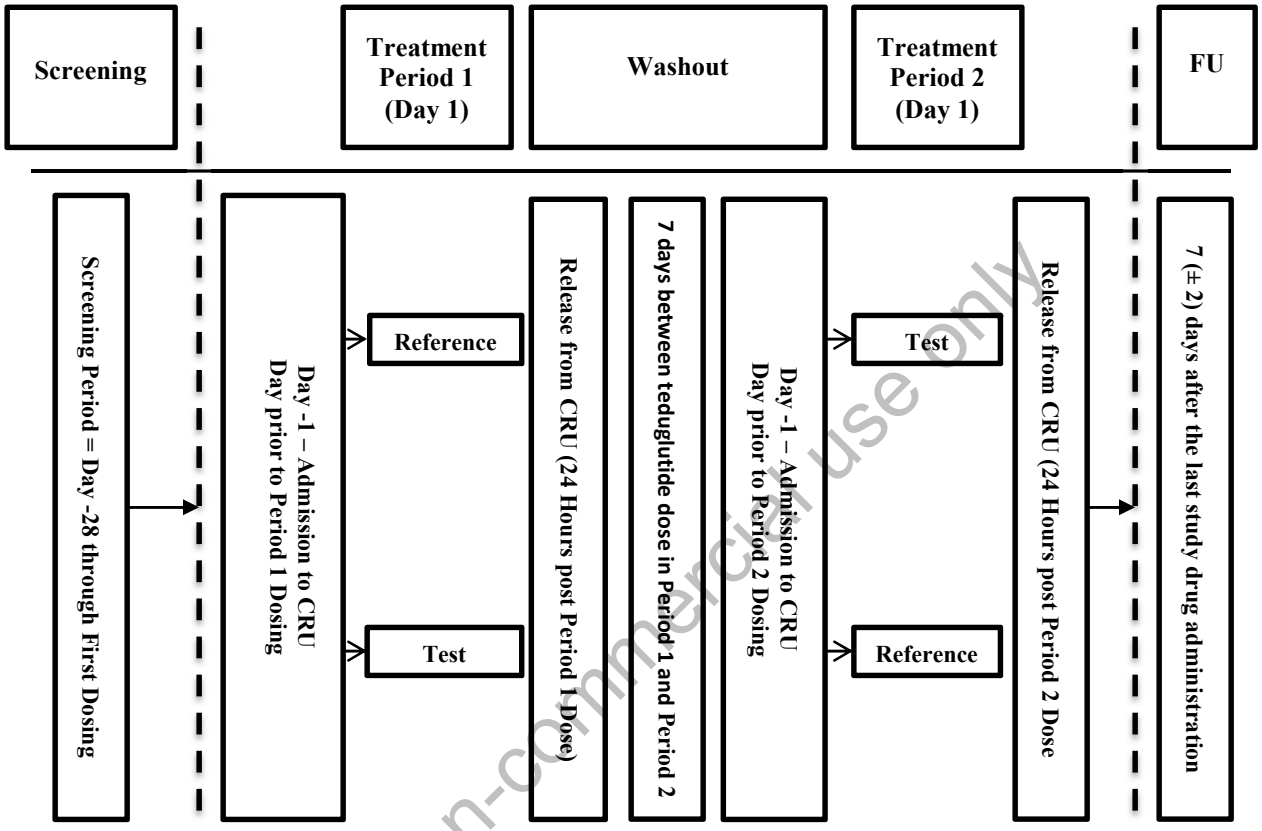
Sample Size Justification:

The overall power for the endpoints ($AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}) with a total sample size of 64 subjects will be 92.6% power based on a 5% type 1 error and a Coefficient of Variation of 21%, assuming a true ratio of test/reference of 1.0 in their relative bio-availabilities based on the acceptance interval of 80.00 to 125.00%. The sample size of 28 subjects within each cohort (14 each sequence) was accounted for approximately 10% potential drop-outs and/or non-reliable concentration time-profiles to yield 32 subjects per cohort (16 subjects per sequence within each cohort). This sample size was calculated with SAS v9.

2. STUDY SCHEMATIC

Cohort 1 (3 mg Teduglutide) and Cohort 2 (4 mg Teduglutide)

2-Period Crossover



FU=Follow up

Fixed teduglutide dose (delivered by pen injector [test] or from approved single-use vials [reference]) is 3 mg for subjects in Cohort 1 (≥40.0 kg to ≤75.0 kg) and 4mg for subjects in Cohort 2 (>75.0 kg to ≤120.0 kg)

3. SCHEDULE OF STUDY PROCEDURES

Study Procedures[a]	**Screening**[b]	**Study Days in Each Period (Period 1 and Period 2)**[c]																**Washout (7 days)**[c]	**ET**[e]	**FU**[f]
Hours →		**C-I**[d]	Predose	0	0.5	1	2	3	4	5	6	8	10	12	14	16	24			
Administrative Procedures																				
Visit	X																			
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X[g]																		
Demography and Medical/Medication History	X																			
Safety Evaluations																				
Full Physical Examination[h]	X																X[m]		X	
Abbreviated Physical Examination[h]		X															X[n]			
Height	X																			
Weight	X	X																		
12-Lead ECG[i]	X																			
Vital Signs (heart rate, blood pressure, respiratory rate, and temperature)[i]	X		X[j]				X										X		X	
Hematology, Serum Chemistry[k], Coagulation (as appropriate), and Urinalysis	X	X															X		X	
Serum Pregnancy Test (females only)	X	X[l]															X[m]		X	
Serum FSH (postmenopausal females only)	X																			
Urine Drug and Alcohol Screen	X	X																		
HIV, HBsAg, and HCV Antibodies	X																			
AE Monitoring	X																			
Concomitant Medication Monitoring	X																			

Study Procedures[a]	**Screening**[b]	**Study Days in Each Period (Period 1 and Period 2)**[c]																**Washout (7 days)**[c]	**ET**[e]	**FU**[f]
Hours →		**C-I**[d]	Predose	0	0.5	1	2	3	4	5	6	8	10	12	14	16	24			
Study Drug Administration / PK																				
Teduglutide Administration[o]				X																
Blood for Teduglutide PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Other Procedures																				
Randomization				X[g]																
Injection Site Reaction and Injection Site Injury Assessment			X	X[p]	X	X	X		X		X	X		X			X			
Device Malfunction Assessment				X[q]																
Confinement in the CRU[r]		X																		

AE=Adverse events; C-I=Check-in; CRU=Clinical research unit; ECG=Electrocardiogram; ET=Early termination; FSH=Follicle-stimulating hormone; FU=Follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; PK=Pharmacokinetics

a For details on Procedures, refer to Section 9.

b Within 28 days prior to first teduglutide administration.

c There will be a washout period of 7 days between the teduglutide dose in Period 1 and Period 2.

d Subjects will be admitted to the CRU on Day -1 of each period at the time indicated by the CRU. Subjects may be admitted earlier for Coronavirus Disease 2019 (COVID-19) testing not related to study protocol as per CRU requirements. If the CRU decides to confine the subjects throughout the study (ie, washout period[s]), some safety events at check-in (eg, clinical laboratory test, urine drug and alcohol screen, pregnancy test, and vital signs) may not be performed at the investigator's discretion.

e To be performed prior to ET from the study.

f All subjects who received at least one dose of study drug (including subjects who terminate the study early) will be contacted by the CRU 7 (±2) days after the last study drug administration to determine if any AE has occurred since the last study visit.

g Will be performed in Period 1 only. Subjects will be assigned to a cohort based on their weight and will receive the study treatments according to the randomization scheme. In each cohort, subjects will be randomized to 1 of 2 sequences and administered a single dose of teduglutide on Day 1 of each period per the randomization sequences, either AB or BA (as defined in the study protocol). To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will also be stratified by injection site within each cohort.

h Full physical examinations will be performed at screening and prior to discharge at Period 2. Abbreviated physical examinations will be performed at check-in for each period and prior to release at Period 1 (See Section 9.2.1). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the investigator or designee.

i ECGs and vital signs will be performed after 5 minutes rest in the supine position.

j To be performed within 24 hours prior to dosing in each period.

