CLINICAL STUDY PROTOCOL

NCT Number: NCT03663582

Study Title: A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support

Study Number: SHP633-306

Protocol Version and Date:

Original Protocol: 23 January 2018
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PROTOCOL: SHP633-306

TITLE:	A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support
NUMBER	SHP633-306
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Protocol: 23 Jan 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	Date: [redacted]
[redacted], MD PhD [redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-306.

Title: A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address:	
(please hand print or type)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events and Non-serious adverse evetns (AEs) as Required by Protocol within 24 hours to the sponsor or designee using the details below. Applicable fax numbers and e-mail address can also be found on the form (sent under separate cover).

Pharmacovigilance SAE Reporting:

[redacted] or [redacted] (Japan domestic line only)

or

Email: [redacted]

For protocol- or safety-related issues, the investigator should contact:

[redacted], MD
Phone: [redacted] (24-hour coverage)
Email: [redacted]
Fax: [redacted]

For protocol- or safety-related issues the investigator may also contact the Shire medical monitor:

[redacted], MD, PhD
[redacted] Global Clinical Development
Office Phone: [redacted]
Mobile Phone: [redacted]
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In-country Clinical Caretaker:

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4-10-18 Takanawa, Minato-ku

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Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

The product quality includes quality of the drug delivery device combination product. As such device defects should be reported according to the instructions in this section. The reporting of product quality occurrences, when the product does not meet specifications, includes the reporting of device defects.

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Origin of Product Quality Complaint	E-mail Address
Ex-US	[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase, equivalent to SGPT
AST	aspartate aminotransferase, equivalent to SGOT
AUC	area under the plasma concentration-time curve
AUC_{0-t}	AUC from zero to the last measurable concentration
BUN	blood urea nitrogen
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EGD	esophagogastroduodenoscopy
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
ICF	informed consent form
ICMJE	International Committee of Medicinal Journal Editors
ICH	International Committee on Harmonisation
IBD	inflammatory bowel disease
I/O	oral fluid intake and urine output
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN/IV	parenteral nutrition/intravenous
PNALD	parenteral nutrition-associated liver disease
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2}$	terminal-phase half-life
t_{max}	time to C_{max}
ULN	upper limit of normal
US	United States
V/F	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP633-306	**Drug:** Teduglutide
Title of the study: A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 5 Japanese subjects will be dosed.	
Investigator(s): Multicenter study.	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 sites in Japan.	
Study period (planned): 2017-2020	**Clinical phase:** 3

Objectives:

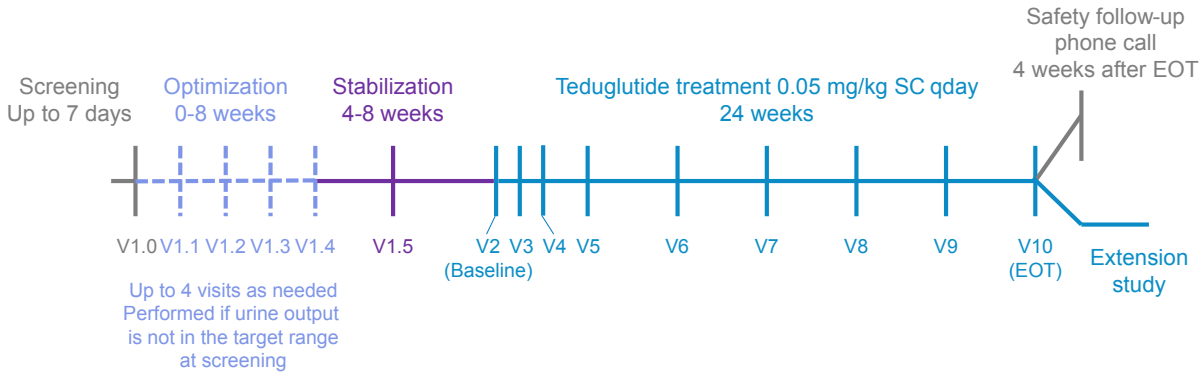
The objectives of this clinical study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of teduglutide in Japanese subjects with short bowel syndrome (SBS) who are dependent on parenteral nutrition/intravenous (PN/IV) over a 24-week treatment period.

Investigational product, dose, and mode of administration:

Teduglutide 0.05 mg/kg subcutaneously (SC) once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.

Methodology:

This is an open-label, multicenter study, consisting of a conditional PN/IV optimization period, a mandatory PN/IV stabilization period, and a 24-week treatment period.



If at screening, a subject does not have an optimized PN/IV volume, defined as a 48-hour urine output between 2 and 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/IV volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/IV volume will be documented.

All subjects will then enter the stabilization period, during which the target PN/IV volume will be maintained for at least 4 consecutive weeks (8 weeks maximum).

Following the stabilization period, subjects will enter a 24 week dosing period, during which all subjects will receive teduglutide 0.05 mg/kg SC once daily. At each site visit during the treatment phase, efficacy (adjustments to PN/IV) and safety will be monitored.

Subjects will have blood samples taken for teduglutide PK analysis at predose, at 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at the baseline visit (Visit 2). Subjects also will have blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at Week 4 (Visit 5) or Week 12 (Visit 7) of the treatment period.

All subjects who complete the study may participate in a long-term extension study in which subjects will continue to receive teduglutide. Subjects who do not enroll in the extension study or who discontinue the study prematurely at any time will receive a follow-up phone call 4 weeks after the last dose of study drug.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Ability to voluntarily provide written, signed, and informed consent to participate in the study.
2. Male or female 16 years of age or older at the time of signing informed consent.
3. Intestinal failure due to SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/IV dependence at the time of informed consent.
4. Parenteral nutrition requirement of at least 3 times per week during the week before the screening visit and during the 2 weeks prior to the baseline visit.
5. Stable PN/IV requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment. Stability is defined as:
    a. Actual PN/IV usage is similar to prescribed PN/IV.
    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ±25% of the respective 48-hour I/O volumes at the last optimization visit.
    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours at the last optimization visit, the stabilization visit, and the baseline visit.
6. For subjects with a history of Crohn's disease, clinical remission for at least 12 weeks prior to the baseline visit as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
7. Females of childbearing potential must agree to comply with the contraceptive requirements of the protocol.
8. An understanding, ability, and willingness to fully comply with study procedures and restrictions.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Participation in a clinical study using an experimental drug within 30 days or 5.5 half-lives, whichever is longer, prior to screening, or concurrent participation in any other clinical study.
2. Use of GLP-2 or human growth hormone or analogs of these hormones within the past 6 months.
3. Use of octreotide, GLP-1 analogs, dipeptidyl peptidase-IV inhibitors, or enteral glutamine within 30 days.
4. Previous use of teduglutide.
5. Subjects with active inflammatory bowel disease (IBD) or subjects with IBD who received a change in immunosuppressant therapy (eg, azathioprine, anti-TNFs) within the past 6 months.
6. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, familial adenomatous polyposis, etc.
7. Chronic intestinal pseudo-obstruction or severe dysmotility.
8. Clinically significant intestinal stenosis or obstruction, or evidence of such on upper gastrointestinal (GI)

series with small bowel follow-through, within the past 6 months.

9. Major GI surgical intervention, including bowel lengthening procedures, within the past 3 months (insertion of feeding tube or endoscopic procedure is allowed).
10. Unstable cardiac disease, (eg, congestive heart failure, cyanotic disease, or congenital heart disease).
11. Moderate or severe renal impairment, defined as creatinine clearance <50 ml/min.
12. Currently diagnosed with cancer or a history of any cancer except surgically curative skin cancer within the past 5 years.
13. Severe hepatobiliary disease including:
    a. Total bilirubin level ≥2 times the upper limit of normal (ULN).
    b. Aspartate aminotransferase (AST) ≥5 times ULN.
    c. Alanine aminotransferase (ALT) ≥5 times ULN.
14. Active clinically significant pancreatic disease, including clinical signs of pancreatitis associated with elevations in serum amylase or lipase ≥2 times ULN.
15. More than 4 SBS-related or PN/IV -related hospital admissions (eg, central line-associated bloodstream infection, bowel obstruction, severe fluid/electrolyte disturbances) within the past 12 months.
16. Unscheduled hospitalization within 30 days prior to screening.
17. Pregnant or lactating female.
18. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevent completion of the study, or interfere with analysis of the study results.

Maximum Duration of Subject Involvement in the Study:

Subjects will undergo up to a 7 day screening period, a conditional PN/IV support optimization period (up to 8 weeks), and a stabilization period (up to 8 weeks) prior to receiving teduglutide treatment. Thus, the screening, optimization period, and stabilization period could last up to 17 weeks in total.

Following the optimization and stabilization periods, the subjects will receive the study drug for 24 weeks.

Endpoints:

Efficacy

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at end of treatment (EOT).
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who are able to completely wean off of PN/IV support.

Pharmacokinetics

The following parameters will be derived: area under the plasma concentration–time curve from zero to the last measurable concentration (AUC_{0-t}); maximum plasma concentration (C_{max}); time to C_{max} (t_{max}); terminal-phase half-life ($t_{1/2}$); apparent clearance (CL/F); and apparent volume of distribution (V/F).

Safety

Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide, and changes in 48-hour urine output, body weight and body mass index will be evaluated. An abdominal ultrasound, esophagogastroduodenoscopy, and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the treatment period. Esophagogastroduodenoscopy will be repeated at the end of the treatment period for subjects with risk factors for gastric cancer. For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed

during the Stabilization Period, prior to the baseline visit.

Statistical Methods:

Efficacy

The absolute and relative change in weekly PN/IV volume, days per week of PN/IV support, and plasma citrulline, from baseline to each scheduled visit, as well as at EOT, will be summarized using descriptive statistics.

The number and percentage of subjects who demonstrate a response at Week 20 and again at Week 24 will be summarized. A response is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume. The number and percentage of subjects who demonstrate at least a 20% reduction from baseline in weekly PN/IV volume at each visit will also be summarized.

The number and percentage of subjects who completely wean off PN/IV support by Week 24/EOT will be summarized. A subject will be considered to have achieved independence from PN/IV (completely weaned off PN/IV) if the investigator prescribes no PN/IV at week 24/EOT and there is no use of PN/IV recorded in the subject diary during the 2 weeks prior to the last dosing visit.

Pharmacokinetics

Teduglutide plasma concentrations will be summarized using descriptive statistics (number, mean and standard deviation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using non-compartmental analysis as appropriate and summarized using descriptive statistics (number, mean, standard deviation, geometric mean, and CV%, minimum, median, and maximum).

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as AEs that started or worsened on or after the date and time of the first dose of study dose. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity, relationship to treatment, and for AEs leading to discontinuation, and death. In addition, SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour oral intake and urine output, vital signs, body weight, and body mass index, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

STUDY SCHEDULES

Table 1 Schedule of Evaluations and Procedures – Optimization/Stabilization

Procedures	**Screening** (up to 7-days)	**PN/IV Optimization Period** (8-week maximum)				**PN/IV Stabilization Period**[a] 4-8 weeks
		Week 2 (± 3 days)	**Week 4** (± 3 days)	**Week 6** (± 3 days)	**Week 8** (± 3 days)	
Visit Number:	**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X[b]					
Eligibility criteria	X					
Medical history, demographics	X					
Crohn's disease assessment	X					
Physical examination[c]	X	X	X	X	X	X
Record PN/IV use and adjust prescription as indicated	X[d]	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Abdominal ultrasound[e]						X
Upper GI contrast series with small bowel follow-through[f]						X
Esophagogastroduodenoscopy[e]						X
Colonoscopy/sigmoidoscopy[g]						X
Prior/Concomitant medication/procedures[h]	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Height	X					
Body weight	X	X	X	X	X	X[i]
12-lead ECG[j]	X					
Safety laboratory tests	X	X	X	X	X	X
Urine pregnancy test[k]	X					
Interim safety evaluation	[X][l]	[X][l]	[X][l]	[X][l]	[X][l]	
Dispense diary[m]	X	X	X	X	X	X

Table 1 Schedule of Evaluations and Procedures – Optimization/Stabilization

Procedures	**Screening** (up to 7-days)	**PN/IV Optimization Period** (8-week maximum) **Week 2** (± 3 days)	**Week 4** (± 3 days)	**Week 6** (± 3 days)	**Week 8** (± 3 days)	**PN/IV Stabilization Period**[a] 4-8 weeks
Visit Number:	**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Review Diary [m]	X	X	X	X	X	X

ECG=electrocardiogram; GI=gastrointestinal; ICF=informed consent form; PN/IV =parenteral nutrition/intraveous; V=visit

[a] The baseline visit must occur 4-8 weeks after the last optimization visit (or screening visit if no optimization is needed). The stabilization visit must occur during this 4-8 week interval, and must occur at least 7 days apart from the preceding visit (screening or optimization visit) and subsequent visit (baseline).

[b] No study-related procedures are to be performed unless the ICF has been signed.

[c] A full physical examination is to be performed at screening. Focused physical exams may be performed at all other visits

[d] PN/IV evaluation is to confirm weekly volume for inclusion criteria.

[e] Abdominal ultrasound and esophagogastroduodenoscopy should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[f] Upper GI contrast series with small bowel follow-through is required for subjects with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[g] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in subjects with any colon remnant including rectal stump evaluation. Colonoscopy/sigmoidoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy documented within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[h] At screening, information on all medications taken in the previous 14 days will be collected.

[i] The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This is the first of 2 body weight measurements that will be used to determine drug volume.

[j] A 12-lead ECG will be performed at the study center after the subject has been resting for at least 5 minutes.

[k] For women of childbearing potential.

[l] Interim safety evaluations will be performed 5 to 7 days after implementing a change to the subject's PN/IV. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[m] Subjects will record their PN/IV support daily throughout the study. Prior to each clinic and safety visit, subjects will also record all enteral fluid intake and urine output over a 48-hour period.