Study Procedures[a]	**Screening[b]**	**Study Days in Each Period (Period 1 and Period 2)[c]**															**Washout (7 days)[c]**	**ET[e]**	**FU[f]**
Hours →		**C-I[d]**	Predose	0	0.5	1	2	3	4	5	6	8	10	12	14	16	24			

k Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of ET or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.

l To be drawn at the same time as the clinical laboratory blood draw, result to be available prior to dosing.

m To be performed on discharge from Period 2.

n To be performed prior to release from Period 1.

o Each subject will receive teduglutide on 2 occasions, (ie, on Day 1 of each period, either by syringe injection [vial and syringe) or pen injector in a crossover fashion).

p The injection sites will be assessed for injection site reactions and injection site injuries immediately postdose (ie, ≤2 minutes).

q To be performed for the test product (pen injector) during preparation, immediately prior, and post teduglutide administration.

r Subjects will be confined in each period for at least 24 hours and will be released from the clinic following completion of the 24-hour study procedures. At all times, a subject may be required to remain at the CRU for longer at the discretion of the investigator or designee.

4. INTRODUCTION

4.1 Background

Teduglutide (ALX-0600, [gly2]-hGLP-2) is a novel, recombinant analog of naturally occurring human glucagon like peptide-2 (GLP-2), formulated for the treatment of short bowel syndrome (SBS). Teduglutide accelerates intestinal adaptation after bowel resection and enhances selective barrier function in the small intestine (Jeppesen et al., 2005; Jeppesen, 2007; Mardini and de Villiers, 2008). Data from previous investigations have shown functional changes in crypts and villi in humans following administration of teduglutide. The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (REVESTIVE®). A New Drug Application for teduglutide (GATTEX®) was approved by the United States (US) Food and Drug Administration (FDA) and teduglutide was recently approved for the treatment of patients aged ≥1 year with SBS in the EU, the US, and Canada. Teduglutide is currently approved in >30 countries.

Efficacy

In pivotal and supportive clinical studies, the evidence demonstrates that teduglutide at a daily dose of 0.05 mg/kg administered SC is effective in treating parenteral support (PS)-dependent adults with SBS by providing a clinically meaningful reduction in weekly PS volume. The results are reproducible and generalizable across a broad population of adult SBS subjects. Results of the long-term extension studies demonstrate the reproducibility as well as the durability of the beneficial effects of teduglutide 0.05 mg/kg/day, without evidence for the development of tolerance during up to 30 months of treatment. In another extension study of subjects treated for an additional 24 months after receiving 24 weeks of teduglutide in the core study, the response to long-term treatment with teduglutide 0.05 mg/kg/day was maintained in subjects initially treated with teduglutide in the core study, with further reductions in PS volume relative to baseline and fewer days per week of PS support. The responses to treatment with teduglutide were accompanied by an increase in mean plasma citrulline, indicating increased enterocyte mass.

Pharmacokinetics

The PK of teduglutide has been investigated following single SC administration at fixed doses of 2.5 to 10 mg (Study 1621/13). Following SC administration, the plasma C_{max} of teduglutide occurred at approximately 3 to 4 hours postdose with the exposure (C_{max} and AUC) increasing approximately in a dose proportional manner. Following a one-time PK sampling conducted at the beginning of the initial 24-week teduglutide treatment period (0.05 mg/kg SC once daily) in Study TED-C14-004, a maximum mean plasma concentration of 49.7 ng/mL was achieved at 2.64±1.02 hours (t_{max}) and the mean AUC_{0-t} and AUC_{0-inf} values were 201±51.6 and 204±51.1 ng•hr/mL, respectively. Teduglutide was absorbed and rapidly eliminated from plasma with mean t½ of 1.21±0.65 hours. The mean plasma clearance was 14.5±4.09 L/hr and the mean body weight normalized plasma clearance was 0.0259±0.0672 L/hr/kg. Teduglutide total exposure after SC administration was shown to be similar, irrespective of the site of administration (abdomen, arm, or thigh) (Study CL0600-015).

Safety

The safety of teduglutide has been examined in 9 studies in healthy subjects. Teduglutide was well-tolerated in these studies. The AEs experienced by the healthy subjects were consistent with those experienced in clinical studies of SBS and Crohn's subjects. There were no treatment-related SAEs or deaths reported in these studies. There were no clinically significant changes or results noted from clinical laboratory evaluations, vital sign measurements, ECG readings, or physical examination findings. The most common adverse reactions across all studies were abdominal pain, injection site reactions, nausea, headaches, abdominal distension, and upper respiratory tract infection.

For further information on teduglutide, refer to the current edition of the Investigator's Brochure (IB).

4.2 Rationale for the Proposed Study

A new pen injector is being developed to simplify the dose preparation and administration of teduglutide. Extensive in vitro device verification work will be performed to evaluate the safety and performance of the device. Device performance will evaluate dose accuracy and consistency of dose delivery using the pen injector in accordance with The International Organization for Standardization: 11608-1 standards.

This clinical bioavailability study is intended to support the bridging between the commercially available vial drug primary container administered via a syringe injection (eg, syringe and approved vials) versus the pen injector.

The purpose of this study is to evaluate the bioavailability of teduglutide administered as a single SC fixed dose (depending upon subject weightband assignment) delivered by a syringe injection and the same fixed dose delivered by the pen injector in healthy subjects.

Throughout the clinical development program for SBS, teduglutide has been administered daily by SC injection via arm, thigh, or abdomen based on individual subject body weight.

Currently the approved preparation and injection material includes off-the-shelf syringes (for manual injection) and needles. Therefore, a clinical bioavailability study is necessary to evaluate the exposure of fixed doses of teduglutide when administered by the pen injector (test) relative to the currently approved configuration by syringe injection (reference). Conducting such a study in healthy population is justifiable to avoid confounding factors from patients with SBS.

Data from this study will be evaluated based on EMA Guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. (EMA 2010) and the FDA's Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations (FDA 2019).

The washout period between doses is considered sufficient to prevent carryover effects of the preceding treatment.

4.3 Benefit/Risk Profile

The risks associated with dosing teduglutide are anticipated to be similar to those previously documented in the IB and product label for teduglutide and are not anticipated to induce any potential risk to healthy subjects participating in this study (current IB edition, GATTEX®, Prescribing Information, 2018).

The doses provided in the study are based on the dosing recommendations of the product label ie, approximately 5 mg for a 100 kg person, as the recommended daily dose of teduglutide is 0.05 mg/kg body weight administered by SC injection once daily (GATTEX®, Prescribing Information, 2018).

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

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

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Hypothesis testing is not relevant for a bioavailability study.

5.2 Study Objectives

5.2.1 Study Primary Objective

To evaluate the bioavailability of teduglutide following the administration of a single, SC fixed dose of 3 mg or 4 mg teduglutide (depending upon subjects assignment in one of two cohorts as defined by body weight) administered via manual injection or via pen injector in healthy subjects.

5.2.2 Study Secondary Objectives

To evaluate the bioavailability of teduglutide, by injection site (ie, thigh, abdomen, and arm), following the administration of a single, SC fixed dose of 3 mg or 4 mg teduglutide (depending upon subjects assignment in one of two cohorts as defined by body weight) administered via manual injection or via pen injector in healthy subjects.

To evaluate other PK parameters of teduglutide, as appropriate, following the administration of a single dose of teduglutide administered via manual injection or pen injector in healthy subjects.

To assess the safety and tolerability of SC injections of teduglutide in healthy subjects.

To assess the safety and performance of the pen injector for SC drug administration in healthy subjects.

5.3 Endpoints

5.3.1 Primary Endpoints

The primary endpoints of the study are the PK metrics* and will include:

- $AUC_{0\text{-}tlast}$: Area under the concentration curve from time zero to the time of last measurable concentration
- C_{max}: Maximum concentration
- $AUC_{0\text{-}\infty}$: Area under the concentration curve extrapolated to infinite time

*Beginning on Day 1 of each period, PK parameters will be calculated from reliable teduglutide concentration-time profiles using non-compartmental methods where all calculations will be based on actual sampling times.

5.3.2 Secondary Endpoints

The secondary endpoints will be assessed through evaluation of the following parameters:

PK metrics* by injection site (ie, thigh, abdomen, and arm) including:

- $AUC_{0\text{-}tlast}$: Area under the concentration curve from time zero to the time of last measurable concentration
- C_{max}: Maximum concentration
- $AUC_{0\text{-}\infty}$: Area under the concentration curve extrapolated to infinite time

*Beginning on Day 1 of each period, PK parameters will be calculated from reliable teduglutide concentration-time profiles using non-compartmental methods where all calculations will be based on actual sampling times.

- Other secondary PK parameters will include:

  t_{max}: Time of first occurrence of C_{max}

  λ_z: Terminal disposition phase rate constant

  $t_{1/2}$: Terminal disposition phase half-life

  CL/F: Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed

  Vz/F: Apparent volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed

- Occurrence of TEAEs, including injection site reactions and injection site injury assessments.
- Routine clinical safety monitoring that includes: vital signs, clinical laboratory test results (hematology, serum chemistry, coagulation (as appropriate), and urinalysis) and physical examinations.
- Occurrence of device malfunctions.

The safety endpoint and safety variables will be captured for both test and reference.

A list of potential device malfunctions will be provided to the study site as a reference list for data capture.

6. STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a randomized, open-label, two-treatment, two-period, two-sequence, single dose, crossover bioavailability study in healthy adult subjects.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dosing.

Subjects will be enrolled into 1 of 2 cohorts based on their weight (≥40.0 kg to ≤75.0 kg [Cohort 1] and >75.0 kg to ≤120.0 kg [Cohort 2]). In each cohort, subjects will be admitted to the clinical facility the day prior to each dosing and will be confined at least 24 hours; subjects will be released following completion of the 24-hour study procedures in each period. On Day 1 of Period 1, subjects in each cohort will be randomized to 1 of 2 treatment sequences as indicated in Table 2 below. Fixed teduglutide doses (delivered by pen injector or from approved single-use vials) is 3 mg for subjects in Cohort 1 and 4 mg for subjects in Cohort 2. Each dose will be separated by a washout period of 7 days. Blood samples for teduglutide PK will be collected predose and for 24 hours following each teduglutide dose.

Table 2 Treatment Scheme for Each Cohort

Weightband	Cohort/ Dose level	No. of Subjects	Sequence*	Treatment Period 1 (Day 1)	Washout Period (7 days)	Treatment Period 2 Day 1)
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3 mg	n=16	AB	Reference (fixed dose by vial and syringe)**	→	Test (fixed dose by pen injector)**
>75.0 kg - ≤120.0 kg	Cohort 2 / 4 mg	n=16				
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3 mg	n=16	BA	Test (fixed dose by pen injector)**	→	Reference (fixed dose by vial and syringe)**
>75.0 kg - ≤120.0 kg	Cohort 2 / 4 mg	n=16				

* To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will be stratified by injection site within each cohort.

**Fixed teduglutide doses (delivered by pen injector or from approved single-use vials) is 3 mg for subjects in Cohort 1 (≥40.0 kg - ≤75.0 kg) and 4mg for subjects in Cohort 2 (>75.0 kg - ≤120.0 kg).

Treatment A: Teduglutide administered by syringe injection

Treatment B: Teduglutide administered by pen injector

Safety and tolerability will be assessed by TEAEs, including injection site reaction and injection site injury assessments, clinical laboratory evaluations, physical examinations, and vital signs.

All subjects who received at least one dose of study drug (including subjects who terminate the study early) will be contacted by the CRU 7 (±2) days after the last study drug administration to determine if any AE has occurred since the last study visit.

6.2 Dose Escalation

Not applicable.

6.3 Rationale for Study Design, Dose, and Endpoints

6.3.1 Rationale of Study Design

The purpose of the study is to test the bioavailability between the two administration devices. By using healthy subjects, the study will mainly focus on the difference in the exposure between the two devices and limit other factors on the dose-exposure response. In order to manage the variability in drug preparation and administration, the site staff will be fully trained in drug administration.

Subjects will be randomized to treatment sequences to minimize assignment bias. A weight stratified, crossover design is used to reduce the residual variability as every subject acts as their own control. To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will also be stratified by injection site within each cohort.

The washout period between doses is considered sufficient to prevent carryover effects of the preceding treatment.

6.3.2 Rationale for Dose

Teduglutide is indicated for the treatment of adult and pediatric patients with SBS. The European Commission granted a centralized marketing authorization valid throughout the EU for teduglutide (REVESTIVE®). A New Drug Application for teduglutide (GATTEX®) was approved by the US FDA and teduglutide was recently approved for the treatment of patients aged ≥1 year with SBS in the EU, the US, and Canada. Teduglutide is currently approved in >30 countries. Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies in adults with SBS.

To simplify dosing procedures and reduce dosing errors, a dosing regimen based on weightbands was explored by population PK modeling and simulation (including PK and exposure-response analyses) based on the available clinical data. The 2 weightbands proposed are (based on modeling) ≥40.0 kg to ≤75.0 kg (Cohort 1) and >75.0 kg to ≤120.0 kg (Cohort 2). Any subject in the weightband of ≥40.0 kg to ≤75 kg (Cohort 1) will receive a fixed 3 mg single dose and the weightband of >75.0 kg to ≤120.0 kg (Cohort 2) will receive a fixed 4 mg single dose. The proposed fixed doses are expected to deliver comparable exposures to those when using the weight-based dose of 0.05 mg/kg once daily.

6.3.3 Rationale for Endpoints

6.3.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this bioavailability study.

6.3.3.2 Safety, Tolerability, and Performance Endpoints

The key safety and tolerability endpoints are typical for Phase 1 studies. The sampling time points selected for AEs, vital signs, clinical laboratory assessments, and injection site reaction injection site injury assessments are considered sufficient to assess safety and detect any TEAEs.

As the study is investigating the potential of a new pen injector to deliver teduglutide, a list of potential device malfunctions will be provided to the study site as a reference list for data capture. The pen injector will be evaluated prior to and post teduglutide administration. The site staff will report any malfunctions whilst using the device.

6.3.4 Future Biomedical Research

Not applicable.