Table 2 Schedule of Evaluations and Procedures – Treatment Period

Procedures	**Baseline**	**Dosing Week 1**	**Dosing Week 2**	**Dosing Week 4**	**Dosing Week 8**	**Dosing Week 12**	**Dosing Week 16**	**Dosing Week 20**	**Dosing Week 24 /EOT[a] (or ET[b])**	**Follow-up Call Week 28[a]**
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7	± 7
Eligibility criteria	X									
Crohn's disease assessment[c]	X									
Physical examination[d]	X	X	X	X	X	X	X	X	X	
Record PN/IV use and adjust prescription as indicated	X[e]		X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X
EGD									X[f]	
Colonoscopy/ Sigmoidoscopy									X	
Concomitant medication /procedures	X	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	
Body weight	X[g]		X	X	X	X	X	X	X	
12-lead ECG[h]	X			X					X	
Safety laboratory tests	X		X	X	X	X	X	X	X	
Citrulline[i]	X			X	X		X		X	
Antibodies to teduglutide[j]	X					X			X	
PK sampling	X[k]			(X)[k]		(X)[k]				
Urine pregnancy test[l]	X		X	X	X	X	X	X	X	
Drug dispensing	X		X	X	X	X	X	X		
Teduglutide dosing[m]	X	X	X	X	X	X	X	X	X[n]	
Confirm administration proficiency	X[o] X[o] X[o]			X		X			X[p]	
Interim safety evaluation[q]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	
Dispense Diary[r]	X	X	X	X	X	X	X	X	X[p]	
Review Diary[r]	X		X	X	X	X	X	X	X	
Compliance[s]		X	X	X	X	X	X	X	X	

Table 2 Schedule of Evaluations and Procedures – Treatment Period

Procedures	Baseline	Dosing Week 1	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 /EOT[a] (or ET[b])	Follow-up Call Week 28[a]
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**

(X) = Possible PK sampling time point; [X] = Possible interim safety evaluation time point; 48-hour I/O=48-hour fluid intake/urine output; ECG=electrocardiogram; EGD=esophagogastroduodenoscopy; EOT=end of treatment; ET=early terminationPK=pharmacokinetic; PN/IV=parenteral nutrition/intraveous; V=visit

[a] The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks after the last dose to query for SAEs, AEs, and concomitant treatments.

[b] Subjects with an ET visit should have all applicable Week 24 (Visit 10) assessments. Call sponsor for guidance.

[c] Subjects with active Crohn's disease are excluded from the study participation, therefore endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease.

[d] A full physical examination is to be performed at baseline and Week 24 (Visit 10); a brief examination will be performed at all other dosing weeks with a clinic visit.

[e] The PN/IV evaluation is to confirm weekly volume for inclusion criteria.

[f] Esophagogastroduodenoscopy at Visit 10 is required for subjects with risk factors for gastric cancer (see Section 7.2.3).

[g] The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This is the second of 2 body weight measurements that will be used to determine drug volume.

[h] A 12-lead ECG will be performed at the study center after the subject has been resting for at least 5 minutes.

[i] Blood sample for measuring citrulline should be drawn from peripheral venous access, if this is not possible, sample may be drawn from a central line.

[j] Blood sample for antibody testing is to be collected at baseline (Visit 2) prior to first investigational product administration. Blood samples for antibody testing at Week 12 (Visit 7) and Week 24 (Visit 10) must be collected prior to that day's dose, and more than 14 hours after the prior day's dose.

[k] Samples for PK analysis will be collected pre-dose and at 15, 30 minutes post-dose and at 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose at Visit 2. Additional PK samples will be collected predose, and 1 and 2 hours post-dose at Week 4 (Visit 5) or Week 12 (Visit 7). The site of teduglutide administration prior (arm, thigh, or abdomen) and the person administering the injection (subject or physician) must be specified. Blood sample for measuring PK must be drawn from peripheral venous access.

[l] For women of childbearing potential.

[m] Teduglutide is dosed once daily during the treatment period. The first dose of study drug must be administered by the study physician.

[n] Dosing will continue if the subject enters the extension study, but will stop at the Week 24 visit if the subject doesn't enter the extension study.

[o] The study physician must observe the subject administering the study drug in compliance with the study drug administration checklist at least twice before the subject is allowed to administer the drug without direct observation by the physician. Refer to Section 6.2.2.1.

[p] For subjects entering the extension study only.

[q] Interim safety evaluations will be performed 5 to 7 days after any change to the subject's PN/IV has been implemented. These measures include 48-hour oral fluid intake, 48-hour urine output, hemoglobin, hematocrit, serum blood urea nitrogen, creatinine, and urine sodium, and may be performed at the investigational site laboratory.

[r] Subjects will record their PN/IV support and teduglutide dosing daily throughout the study. Prior to each clinic and safety visit, subjects will also record all

Table 2 Schedule of Evaluations and Procedures – Treatment Period

Procedures	Baseline	Dosing Week 1	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 /EOT[a] (or ET[b])	Follow-up Call Week 28[a]
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**

enteral fluid intake and urine output over a 48-hour period.

[s] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare, serious, disabling, socially incapacitating and potentially life-threatening condition which is the leading cause of intestinal failure (Nightingale and Woodward, 2006; Pironi et al., 2015). Intestinal failure from SBS results from surgical resection or congenital defects and is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth. Patients with SBS are highly prone to malnutrition, diarrhea, dehydration, and an inability to maintain weight due to the reduced intestinal capacity to absorb macronutrients, water, and electrolytes (Dudrick et al., 1991; Nightingale, 1999; Rombeau and Rolandelli, 1987; Shanbhogue and Molenaar, 1994; Vanderhoof and Langnas, 1997; Wilmore et al., 1997). Additional potential consequences of SBS include dehydration, electrolyte disturbances, malabsorption of nutrients, gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhea, diarrhea, small bowel bacterial overgrowth and weight loss (Nightingale and Woodward, 2006; O'Keefe et al., 2006).

Following resection, intestinal adaptation may occur in adults during the first 1 to 2 years postsurgery. The adaptive response characterized by mucosal hyperplasia, increased mucosal blood flow, improved segmental absorption and increased hepatobiliary secretions (O'Keefe et al., 2006). These morphologic and functional changes are coordinated by the release of glucagon-like peptide 2 (GLP-2) from L-type enteroendocrine cells. In response to lumenal nutrients reaching the distal ileum and colon, L-cells secrete GLP-2, which regulates gastrointestinal secretions, motility, and the local production of additional hormones, cytokines, and growth factors.

The clinical care of SBS is mainly supportive and focuses on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, antidiarrheal and antisecretory agents. Despite intestinal adaptation following resection, many SBS develop intestinal failure, characterized by the requirement for chronic use of parenteral nutrition/intravenous (PN/IV) to maintain hydration, electrolyte balance, and/or nutritional needs.

Although PN/IV can meet basic nutrition and fluid requirements, it does not improve the body's ability to absorb nutrients. Parenteral nutrition dependence is associated with shortened life span (Messing et al., 1999; Scolapio et al., 1999), life threatening complications (eg, sepsis, blood clots, or liver damage), as well as reduced quality of life (DeLegge et al., 2007; Jackson and Buchman, 2005; Jeppesen, 2006). The development of parenteral nutrition-associated liver disease (PNALD) predisposes patients to sepsis, increased mortality rates, and the potential to develop irreversible liver damage (Tazuke and Teitelbaum, 2009). The American Gastroenterological Association Medical Position Statement on Short Bowel Syndrome recommends that management of PNALD should include reducion of toxic Parenteral nutrition constituents such as phytosterols, a component of soy-based lipid emulsions (American Gastroenterological Association, 2003).