6.3.5 Critical Procedures Based on Study Objectives: Timing of Procedures

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

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

The dose and administration of the study drug to any subject may not be modified. If necessary, a subject may be discontinued for the reasons described in Section 7.5. Discontinued subjects may be replaced at the discretion of the Sponsor and the investigator.

6.5 Study Beginning and End/Completion

6.5.1 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 subject.

6.5.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure (ie, the follow-up contact on Day 7 [±2 days] for all subjects including those who received at least one dose of study drug and withdrawn early) as outlined in the Schedule of Study Procedures (Section 3).

6.5.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the follow-up contact for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.5.4 Definition of Study Discontinuation

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

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

6.5.5 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 medication that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.6 Criteria for Premature Termination or Suspension of a Site

There is no predetermined criteria for termination of suspension of a site.

Termination or suspension of a site may occur at any time at the discretion of the Sponsor.

7. SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

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

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent and assent as applicable to participate in the study.
3. Aged 18 - 45 inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential, refer to Appendix D.
5. Considered "healthy" by the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a full physical examination including vital signs, 12-lead ECG, hematology, coagulation (as appropriate), serum chemistry, and urinalysis.
6. BMI ≥18.0 and ≤32.0 kg/m^2 at screening. Body weight for a subject in Cohort 1 will be ≥40.0 kg to ≤75.0 kg, and body weight for a subject in Cohort 2 will be >75.0 kg to ≤120.0 kg, inclusive. This inclusion criterion will be assessed at the screening visit and confirmed at first check-in.

7.2 Exclusion Criteria

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

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Positive PCR test for SARS-CoV-2, either with the absence or presence of the clinical symptoms of COVID-19.
4. Known or suspected intolerance or hypersensitivity to teduglutide, closely-related compounds, or any of the stated ingredients.

5. Significant illness, as judged by the investigator, within 2 weeks of the first dose of teduglutide.
6. Known history of alcohol or other substance abuse within the last year prior to screening.
7. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of teduglutide.
8. Pregnant or lactating female.
9. Within 30 days prior to the first dose of teduglutide:
    - Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
    - Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's (or designee's) opinion, may impact this study.
    - Have had any substantial changes in eating habits, as assessed by the investigator (or designee).
10. Use of dipeptidyl peptidase 4 inhibitors within 30 days or 5 half-lives, whichever is greater, prior to administration of the first dose of teduglutide.
11. Confirmed systolic blood pressure >140 mmHg or <90 mmHg, and diastolic blood pressure >90 mmHg or <40 mmHg at screening.
12. Twelve (12)-lead ECG demonstrating QTcF >450 msec at screening. If the QTcF exceeds the aforementioned limits, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
13. Positive screen for drugs of abuse or alcohol at screening and at each check-in.
14. Male subjects who consume more than 21 units of alcohol per week or regularly consume more than 3 units per day. Female subjects who consume more than 14 units of alcohol per week or regularly consume more than 2 units per day. (1 alcohol unit=150 mL of wine, or 360 mL of beer, or 45 mL of 45% alcohol).
15. Positive HIV, HBsAg, or HCV antibody screen at screening.
16. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch) based on subject self-reporting. Ex-users must report that they have stopped using tobacco for at least 3 months prior to receiving the first dose of teduglutide.
17. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. One caffeine unit is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz (360 mL) cup of tea, three 1 oz (85 g) chocolate bars.
18. Prior screen failure, randomization, participation, or enrollment in this study, or prior exposure to any GLP-2 analogs.
19. Presence of lesions, rashes, tattoos, and moles etc. on administration sites not allowing adequate conduct of injection site reaction and injection site injury assessments.

20. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of occasional use of ibuprofen [1.2 g per 24 hour period] or acetaminophen [2 g per 24 hour period]). Current use is defined as use within 14 days of the first dose of teduglutide and throughout the study.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After the first dose, ibuprofen (1.2 g per 24 hour period) or acetaminophen (up to 2 g per 24 hour period) 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 subject may continue participation in the study.

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

Use of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 3.

Table 3 Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and Randomization (Days -28 to predose [Day 1 Period 1])	Post-Randomization (Day 1 Period 1) up to Last PK Sample Collection
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from first dosing in Period 1 and Period 2 until the completion of the last PK sample in each period
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing	Prohibited from first dosing in Period 1 and Period 2 until the completion of the last PK sample in each period
Medications	See Section 7.1 and Section 7.2[a]	See Section 7.1 and Section 7.2[a]
Nicotine- and tobacco-containing products	Prohibited from 3 months prior to first dosing	Prohibited from first dosing in Period 1 until the completion of the last PK sample in Period 2

[a] If medications are required to treat an AE, certain medications may be allowed after discussion and agreement between the Sponsor and investigator.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

When confined, standard meals and snacks will be provided at appropriate times, except when subjects are required to fast. The meals served on the day of dosing should be identical for each treatment arm in the study.

7.4.2 Activity

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

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

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

7.5 Criteria for Discontinuation or Withdrawal of a Subject

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the investigator or designee for the following reasons:

- A positive pregnancy test for females.
- Positive urine drug or alcohol results.
- Difficulties in blood collection.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject'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.

7.7 Subject Replacement

Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis to ensure a minimum of 14 subjects complete each treatment sequence (per cohort weightband) within each cohort of the study.

8. CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Teduglutide will be administered as a subcutaneous (SC) injection only.

Subjects will receive teduglutide in each period either by a syringe injection ([syringe and vial], reference; Treatment A) or a pen injector (test; Treatment B) as single SC fixed doses, based on subject weightband assignment (≥40.0 kg to ≤75.0 kg [Cohort 1] and >75.0 kg to ≤120.0 kg [Cohort 2]).

Cohort 1 will receive 3 mg teduglutide and Cohort 2 will receive 4 mg teduglutide.

8.1.1 Clinical Study Drug Labeling

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

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

8.1.2 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of teduglutide products, including supplies for retention, and pre-filled pen injectors to allow completion of this study. The same lot number will be used throughout the study. Full details pertaining to pharmacy and dosing supplies will be described in a separate document.

The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report. Study drugs 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

Subjects 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 corresponding product, according to a randomization scheme generated at Celerion.

Subjects will be assigned to a cohort based on their weight and then provided the study treatments according to the randomization scheme. In each cohort, subjects will be randomized to 1 of 2 sequences and administered a single dose of teduglutide on Day 1 of each period per randomization sequences, either AB or BA as outlined in Table 2. To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will also be stratified by injection site within each cohort.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

At the conclusion of the study, any unused study drugs will be retained by Celerion, or destroyed, as per Sponsor instructions. Unused pen injectors will be returned to the Sponsor, or destroyed at Sponsor request. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9. 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 subjects in non-technical terms. Subjects 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.

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Allocation Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

This is a 2-way, crossover study. All subjects will receive study drugs as detailed in Section 6.1.

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 subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3) 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 subject safety.

For this study, the collection of blood for teduglutide 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 nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The blood collection time deviation windows are presented below:

Protocol Hour	Deviation Window
Predose	≤ - 2 minutes (prior to dose)
>0.0 – 8.0 hour	≤ ± 2 minutes
>8.0 – 24.0 hour	≤ ± 5 minutes

9.2.1 Full Physical Examination

A full physical examination will be performed at screening and end of Period 2 as outlined in the Schedule of Study Procedures (Section 3).

An abbreviated physical exam will be performed at check-in for each period and prior to release in Period 1. An abbreviated physical examination will include at the minimum, examination of respiratory, cardiovascular, and gastrointestinal systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

Symptom-driven 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).