The severity of SBS is illustrated by the shortened life-span in patients with moderate to severe disease (Messing et al., 1999). In SBS, survival can be impacted by the underlying condition, by severe clinical manifestations of malabsorption, and treatment-associated life-threatening complications (O'Keefe et al., 2006). With current medical management practices, the overall 10 year survival in SBS patients is 52%, and is significantly lower in patients who remain chronically PN/IV -dependent compared to patients who wean off PN/IV (40.7% versus 67%) (Amiot et al., 2013).

In addition, the symptoms of SBS and the inconveniences and complications in relation to PN/IV support may cause potential restrictions in the lifestyle of these patients leading to significant impairment of their quality of life (Jeppesen et al., 1999; Baxter et al., 2006; Winkler and Smith, 2014). The impact of SBS and PN/IV on quality of life may be significant with patients, on average, moving their bowels at least 10 times a day, with multiple ostomy bag changes per day, and having a typical output of 2 to 3 liters of watery diarrhea per day. Patients may be on PN/IV 10 to 15 hours a day for up to 7 days a week. Sleep is disrupted and patients typically cannot work.

1.2 Product Background and Clinical Information

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours in healthy subjects and 1.3 hours in adult SBS subjects compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines.

Results of the pivotal study, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/IV support in adult subjects with SBS. In this study the responder rate (defined as at least a 20% reduction from baseline in weekly PN/IV volume at Week 20 and Week 24) was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/IV volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/IV volume reduction, gaining additional days off per week, and achieving complete weaning of PN/IV. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in CL0600-020 and continued treatment in CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/IV support and 18/30 (60.0%) had a reduction in their PN/IV requirement of at least 3 days per week. It was encouraging that efficacy was also observed for subjects who initiated treatment in CL0600-021 (ie, those who received placebo or were not treated in CL0600-020). After only 6 months of

treatment, 37.1% of subjects who had received placebo in CL0600-020 had at least a 20% reduction in weekly PN/IV volume, which increased to 55.2% by Month 24. Two of these subjects completely weaned off of their PN/IV support. In subjects who had not been treated in CL0600-020, 50.0% had at least a 20% reduction in weekly PN/IV volume after 6 months of treatment, which increased to 66.7% by Month 24. One of these subjects completely weaned off of their PN/IV support. Overall, a total of 13 subjects achieved enteral autonomy (independence of PN/IV support), and 25/65 (38.5%) subjects demonstrated a reduction of ≥3 days/week in their PN/IV by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect. The results of this study support the efficacy of long-term treatment with teduglutide in PN/IV -dependent SBS subjects.

Teduglutide (0.05 mg/kg/day) is currently indicated for the treatment of adult patients with SBS. The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (REVESTIVE®) on 30 Aug 2012. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS. A New Drug Application for teduglutide (GATTEX®) was approved by the United States (US) Food and Drug Administration (FDA) on 21 Dec 2012. Teduglutide is currently approved in >30 countries.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the EU and the US. The clinical profile and medical issues related to SBS and PN/IV in Japan are similar to those in the EU and US. Therefore, there is an unmet medical need for Japanese patients with PN/IV -dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

2.2 Study Objectives

The objectives of this clinical study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of teduglutide in Japanese subjects with SBS who are dependent on PN/IV over a 24-week treatment period.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is an open-label, multicenter study, consisting of a conditional PN/IV optimization period, a mandatory PN/IV stabilization period, and a 24-week treatment period. A schematic representation of the study design is presented in Figure 1.

3.1.1 Optimization and Stabilization Periods

If at screening, a subject does not have an optimized PN/IV volume, defined as a 48-hour urine output between 2 and 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/IV volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/IV volume will be documented. For subjects who don't have an optimization period, the "last optimization visit" is the screening visit.

All subjects will then enter the stabilization period, during which the target PN/IV volume will be maintained for at least 4 consecutive weeks (8 weeks maximum). Those subjects who fail to stabilize will not proceed further and will not be included in the treatment period.

Appendix 1 provides details of the optimization procedure. Schedules of evaluations for the optimization/stabilization period can be found in Table 1.

3.1.2 Treatment Period

Following the stabilization period, subjects will enter a 24-week dosing period, during which all subjects will receive teduglutide 0.05 mg/kg SC once daily. At each site visit during the treatment phase, efficacy (adjustments to PN/IV) and safety will be monitored.

Subjects will have blood samples taken for teduglutide PK analysis at predose, at 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at the baseline visit (Visit 2). Subjects will also have blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at Week 4 (Visit 5) or Week 12 (Visit 7) of the treatment period.

All subjects who complete the study may participate in a long-term extension study in which eligible subjects will continue to receive teduglutide.

Schedules of evaluations for the Treatment Period can be found in Table 2. Procedures to adjust or reduce PN/IV volume during the Treatment Period is provided in Appendix 2, and should be followed carefully throughout the study.

3.2 Study Duration

Subjects will undergo up to a 7 day screening period, a conditional PN/IV support optimization period (up to 8 weeks), and a stabilization period (up to 8 weeks) prior to receiving teduglutide treatment. Thus, the screening, optimization period, and stabilization period could last up to 17 weeks in total.

Following the optimization and stabilization periods, and appropriate training on study drug administration, the subjects will receive the study drug for 24 weeks.

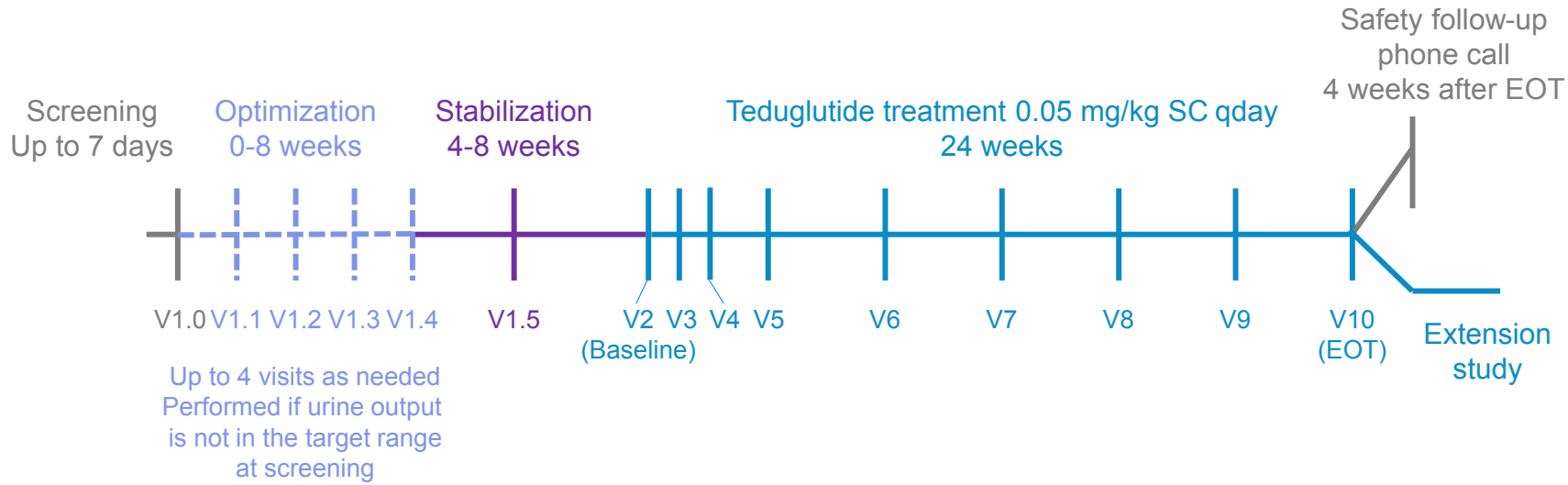
Subjects who do not enroll in the extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks after the last dose of study drug.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact (last safety contact), whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