9.2.3 Body Mass Index (BMI)

BMI will be calculated based on the height and weight measured at screening. If applicable, BMI will be recalculated with the subsequent measures of height from screening and the most current weight measurement.

9.2.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Schedule of Study Procedures (Section 3). Additional vital signs may be taken at any other times, if deemed necessary.

Vital signs measurements will be performed following 5 minutes rest in a supine position, except when they are seated or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the investigator or designee.

At the predose time points, vital signs will be measured within 24 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). Additional ECGs may be taken at any other times, if deemed necessary by the investigator or designee.

ECGs will be performed following 5 minutes rest in the supine position. All ECG tracings will be reviewed by the investigator or designee.

At screening, if the QTcF exceeds the limits as referenced in Section 7.2, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.

9.2.6 Injection Site Reaction and Injection Site Injury Assessments

Local tolerability, reactions, and injuries at the injection site will be evaluated by the investigator/designee as indicated in Section 3. Local tolerability will be assessed before, during, and after the end of the infusion at the time points.

Additionally, Subjects will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injection site pain, redness, bruising, and/or swelling, etc, that may represent an administration-related reaction or injury to the study medication or administration method. Subjects will be asked to report AEs to the CRU staff immediately as they are experienced. Appropriate treatment and follow-up will be determined by the investigator. Subjects with a severe or serious administration-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs, severe injection site reactions) must be withdrawn from the study and treated and followed up appropriately.

Any injection site reaction or injury will be collected and graded as mild, moderate, or severe.

Additional instructions concerning the collection of injection site reactions and injuries will be provided to the site prior to study start.

9.2.7 Study Drug Administration

Prior to receiving the first dose of teduglutide, subjects are to be randomized to a treatment as depicted in Table 1.

In each period, subjects will receive teduglutide administered SC to the arm, thigh, or abdomen either by syringe injection (syringe and vial) or pen injector. The same location (ie, arm, thigh or abdomen) but different puncture spot will be used for administration in the subsequent period. Time of administration and administration site location will be recorded.

Additional administration instructions will be provided in a separate document for the test injection

Administration of teduglutide reference will be done according to the full prescribing information of teduglutide (GATTEX®, Prescribing Information, 2018).

9.2.8 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10.

9.2.9 Laboratory Procedures and Assessments

9.2.9.1 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, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.

Chemistry evaluations will consist of the following standard serum chemistry panel:

Blood Urea Nitrogen	Albumin
Bilirubin (total and direct)	Sodium
Alkaline phosphatase	Potassium
Aspartate aminotransferase (AST)	Chloride
Alanine aminotransferase (ALT)	Glucose
Lipase	Creatinine *
Amylase	

* 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 positive 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

PCR Test (COVID-19)	Urine drug screen ➢ Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone) ➢ Amphetamines ➢ Barbiturates ➢ Benzodiazepines ➢ Cocaine ➢ Cannabinoids
HIV test	
HBsAg	
HCV *(if antibody positive, confirm ribonucleic acid negative)*	
Urine alcohol screen *Female subjects only* Serum human chorionic gonadotropin (hCG) (for pregnancy) FSH (to confirm postmenopausal status, as applicable)	

*Coagulation**

Coagulation evaluations will consist of the following tests:

Prothrombin time	International normalized ratio (INR)

* To be performed for subjects who develop ALT >3x upper limit of normal (ULN) (See Section 10.2.7.5).

9.3 PK Samples

Instructions for PK sample collection, processing, and shipping will be provided in separate documents.

Primary specimen collection parameters are provided in Table 4.

Table 4 Primary Specimen Collections

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

9.3.1 PK Measurements

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

Pharmacokinetic Parameter	Definition
$AUC_{0\text{-tlast}}$	Area under the concentration curve from time zero to the last measurable concentration
$AUC_{0\text{-}\infty}$	Area under the concentration curve extrapolated to infinite time
C_{max}	Maximum concentration
t_{max}	Time of first occurrence of C_{max}
λ_z	Terminal disposition phase rate constant
$t_{½}$	Terminal disposition phase half-life
CL/F	Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed
Vz/F	Apparent volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed

No value for $AUC_{0\text{-}\infty}$, λ_z or $t_{½}$ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

PK parameters will be calculated from reliable teduglutide concentration-time profiles using non-compartmental methods where all calculations will be based on actual sampling times.

Individual and mean serum concentration time 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

Subjects will be housed the day before dosing in each period until the last PK sample is collected and the 24-hour study procedures are completed for each period, at which time subjects will be released from the clinic. Check-in times for each period will be indicated by the CRU. Subjects may be admitted earlier for COVID-19 testing not related to study protocol as per CRU requirements.

All subjects who received at least one dose of study drug (including subjects who terminate the study early) will be contacted by the CRU 7 (±2) days after the last study drug administration to determine if any AE has occurred since the last study visit.

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

10. ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject 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 AE also means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

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 medication 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 noninvasive 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, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject 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 subject 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 subject 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 subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, 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 subject experiences a change in the severity of an AE that is not associated with a change in study medication or investigational device, 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 subject's medical condition should not be recorded as AEs but should be documented in the subject'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 investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject 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 case report form (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.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.7.
- In the event of drug overdose, the subject 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 subject 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 subject 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 5).

Table 5 Takeda Medically Significant AE List

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

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 Section 10.1 and Section 10.1.1).

10.1.2 Special Interest AEs

One subject had a cecal polyp identified during a colonoscopy (SHP633-304). This event was reported as an AE of special interest of large intestinal polyp that was assessed as moderate in intensity and related to teduglutide by the investigator.

Based on the pharmacologic activity and findings in animals, teduglutide has the potential to cause hyperplastic changes, including neoplasia, in the small bowel and hepatobiliary tract.

Further details are provided in the current IB edition.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An adverse event 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 adverse event 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 adverse event 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 medication(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.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

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

- Recovered/resolved – subject 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 subject 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 subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/resolved with sequelae – the subject 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 subject's participation in the study.

10.2.7 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal Liver Function Tests

10.2.7.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal Liver Function Tests) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call on Day 8 (±2 days) of Period 2, approximately 7 days after the last dose of investigational product. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.7.2 Reporting AEs

At each study visit and at the follow-up contact, the investigator or designee 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. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to investigational product 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. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication 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 drug treatment. 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[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.7.3 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.
- Subject identification number.
- Investigator's name.
- Name of the study medication(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 investigational product 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.

10.2.7.4 Reporting Special Interest AEs

Occurrence of AEs of special interest as outlined in Section 10.1.2 will be reported directly to the Sponsor.

10.2.7.5 Close Monitoring and Treatment Discontinuation for Potential Drug-Induced Liver Injury (DILI)

Subjects who develop ALT >3x ULN after first dosing administration should be monitored closely and the clinical significance of the elevation should be assessed by the investigator. Close observation includes the following:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; Nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, international normalized ratio [INR], direct bilirubin).
- Considering gastroenterology or hepatology consultations.

If a subject develops any of the following after the first dose, treatment should be discontinued, the medical monitor should be contacted immediately, and the subject should be withdrawn from the study:

- ALT or AST >8xULN
- ALT or AST >5xULN at the end of the 7 day washout period

- ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. Pertinent elements of the case should be captured in the DILI CRF.

10.2.8 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. 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 statistical analysis plan (SAP). The SAP will be prepared and finalized before database lock. A separate PK analysis plan will be finalized prior to database lock. These documents will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. 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 PK Set

All subjects who comply sufficiently with the protocol and display an evaluable PK profile for both periods (exposure to treatment, availability of measurements, completion of washout period, and absence of major protocol violations) will be included in the statistical analyses.

11.1.1.2 Safety Set

All subjects who received at least one dose of the study drug will be included in the safety evaluations.

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, gender, 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 analysis data set.

All individual concentration data and PK metrics will be listed for each subject and treatment together with summary statistics such as geometric mean, median, arithmetic mean, SD, coefficient of variation, geometric coefficient of variation, and minimum and maximum grouped by treatment and cohort. The time until first occurrence of C_{max} is reached (t_{max}) will be also listed for each subject and treatment and summarized by medians, minimum and maximum grouped by treatment and cohort. The number of time points of the terminal log-linear phase used to estimate the terminal rate constant (λ_z) and the residual area will be also provided for each subject and treatment.

Individual concentration-time curves will be presented in linear/linear and log/linear scale. Figures showing the mean (with ±SD as error bars) as well as the median (with 25^{th} to 75^{th} quantiles as error bars) concentration time profiles grouped by treatment and cohort will be also presented in linear/linear and log/linear scale. The PK endpoints will also be analyzed by injection site (ie, thigh, abdomen, and arm).

PK metrics $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}, will be analyzed using an ANOVA model for each cohort separately.

PK metrics will be transformed prior to analysis using a logarithmic transformation. The difference in means and the corresponding two-sided 90% CI on the log-transformed scale will be obtained from that model. The difference in means and the corresponding CI will be back-transformed to obtain the ratio of geometric means and the corresponding two-sided 90% CI for the ratio on the original scale. The terms used in the ANOVA model will be sequence, subject within sequence, period and treatment. According to EMA guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) (EMA 2010), subjects who will not provide evaluable data for both periods will not be included and fixed effects will be used for all terms.

To assess bioavailability between test and reference, the 90% CI for the ratio of geometric means for PK metrics, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} will be derived and compared (and would be contained within the acceptance interval of 80.00 to 125.00% if bioequivalent).

11.1.4 Pharmacodynamic Analysis

Not applicable.

11.1.5 Safety Analysis

Statistical analysis of safety data will be based on the safety analysis data set.

Safety data will be listed by subject and summarized by cohort and treatment using descriptive statistics. Continuous variables will be summarized by sample size, mean, SD, median, minimum, and maximum. Categorical variables will be summarized by number of subjects and the percent of subjects in each category.

TEAEs will be analyzed using the number and percentage of subjects reporting events, as well as the number of events, by system organ class and preferred term, severity, and causal relationship to the study treatment and device. Among TEAEs, injection site reactions and injection site injuries will be analyzed using the number and percentage of subjects reporting events, by preferred term, severity, and causal relationship to study treatment and device. Laboratory tests, vital signs, physical examinations, and corresponding changes from baseline will be summarized by study visit where baseline will be defined as the last non-missing assessment on or before Day 1 prior to the first dose.

Device malfunctions will be listed for each subject and summarized by cohort using the number and percentage of events.

11.2 Interim Analysis and Criteria for Early Termination

Not applicable.

11.3 Determination of Sample Size

The overall power for the endpoints ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max}) with a total sample size of 64 subjects will be 92.6% power based on a 5% type 1 error and a Coefficient of Variation of 21%, assuming a true ratio of test/reference of 1.0 in their relative bio-availabilities based on the acceptance interval of 80.00 to 125.00%. The sample size of 28 subjects within each cohort (14 each sequence) was accounted for approximately 10% potential drop-outs and/or non-reliable concentration time-profiles to yield 32 subjects per cohort (16 subjects per sequence within each cohort). This sample size was calculated with SAS v9.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site may 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 (contract 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 (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject 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 subjects. 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 subject, 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. 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 Council 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 informed consent form, and, if applicable, subject 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 subject 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, informed consent form) 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 informed consent form, recruitment materials intended for viewing by subjects, 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.

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

13.2 Subject Information, Informed Consent, and Subject 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 informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject 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 informed consent form 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 informed consent form and, if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. 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 subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject'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 subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject'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 informed consent form and subject authorization (if applicable) at the time of consent and prior to subject 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 informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject'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 subject's medical record, and the subject should receive a copy of the revised informed consent form.

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject'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 subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject'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 subject'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 subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject'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 American 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 subjects 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 subject 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 trials 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 subject in the study must be insured in accordance with the regulations applicable to the site where the subject 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 subjects. Refer to the study site agreement regarding the Sponsor's policy on subject 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. ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information - SAE

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Shire Fax: [redacted] E-mail: [redacted]

14.1.2 Study Contact Information – Product Quality Complaint

Contact Type / Role	Contact
Product Quality Complaint	Shire Tel: [redacted] E-mail: [redacted]

14.1.3 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, 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 subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.8 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)

14.1.4 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.

14.1.5 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration curve extrapolated to infinite time
$AUC_{0-tlast}$	The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
C_{max}	Maximum observed concentration
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRU	Clinical Research Unit
DNA	Deoxyribonucleic acid
DILI	drug-induced liver injury
ECG	Electrocardiogram
EU	European Union
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GLP-2	Glucagon-like peptide 2
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	Identifier
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
kg	Kilogram
m^2	Meters squared

MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
oz	Ounce
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PS	Parenteral support
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SBS	Short-bowel syndrome
SC	Subcutaneous
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal disposition phase half-life
t_{max}	Time of first occurrence of C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
USA	United States of America
λ_z	Terminal disposition phase rate constant

15. DATA HANDLING AND RECORDKEEPING

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 Medical Dictionary for Regulatory Activities (MedDRA®). Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Completed CRFs are required for each subject who signs an informed consent.

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs must be completed in English. Data are transcribed directly onto CRFs.

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 subject'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 subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), 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 subject'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 8.0) 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. REFERENCES

Jeppesen, P. B. 2007. Growth factors in short-bowel syndrome patients. *Gastroenterol Clin North Am,* 36, 109-21, vii.

Jeppesen, P. B., Sanguinetti, E. L., Buchman, A., Howard, L., Scolapio, J. S., Ziegler, T. R., Gregory, J., Tappenden, K. A., Holst, J. & Mortensen, P. B. 2005. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. *Gut,* 54, 1224-31.

Mardini, H. E. & de Villiers, W. J. 2008. Teduglutide in intestinal adaptation and repair: light at the end of the tunnel. *Expert Opin Investig Drugs,* 17, 945-51.

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 (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, 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 subjects. 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 subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject'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 Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject'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 subjects involved in the study.
7. A description of the subject'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 subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject 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 informed consent form, the subject or the subject'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 subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject'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 subjects 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 medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects 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 subject's identity will remain confidential in the event that study results are published.
25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active with a nonsterilized male partner 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 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects.

26. Nonsterilized male subjects who are sexually active with a female partner of childbearing potential 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.
27. 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 medication.
- 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 Subjects

From signing of informed consent, throughout the duration of the study, and for at least 90 days after last dose of study drug, nonsterilized** male subjects 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 Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for at least 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/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

* 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 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 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). The only acceptable methods of contraception are:
    - Non-Hormonal Methods:
        - Intrauterine device (IUD).
        - Bilateral tubal ligation.
        - Vasectomised partner (provided that partner is the sole sexual partner of the study subjects and that the vasectomised 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 subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 30 days after last dose.