This study is planned to be conducted in approximately 5 sites in Japan.

Figure 1 Study Schematic



4 STUDY POPULATION

At least 5 Japanese subjects with PN/IV-dependent SBS will be dosed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Ability to voluntarily provide written, signed, and informed consent to participate in the study.
2. Male or female 16 years of age or older at the time of signing informed consent.
3. Intestinal failure due to SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/IV dependence at the time of informed consent.
4. Parenteral nutrition requirement of at least 3 times per week during the week before the screening visit and during the 2 weeks prior to the baseline visit.
5. Stable PN/IV requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment. Stability is defined as:
    a. Actual PN/IV usage is similar to prescribed PN/IV.
    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ±25% of the respective 48-hour I/O volumes at the last optimization visit.
    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours at the last optimization visit, the stabilization visit, and the baseline visit.
6. For subjects with a history of Crohn's disease, clinical remission for at least 12 weeks prior to the baseline visit as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
7. Females of childbearing potential must agree to comply with the contraceptive requirements of the protocol.
8. An understanding, ability, and willingness to fully comply with study procedures and restrictions.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Participation in a clinical study using an experimental drug within 30 days or 5.5 half-lives, whichever is longer, prior to screening, or concurrent participation in any other clinical study.
2. Use of GLP-2 or human growth hormone or analogs of these hormones within the past 6 months.
3. Use of octreotide, GLP-1 analogs, dipeptidyl peptidase-IV inhibitors, or enteral glutamine within 30 days.
4. Previous use of teduglutide.
5. Subjects with active inflammatory bowel disease (IBD) or subjects with IBD who received a change in immunosuppressant therapy (eg, azathioprine, anti-TNFs) within the past 6 months.
6. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, familial adenomatous polyposis, etc.
7. Chronic intestinal pseudo-obstruction or severe dysmotility.
8. Clinically significant intestinal stenosis or obstruction, or evidence of such on upper GI series with small bowel follow-through, within the past 6 months.
9. Major GI surgical intervention, including bowel lengthening procedures, within the past 3 months (insertion of feeding tube or endoscopic procedure is allowed).
10. Unstable cardiac disease, (eg, congestive heart failure, cyanotic disease, or congenital heart disease).
11. Moderate or severe renal impairment, defined as creatinine clearance <50 ml/min.
12. Currently diagnosed with cancer or a history of any cancer except surgically curative skin cancer within the past 5 years.
13. Severe hepatobiliary disease including:
    a. Total bilirubin level ≥2 times the upper limit of normal (ULN).
    b. Aspartate aminotransferase (AST) ≥5 times ULN.
    c. Alanine aminotransferase (ALT) ≥5 times ULN.
14. Active clinically significant pancreatic disease, including clinical signs of pancreatitis associated with elevations in serum amylase or lipase ≥2 times ULN.
15. More than 4 SBS-related or PN/IV-related hospital admissions (eg, central line-associated bloodstream infection, bowel obstruction, severe fluid/electrolyte disturbances) within the past 12 months.
16. Unscheduled hospitalization within 30 days prior to screening.
17. Pregnant or lactating female.
18. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevent completion of the study, or interfere with analysis of the study results.

4.3 Reproductive Potential

To be eligible for treatment with teduglutide, sexually active females of childbearing potential must use a medically acceptable form of contraception. Females of childbearing potential must be advised to use medically acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use medically acceptable contraception if they become sexually active during the period of the study and for 30 days following the last dose of investigational product.

Females of childbearing potential must have a negative urine β-HCG pregnancy test at all visits where it is tested to participate in the study (see Section 8.1.6 for information about reporting a pregnancy).

Females of childbearing potential must agree to use medically acceptable methods of contraception at all times during the study and for 30 days following the last dose of investigational product.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Visit 10 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also receive a follow-up phone call 4 weeks after the last dose of study drug unless the subject has withdrawn consent. Comments (spontaneous or elicited) or complaints pertaining to study drug discontinuation made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks after the last dose of study drug.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by subject
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 14 days prior to the Screening Visit (Visit 1.0) (or pharmacokinetic equivalent of 5 half lives, whichever is longer must be recorded on the appropriate eCRF page. Any diagnostic, surgical or other therapeutic treatments received by a subject within 14 days prior to the Screening Visit (Visit 1.0) will also be recorded on the eCRF.

5.2 Concomitant Treatment

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins),-must be recorded from screening and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, digoxin), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index, are given.

5.2.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.2.2 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the baseline visit (Table 3):

Table 3 Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Baseline Visit
Teduglutide	Any
Glucagon-like peptide-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, dipeptidyl peptidase 4 inhibitors, GLP-1 analogs, and enteral glutamine	30 days

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 5 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product

6.2.1 Allocation of Subjects to Treatment

All subjects will receive teduglutide 0.05 mg/kg once daily.

6.2.2 Dosing

Teduglutide 0.05 mg/kg once daily will be administered daily by subcutaneous (SC) injection into either thigh or arm or 1 of the 4 quadrants of the abdomen (in subjects without a stoma). Each day, the injection site should be rotated. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

Any subject who achieves complete independence from PN/IV support at any time during the treatment period will continue to receive teduglutide treatment.

6.2.2.1 Subject Administration

The first dose of teduglutide will be administered by a study physician.

The processes for training the subject to self-administer teduglutide and for providing oversight of study drug administration are described in the Site Training Guide. Before a subject is permitted to administer teduglutide, the study physician must observe the subject administering the study drug at least twice in compliance with the teduglutide administration checklist. The checklist is included as an appendix to the Site Training Guide.

After the study physician certifies that the subject can safely administer the study drug, subsequent doses may be administered by the subject at home without direct supervision by the physician. However, at selected study visits during the dosing period (refer to Table 2), administration of the study drug must be performed under direct supervision by the study

physician, and the teduglutide administration checklist must be completed again. This ensures that the subject continues to administer the study drug correctly and safely throughout the dosing period.