2. 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.
   - Hormonal contraception
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject 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.
4. During the course of the study, regular hCG pregnancy tests will be performed for all women and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm or ova 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 (i.e., condom) in males with pregnant partners
   c) assessment of subject 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?
5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses; with the exception of female subjects using a protocol acceptable contraception method that has a known side effect of delayed or irregular menses), and, a negative serum hCG pregnancy test at each check-in prior to receiving any dose of study medication.

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 (i.e., condom) in males with pregnant partners.
- assessment of subject 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 subject is found to be pregnant during the study she should be withdrawn and any Sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose, should also be recorded following authorization from the subject's partner.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

All pregnancies, including female partners of male subjects will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after the birth of the child will also be conducted.

Appendix E Detailed Description of Amendments to Text

Amendment 1

Change 1. The term bioequivalence has been updated to bioavailability throughout the protocol.	
The change occurs in the protocol title and throughout the study protocol.	
Initial wording (Title):	A Randomized, Open-label, Two-treatment, Two-period, Single-dose, Crossover Study to Evaluate the Bioequivalence of Teduglutide Administered Subcutaneously by Syringe Injection Versus Pen Injector in Healthy Adult Subjects
Amended or new wording (Title):	A Randomized, Open-label, Two-treatment, Two-period, Single-dose, Crossover Study to Evaluate the Bioavailability of Teduglutide Administered Subcutaneously by Syringe Injection Versus Pen Injector in Healthy Adult Subjects

Change 2. The analysis conclusion for the primary objective has been modified.	
Due to the change from bioequivalence to bioavailability, the wording in the Synopsis - Statistical Methodology for Pharmacokinetic Endpoints and in Section 11.1.3 (PK Analysis) has been modified.	
Initial wording:	To claim bioequivalence between test and reference, the 90% CI for the ratio of geometric means for PK metrics, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}, would be contained within the acceptance interval of 80.00 to 125.00%.
Amended or new wording:	To assess bioavailability between test and reference, the 90% CI for the ratio of geometric means for PK metrics, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} will be derived and compared (and would be contained within the acceptance interval of 80.00 to 125.00% if bioequivalent).

Change 3. Hypothesis verbiage was removed from the study protocol.	
Hypothesis verbiage has been removed from Section 5.1 (Hypothesis).	
Initial wording:	The plasma PK ($AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}) of teduglutide following single SC administration by syringe injection (reference) and pen injector (test) will be bioequivalent, ie, the 90% CI for the ratio of geometric means for PK metrics, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}, are contained within the acceptance interval of 80.00 to 125.00%.
Amended wording:	Hypothesis testing is not relevant for a bioavailability study.

Change 4. Additional PK parameters have been added to the secondary endpoints.

Additional PK parameters for CL/F (apparent total body clearance) and Vz/F (apparent volume of distribution) have been added to the following sections of the protocol: Synopsis (Criteria for Evaluation and Analyses), Section 5.3.2 (Secondary Endpoints), and Section 9.3.1 (PK Measurements)

New wording:

CL/F: Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed

Vz/F: Apparent volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed

Change 5. Sample size for the study has been updated.

The sample size for each cohort has been increased from 15 subjects to 16 subjects and the number of planned subjects has thus been updated from 60 to 64 subjects. The following sections were updated (Synopsis [Table 1, Planned Number of Subjects, and Sample Size Justification], Section 6.1 (Study Design [Table 2]), and Section 11.3 (Determination of Sample Size).

Initial wording:

Weightband	Cohort/ Dose level	No. of Subjects	Sequence	Treatment Period 1 (Day 1)	Washout Period (7 days)	Treatment Period 2 Day 1)
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=15	AB	Reference (fixed dose by vial and syringe)*	→	Test (fixed dose by pen injector)*
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=15				
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=15	BA	Test (fixed dose by pen injector)*	→	Reference (fixed dose by vial and syringe)*
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=15				

Amended wording:

Weightband	Cohort/ Dose level	No. of Subjects	Sequence	Treatment Period 1 (Day 1)	Washout Period (7 days)	Treatment Period 2 Day 1)
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=16	AB	Reference (fixed dose by vial and syringe)*	→	Test (fixed dose by pen injector)*
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=16				
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=16	BA	Test (fixed dose by pen injector)*	→	Reference (fixed dose by vial and syringe)*
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=16				

Initial wording:	The planned total sample size for this study is 60 randomized subjects
Amended wording:	The planned total sample size for this study is 64 randomized subjects

Initial wording:	The sample size of 26 subjects within each cohort (13 each sequence) would yield 86% power for the co-primary endpoints ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max}) with a 5% type 1 error assuming a true ratio of test/reference of 1.0 in their relative bio-availabilities based on the acceptance interval of 80.00 to 125.00% and a Coefficient of Variation of 21%. To account for approximately 10% potential drop outs and/or non-reliable concentration time-profiles, 30 subjects per cohort (15 subjects per sequence within each cohort) will be enrolled leading to a total sample size of 60 subjects. This sample size was calculated with Nquery.
Amended wording:	The overall power for the endpoints ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max}) with a total sample size of 64 subjects will be 92.6% power based on a 5% type 1 error and a Coefficient of Variation of 21%, assuming a true ratio of test/reference of 1.0 in their relative bio-availabilities based on the acceptance interval of 80.00 to 125.00%. The sample size of 28 subjects within each cohort (14 each sequence) was accounted for approximately 10% potential drop-outs and/or non-reliable concentration time-profiles to yield 32 subjects per cohort (16 subjects per sequence within each cohort). This sample size was calculated with SAS v9.

Change 6. The minimum number of subjects to complete each cohort has been increased.
Verbiage in Section 7.7 (Subject Replacement) has been updated to reflect 14 subjects are to complete each cohort.

Initial wording:	Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis to ensure a minimum of 13 subjects (per cohort weightband) complete each treatment in the study.
Amended wording:	Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis to ensure a minimum of 14 subjects (per cohort weightband) complete each treatment in the study.

Amendment 2

Change 1. The IB edition number has been removed from the protocol. Due to ongoing updates to the IB, the protocol will reference "the current edition" of the IB or "current IB edition"
The change occurs in the following sections: Section 4.1 - Introduction Section 4.3 - Benefit/Risk profile Section 10.1.2 - Special Interest AEs

Initial wording:	Investigator's Brochure (IB Edition 16.0)
Amended or new wording:	The current edition of the Investigator's Brochure (IB) (Section 4.2) or current IB edition (Section 4.3 and Section 10.1.2)

Change 2. Verbiage has been added to the pharmacokinetics section of the introduction to clarify study information source.
The change occurs in the following section: Section 4.1 - Introduction

Initial wording:	A maximum mean plasma concentration of 49.7 ng/mL was achieved at 2.64±1.02 hours (t_{max}) and the mean AUC_{0-t} and AUC_{0-inf} values were 201±51.6 and 204±51.1 ng•hr/mL, respectively. Teduglutide was absorbed and rapidly eliminated from plasma with mean t½ of 1.21±0.65 hours. The mean plasma clearance was 14.5±4.09 L/hr and the mean body weight normalized plasma clearance was 0.0259±0.0672 L/hr/kg.
Amended or new wording:	Following a one-time PK sampling conducted at the beginning of the initial 24-week teduglutide treatment period (0.05 mg/kg SC once daily) in Study TED-C14-004, a maximum mean plasma concentration of 49.7 ng/mL was achieved at 2.64±1.02 hours (t_{max}) and the mean AUC_{0-t} and AUC_{0-inf} values were 201±51.6 and 204±51.1 ng•hr/mL, respectively. Teduglutide was absorbed and rapidly eliminated from plasma with mean t½ of 1.21±0.65 hours. The mean plasma clearance was 14.5±4.09 L/hr and the mean body weight normalized plasma clearance was 0.0259±0.0672 L/hr/kg.