If at any time a study physician suspects that the subject is no longer capable of administering the study drug safely and accurately, the subject should be re-assessed by a study physician using the teduglutide administration checklist. If the subject is deemed unable to administer the study drug, dosing must be performed by a study physician until the subject is re-trained and proficiency is confirmed using the teduglutide administration checklist.

Eligibility for teduglutide to be administered by a subject will be judged by a study physician using the following criteria. Refer to the checklist included as an appendix to the Site Training Guide.

Criteria to Initiate Teduglutide Administration by the Subject:

- The subject's condition is stable.
- The subject has been sufficiently trained and is able to administer teduglutide in compliance with the checklist.

Criteria to Discontinue Teduglutide Administration by the Subject:

- The subject is unable to administer teduglutide in compliance with the checklist.
- The subject's condition has deteriorated such that the study physician assesses it is inappropriate for the subject to have teduglutide self-administered. In addition to discontinuing administration of teduglutide by the subject, if a subject sustains an adverse drug reaction where the symptoms are considered intolerable, dose interruption or study drug discontinuation should be considered.
- In the study physician's judgment, it is inappropriate for the subject to continue administration of the study drug for any other reason.

6.2.3 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.3 Labeling, Packaging, Storage and Handling

6.3.1 Labeling and Packaging

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2 ^{o}C to 8^{o}C (35.6°F to46.4°F) until dispensed to a subject. The prefilled sterile water for injection syringes will be stored at a temperature between 2°C to 25°C. Once dispensed/supplied to a subject, the investigational product and ancillary kits can be stored refrigerated up to a controlled room temperature (acceptable range of 2°C to 25^{o}C, or 35.6°F to77°F). The subject will be instructed to keep the investigational product and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the investigational product may be refrigerated. The study drug is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product and ancillary kits are maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject if he/she has administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and adverse events (AEs), a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7 STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

Subjects who drop out of the study prior to the final visit should have all early termination procedures done whenever possible.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1.

7.1.2 Optimization and Stabilization Periods

Subjects who are eligible for the study during the screening visit will proceed to the optimization or stabilization period depending on urine ouput evaluated at the screening visit. Assessments will be performed as outlined in Table 1.

During the optimization period, PN/IV adjustments will be made according to the algorithm in Appendix 1. Optimization visits will occur approximately every 2 weeks (for up to 8 weeks) until the subject achieves an optimized volume of PN/IV indicated by targeted urine output of 1.0 L/day to 2.0 L/day.

Once an optimal tolerated PN/IV volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/IV adjustments should take place during the stabilization period. Subjects who do not achieve stable PN/IV support during this period will not be eligibile to continue in the study.

7.1.3 Treatment Period

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments will be performed as outlined in Table 2.

7.1.4 Follow-up Period

Long-term safety and efficacy data will be obtained from subjects enrolling into the extension study at the Week 24 visit (Visit 10).

Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks (Week 28) after the last dose of study drug.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

7.2.1.1 Demographics and Medical History

Information on medical history and demographic data is to be recorded on the appropriate eCRF.

7.2.1.2 Clinical Assessment of Crohn's Disease Activity

Any subject with a history of Crohn's disease will have their clinical disease status assessed at screening and again at the baseline visit of the treatment period to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation. For all subjects, upper endoscopy and colonoscopy/sigmoidoscopy are required during the stabilization period if they have not been completed within 6 months prior to screening. For subjects with Crohn's disease, it may be necessary to perform upper endoscopy and colonoscopy prior to the baseline visit in subjects with clinical suspicion of active disease, even if these procedures had been completed within 6 months prior to screening. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant stenosis or stricture.

7.2.2 Efficacy Assessments

7.2.2.1 Subject Diaries

Diaries will be distributed to subjects at the time of informed consent and at clinic visits according to the study schedules. Subjects will record their PN/IV support daily throughout the study. Prior to each clinic and safety visit, subjects will also record all enteral fluid intake and urine output over a 48-hour period. Forty-eight hours of output data must be collected during Screening (Visit 1.0) in order to assess the need for the optimization period. Diaries may be completed by the subject or the subject's designee if the subject is physically unable to enter data on his/her own.

7.2.2.2 Prescribed Parenteral Nutrition

All attempts should be made to follow the PN/IV adjustment algorithm specified in the appendices. At the interim visits the PN/IV will be changed if the previous adjustment was not tolerated. Physician-directed changes in a subject's PN/IV volume must be followed by an interim safety visit 5 to 7 days after the adjustment has been implemented. If the subject has a AE that prevents him/her from adhering to study requirements, including the PN/IV adjustment algorithms, the subject may be withdrawn from the study.

The prescribed PN/IV weekly total volume, calories, and days per week will be recorded. Changes in parenteral support prescription that reflect changes in the subject's intestinal absorption are recorded. Temporary adjustments to parenteral nutrition or IV fluids that last less than 72 hours may be recorded at the discretion of the investigator, but all parenteral support prescriptions that last more than 72 hours must be recorded. The PN/IV constituents are at the discretion of the physician; the identities of parenteral support constituents do not recorded.

7.2.2.3 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass. If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

7.2.3 Safety Assessments

7.2.3.1 Laboratory Evaluations

Safety laboratory tests are to be performed at site visits with results processed by a central laboratory. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/IV with lipids, within 3 hours of the clinic visit to permit consistent assessment.

Safety lab tests performed at interim safety visits after PN/IV adjustments will consist of hemoglobin, hematocrit, serum blood urea nitrogen, creatinine, and urine sodium, and may be performed at the investigational site laboratory.

The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved. New clinically significant lab tests results should be reported as AEs (see Section 8).

Tests include the following (Table 4):

Table 4 List of Laboratory Tests

Hematology:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Urinalysis:
- Blood
- Glucose
- Leucocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity
- Urine Sodium

Pregnancy tests (females of childbearing potential):
- Urine β-HCG

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bilirubin (total, direct and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- Citrulline (plasma)
- C-reactive protein
- Creatinine
- Creatinine clearance
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides
- Uric acid

7.2.3.2 Antibodies to Teduglutide

Blood samples for analyses of antibodies to teduglutide will be collected. Blood sample for antibody testing is to be collected at study site prior to first investigational product administration. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing.

Anti-teduglutide antibody testing is a 3-step process. If a sample tests negative, no further testing is done. If a sample tests positive, further testing is done for teduglutide-specific antibodies. If teduglutide-specific antibodies are detected, the test is deemed "positive" and the titer derived, and neutralizing antibody testing is done. Subjects who test positive for teduglutide-specific antibodies may remain on treatment and blood samples for antibody testing will continue to be collected as per protocol schedule (Table 2).

Blood samples for anti-teduglutide antibody testing may be stored and then analyzed together periodically to streamline the testing procedure. However, if an investigator suspects that a subject is experiencing an AE that may be associated with the development of anti-drug antibodies, relevant samples will be tested for the presence of anti-drug antibodies upon request.

7.2.3.3 Physical Examinations

Physical examinations will be performed according to the study schedules to assess the subject's physical status. New clinically significant abnormalities that are detected or diagnosed after study evaluations have begun (after signing of the informed consent) should be recorded on the appropriate AE page of the eCRF. Complete physical exams are required at screening, baseline, and Week 24/ET. Focused physical exams may be performed at all other visits.