Change 3. An exclusion criterion has been added for subject(s) with a positive COVID-19 test. Additionally, the exclusion criterion in relation to the safety 12-lead ECG requirement and the inclusion criterion in relation to the age range (updated for Arizona state) has been updated.
The change occurs in the following sections: Section 1 - Study Summary Section 7.2 - Exclusion Criteria Section 7.1 – Inclusion Criteria

Section 7.2 – Exclusion Criteria (Criterion 3 [new])	
Initial wording:	Not applicable
Amended or new wording:	Positive PCR (polymerase chain reaction) testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), either with the absence or presence of the clinical symptoms of COVID-19.

Section 7.2 - Exclusion Criteria (Criterion 12)	
Initial wording:	Twelve-lead (12)-ECG demonstrating QTcF >470 msec for females and >460 msec for males at screening. If the QTcF exceeds the aforementioned limits, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
Amended or new wording:	Twelve (12)-lead ECG demonstrating QTcF >450 msec at screening. If the QTcF exceeds the aforementioned limits, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.

Section 7.1 – Inclusion Criteria (Criterion 3)	
Initial wording:	Aged 19 - 45 inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
Amended or new wording:	Aged 18 - 45 inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.

Change 4. Verbiage has been included for the possible extension of confinement due to COVID-19 testing.
The change occurs in the following sections: Section 3 - Schedule of Study Procedures Section 9.3.5 - Confinement

Initial wording:	Subjects will be admitted to the CRU on Day -1 of each period at the time indicated by the CRU (Section 3).
Amended or new wording:	Subjects will be admitted to the CRU on Day -1 of each period at the time indicated by the CRU. Subjects may be admitted earlier for Coronavirus Disease-19 (COVID-19) testing not related to study protocol as per CRU requirements. If the CRU decides to confine the subjects throughout the study (ie, washout period[s]), some safety events at check-in (e.g., clinical laboratory test, urine drug and alcohol screen, pregnancy test, and vital signs) may not be performed at the investigator's discretion.
Amended or new wording:	Subjects may be admitted earlier for COVID-19 testing not related to study protocol as per CRU requirements. (Section 9.3.5)

Change 5. Two additional conditions related to COVID-19 have been added to the Takeda Medically Significant AE list.
The change occurs in the following section: Section 10.1.1 – SAEs (Table 5)

Initial wording:	Not Applicable.
Amended or new wording:	The terms COVID-19 pneumonia and COVID-19 related disease have been added to Table 5. In addition the following footnote to Table 5 has been added: "Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements."

Change 6. Verbiage has been updated to allow for the possibility of remote monitoring due to COVID-19.
The change occurs in the following section: Section 12.1 – Study Site Monitoring Visits

Initial wording:	Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed.
Amended or new wording:	Monitoring visits to the study site may 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.

Change 7. Verbiage has been added relevant to the recording of protocol deviations surrounding COVID-19.

The change occurs in the following section:

Section 12.2 – Protocol Deviations

Initial wording:	Not Applicable.
Amended or new wording:	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.

Change 8. As requested by the Food and Drug Administration, 2 additional injection sites were added. Subjects will also be randomized for injection site.

The change occurs in the following sections:

Section 1 - Synopsis (Table 1 and exclusion criteria)

Section 3 - Schedule of Study Procedures

Section 6.1 - Study design (Table 2)

Section 6.3.1 - Rationale for Study Design

Section 7.2 - Exclusion Criteria

Section 8.1.4 - Randomization Code and Storage

Section 9.2.7 - Study Drug Administration

Initial wording:	Not Applicable.
Amended or new wording:	The following verbiage has been added to Section 1, Section 6.3.1, and Section 8.1.4: “To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will be stratified by injection site within each cohort”
Initial wording:	Will be performed in Period 1 only (Footnote “g” of Section 3 [Randomization])

Amended or new wording:	Will be performed in Period 1 only. Subjects will be assigned to a cohort based on their weight and will receive the study treatments according to the randomization scheme. In each cohort, subjects will be randomized to 1 of 2 sequences and administered a single dose of teduglutide on Day 1 of each period per the randomization sequences, either AB or BA (as defined in the study protocol. To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will also be stratified by injection site within each cohort.
Initial wording:	Presence of lesions, rashes, tattoos, and moles etc. on administration sites on the abdomen not allowing adequate conduct of injection site reaction and injection site injury (Synopsis and Section 7.2)
Amended or new wording:	Presence of lesions, rashes, tattoos, and moles etc. on administration sites not allowing adequate conduct of injection site reaction and injection site injury
Initial wording:	In each period, subjects will receive teduglutide administered SC to the abdomen either by syringe injection (syringe and vial) or pen injector. A different abdominal site will be used for administration in the subsequent period. Time of administration and administration site location will be recorded (Section 9.2.7)
Amended or new wording:	In each period, subjects will receive teduglutide administered SC to the arm, thigh or abdomen either by syringe injection (syringe and vial) or pen injector. The same location (ie, arm, thigh or abdomen) but a different puncture spot will be used for administration in the subsequent period. Time of administration and administration site location will be recorded.

Change 9. Minor editorial changes have been made throughout the protocol and consistency verbiage updates to Appendix B on male/female contraception were made to match Appendix D.

Amendment 3

Change 1. As requested by The Food and Drug Administration, blood sampling for anti-drug antibody analysis is not required and has been removed from the protocol.

The following updates were made:

Section 3 (Schedule of Study Procedures) – row for immunogenicity sampling has been removed.

Section 9.3 (PK Samples) - Table 4 for Primary Specimen Collections, row for immunogenicity sample has been removed.

Section 9.3.4 (Immunogenicity) has been removed.

Change 2. As requested by The Food and Drug Administration, PK analysis is also required to be evaluated by injection site.

The following secondary objective was added to the Synopsis and Section 5.2.2 (Study Secondary Objectives):

To evaluate the bioavailability of teduglutide, by injection site (ie, thigh, abdomen, and arm), following the administration of a single, SC fixed dose of 3 mg or 4 mg teduglutide (depending upon subjects assignment in one of two cohorts as defined by body weight) administered via manual injection or via pen injector in healthy subjects.

The following PK endpoints were added to the Synopsis and Section 5.3.2 (Secondary Endpoints)

PK metrics* by injection site (ie, thigh, abdomen, and arm) including:

- $AUC_{0\text{-}tlast}$: Area under the concentration curve from time zero to the time of last measurable concentration
- C_{max}: Maximum concentration
- $AUC_{0\text{-}\infty}$: Area under the concentration curve extrapolated to infinite time

*Beginning on Day 1 of each period, PK parameters will be calculated from reliable teduglutide concentration-time profiles using non-compartmental methods where all calculations will be based on actual sampling times.

The following sentence was added to the Synopsis (Statistical Considerations) and to Section 11.1.3 (PK Analysis) (Third Paragraph):

“The PK endpoints will also be analyzed by injection site (ie, thigh, abdomen, and arm)”

Change 3. An error in the lower age range was corrected.	
The correction occurred in the following section: Section 1 (Study Summary) – Study Subject Population (First Sentence)	
Initial wording:	Healthy male and female subjects aged 19 – 45 years inclusive, at time of consent.
Amended or new wording:	Healthy male and female subjects aged 18 – 45 years inclusive, at time of consent.