7.2.3.4 Vital Signs, Body Weight, and Height

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse rate, and body temperature (°C). Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Subjects should be weighed on the same scale at each study visit. Height will be measured at the screening visit.

7.2.3.5 Electrocardiograms

A 12-lead ECG will be performed at the study center after the subject has been resting for at least 5 minutes. Results will include general findings (normal, abnormal-not clinically significant, abnormal-clinically significant). If abnormal, the nature of the abnormality will be collected. Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the eCRF.

Electrocardiogram tracings should be printed, signed and dated by the investigator, and kept with the subject's source documents.

7.2.3.6 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below.

Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization if not completed within 6 months prior to screening) in subjects with any colon remnant including a rectal stump. This will be repeated at Visit 10 (or early termination). The date and result of colonoscopy are to be recorded in the eCRF.

Abdominal Ultrasound

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented).

Upper GI Contrast Series with Small Bowel Follow-through

Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy (EGD) will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening. Esophagogastroduodenoscopy will be performed on all subjects prior to teduglutide exposure (during the stabilization period if not completed within 6 months prior to screening). Esophagogastroduodenoscopy will be repeated at Week 24/Visit 10 (or ET) for subjects with any of the following risk factors:

- Age 40 or over at Week 24/Visit 10/ET
- History of H pylori gastritis
- History of atrophic gastritis
- History of intestinal metaplasia or dysplasia in the stomach

For subjects that do not have any of the above risk factors, EGD may be repeated at Visit 10/ET at the discretion of the investigator. The dates and results of all EGDs are to be recorded in the eCRF.

48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to study visits as required. The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring I/O, and to record these measurements into the diary. During the 48-hour measurements, the subject should maintain their usual oral fluid intake. 48-hour urine output measurements will also be collected prior to all interim safety visits.

7.2.4 Pharmacokinetic Assessments

The first dose of teduglutide will be administered by the study physician at the baseline visit (Visit 2). At this visit, subjects will have blood samples taken for teduglutide PK analysis:

- 0-hour (predose) draw: any time prior to the dose
- 15 minutes postdose: ±5 minutes
- 30 minutes postdose: ±5 minutes
- 1 hour postdose: ±10 minutes
- 2 hours postdose: ±10 minutes
- 3 hours postdose: ±10 minutes
- 4 hours postdose: ±30 minutes
- 6 hours postdose: ±30 minutes
- 8 hours postdose: ±30 minutes
- 10 hours postdose: ±30 minutes
- 12 hours postdose: ±30 minutes

Subjects also will have blood samples taken for teduglutide PK analysis at Week 4 (Visit 5) or Week 12 (Visit 7):

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose
- 1 hour postdose: ±10 minutes
- 2 hours postdose: ±10 minutes

Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) and the person administering the injection (physician or subject) must be recorded in the eCRF.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation [ICH] Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until until the defined follow-up period stated in Section 7.1.4. This includes events occurring during screening, optimization, and stabilization phases of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

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

Moderate: A type of AE that is usually alleviated with 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 subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related." The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to investigational product that are not resolved at EOT will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign can represent an AE if the change is clinically relevant or if, during treatment with investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the EOT with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values or vital signs which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to Quintiles Transnational Japan K.K. using the Shire Investigational and Marketed Products Pregnancy Report Form. In the event a subject becomes pregnant during the study, teduglutide administration must be immediately and permanently discontinued.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered serious adverse events (SAEs) and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events and Non-serious AEs as Required by Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that complications of the pregnancy meet serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event

Form for SAEs and Non-serious AEs as Required by Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor using SAE reporting form whether or not they result in an AE/SAE as described in Section 8.2, but such events are only recorded in the eCRF if they result in an AE. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).

- Overdose – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.

- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator's brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the sponsor or designee within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the sponsor or designee within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). The investigator must fax or e-mail the completed form to Quintiles Transnational Japan K.K. Applicable fax numbers and email addresses are found in the Emergency Contact Information.

8.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” 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 which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for preexisting conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent is obtained until the defined follow-up period stated in Section 7.1.4, and must be reported to the sponsor or designee within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the sponsor or designee within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or designee is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs.

In addition, the sponsor and/or designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the teduglutide program.

The investigator is responsible for notifying the local Institutional Review Board (IRB) or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting for this study include the following:

- Growth of preexisting polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor or designee must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill seriousness criterion.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. It is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The data collected in this study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis

Interim analyses may be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.

9.5 Sample Size Calculation and Power Considerations

The sample size of the SHP633-306 study is based on patient prevalence and study design elements; no statistical estimation was involved. Possible medical institutes for SBS studies are limited, given the rarity of the disease and the very limited number of patients with SBS (<1000) in Japan. The applicant considers that 5 treated subjects in SHP633-306 should provide sufficient basic information concerning the efficacy, safety and tolerability as well as PK of teduglutide in the Japanese study population.

9.6 Study Population

The intent-to-treat (ITT) population will include all subjects who are deemed eligible for teduglutide treatment at the baseline visit (Visit 2).

The per protocol population will include all subjects in the ITT population who complete the Treatment Period without any major protocol violations that could potentially affect the efficacy conclusions of the study.

The safety population will include all subjects in the ITT population who receive at least 1 dose of study drug.

The pharmacokinetic population will include all subjects who receive at least 1 dose of teduglutide and have at least 1 evaluable post-dose pharmacokinetic concentration value.

9.7 Efficacy Analyses

The following efficacy endpoints will be analyzed:

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at end of treatment (EOT).
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who are able to completely wean off of PN/IV support.

The absolute and relative change in weekly PN/IV volume, days per week of PN/IV support, and plasma citrulline, from baseline to each scheduled visit, as well as at EOT, will be summarized using descriptive statistics.

The number and percentage of subjects who demonstrate a response at Week 20 and again at Week 24 will be summarized. A response is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume. The number and percentage of subjects who demonstrate at least a 20% reduction from baseline in weekly PN/IV volume at each visit will also be summarized.

The number and percentage of subjects who completely wean off PN/IV support by Week 24/EOT will be summarized. A subject will be considered to have achieved independence from PN/IV (completely weaned off PN/IV) if the investigator prescribes no PN/IV at Week 24/EOT and there is no use of PN/IV recorded in the subject diary during the 2 weeks prior to the last dosing visit.

For efficacy analysis, the ITT population will be the primary analysis population; the per-protocol population will be used for secondary/sensitivity analysis.

9.8 Safety Analyses

The safety endpoints include AEs, 12-lead ECG, vital signs, laboratory safety data, antibodies to teduglutide, and 48-hour urine output, body weight, BMI and gastrointestinal-specific tests.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as AEs that started or worsened on or after the date and time of the first dose of study dose. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity, relationship to treatment, and for AEs leading to discontinuation, and death. In addition, SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, body mass index, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each time point.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

The safety population will be the analysis population for all the safety data analysis.

9.9 Pharmacokinetics Analyses

Teduglutide plasma concentrations will be summarized using the PK population with descriptive statistics (number, mean and standard deviation, minimum, median, and maximum) at nominal time points.

The following parameters will be derived: area under the plasma concentration–time curve from zero to the last measurable concentration (AUC_{0-t}); maximum plasma concentration (C_{max}); time to C_{max} (t_{max}); terminal-phase half-life ($t_{1/2}$); apparent clearance (CL/F); and apparent volume of

distribution (V/F). Pharmacokinetic parameters will be estimated using non-compartmental analysis as appropriate and summarized using descriptive statistics (number, mean, standard deviation, geometric mean, and CV%, minimum, median, and maximum).

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied, as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the

Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designe and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator. The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, original clinical laboratory reports, and imaging reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, European Medicines Agency [EMA], UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Original signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to,

and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results

from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12 APPENDICES

APPENDIX 1 PARENTERAL NUTRITION/INTRAVENOUS OPTIMIZATION

After signing the ICF, the investigator will determine if the subject's PN/IV volume produces an appropriate urine output target of 1.0 L/day to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/IV volume should be adjusted appropriately to reach the targeted urine output of between 1.0 L/day to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- <1.0 L/day, then PN/IV should be increased.
- >2.0 L/day, then PN/IV should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/IV volume should be documented. Keep in mind the following:

- During optimization, total weekly PN/IV volume should be adjusted in increments or decrements of 10-30% of the screening volume.
- Parenteral nutrition constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/IV volume:

1. **Screening and Optimization Visits:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.
2. **Interim Safety Evaluations:** If any PN/IV adjustments are made, the clinical effect and the health status of the subject will be assessed 5 to 7 days after the adjustment is implemented. Laboratory safety samples should be evaluated following a PN/IV adjustment (see Table A3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/IV should be increased if the decrease was not tolerated. No further reductions to PN/IV volume are made at the interim safety visit.
3. Maintain the PN/IV level until the next scheduled optimization visit.
4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/IV indicated by targeted urine output of 1.0 L/day to 2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/IV after 8 weeks, consult the sponsor's Medical Monitor.
5. **Parenteral Nutrition Stabilization:** Once an optimal tolerated PN/IV volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/IV adjustments should take place during this time period.

APPENDIX 2 PARENTERAL NUTRITION/INTRAVEOUS ADJUSTMENT DURING TREATMENT PERIOD

Points to keep in mind when adjusting PN/IV volume during dosing:

- There will be no PN/IV reduction attempts at baseline and Week 1.
- Parenteral nutrition/intravenous reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/IV will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- Parenteral nutrition/intraveous adjustments are targeted to be at least 10% but no more than 30% of **baseline** PN/IV level.
- Adjustments should be based on the actual PN/IV volume the subject infuses. Subjects should remain compliant with the PN/IV prescription during the length of the study.
- Parenteral nutrition/intravenous constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/IV adjustments are in Table A1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/IV volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2).
- Subjects who fail to maintain a PN/IV reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the sponsor's Medical Monitor.

Table A1 Parenteral Nutrition Adjustments at Scheduled Clinic Visits based on 48-hour Urinary Output

Urine Output	Parenteral Nutrition/Intravenous Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/IV by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2), increase PN/IV If not, maintain PN/IV.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/IV
At least a 10% increase over Baseline	Reduce PN/IV by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

L=liter; PN/IV=parenteral nutrition/intravenous (volume)

Table A2 Targeted Criteria for Hydration and Nourishment at all Clinic Visits and Interim Safety Visits

Hydration Assessment	Hydration Adequate
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/L or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal
Note: In combination with Table A1, any one of the above criteria determines dehydration.

Steps for adjusting PN/IV volume:

1. **DOSING WEEKS 2, 4, 8, 12, 16, and 20:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. Blood and urine samples will be collected to evaluate hydration and nutrition (see Table A2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **Parenteral Nutrition Changes:** Review Table A1 and Table A2 to take appropriate action.

3. **Interim Safety Evaluations:** If any PN/IV adjustments are made, the clinical effect and the health status of the subject will be assessed 5 to 7 days after the adjustment is implemented. Laboratory safety samples should be evaluated following a PN/IV adjustment (see Table A3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/IV should be increased if the decrease was not tolerated. No further reductions to PN/IV volume are made at the interim safety visit.

Table A3 Assessment of Tolerance of Pareneteral Nutrition/Intravenous Adjustments at Interim Safety Visits

Urine Output, Hydration and Nutrition	Parenteral Nutrition/Intravenous Action
Output less than Baseline	Increase PN/IV to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2)	Increase PN/IV to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2)	If possible, maintain PN/IV volume and increase nutrition. If not, increase PN/IV to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2)	Maintain PN/IV

L=liter; PN/IV=parenteral nutrition/intravenous (volume)
[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/IV is allowed.

4. Maintain the adjusted PN/IV level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

    a. It is preferred that when the total weekly PN/IV needs have been reduced to a level that safely allows for a day or days off PN/IV, the physician should consider instituting a day(s) off PN/IV.

    b. If the total weekly PN/IV is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/IV completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

    c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra IV fluid that will be included in the weekly PN/IV volume total.

PROTOCOL: SHP633-306

TITLE:	A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support
NUMBER	SHP633-306
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Amendment 1: 27 Sep 2018 Original Protocol: 23 Jan 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD PhD [redacted]	
[redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-306.

Title: A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____
	_____
	_____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 Sep 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Changed name and contact information of Shire medical monitor to [redacted], MD.		Emergency Contact Information
Changed Quintiles Transnational Japan K.K. to IQVIA Services Japan K.K. to reflect a corporate name change.		Emergency Contact Information Section 8.1.6, Section 8.2.2
Clarified the prohibited use of enteral glutamine. (Administrative Amendment dated 26 Sep 2018)		Section 5.2.2
Added language on rescreening of subjects. Subjects may be rescreened no more than twice and only with prior sponsor medical approval. In the event of rescreening, a new subject number will be assigned. Subjects who are rescreened will be reconsented.		Section 7.1.1
Corrected an error in the prescribed PN/IV parameters to be recorded; only prescribed parenteral support volume and days per week will be recorded. 'Parenteral support calories' has been deleted. (Administrative Amendment dated 10 May 2018)		Section 7.2.2.2
Specified that the pregnancy outcome in female partner of male study participant will also be reported. Specified that the collection of data for outcomes of pregnancies will be conducted up to 1-year postpartum. Every effort should be made to gather information on pregnancy outcome and condition of the infant within 30 calendar days after the initial notification, and approximately 30 calendar days and 1 year postpartum.		Section 8.1.6
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events and Non-serious adverse evetns (AEs) as Required by Protocol within 24 hours to the sponsor or designee using the details below. Applicable fax numbers and e-mail address can also be found on the form (sent under separate cover).

Pharmacovigilance SAE Reporting:

[redacted] or [redacted] (Japan domestic line only)

or

Email: [redacted]

For protocol- or safety-related issues, the investigator should contact:

[redacted], MD
Phone: [redacted] (24-hour coverage)
Email: [redacted]
Fax: [redacted]

For protocol- or safety-related issues the investigator may also contact the Shire medical monitor:

[redacted], MD
Mobile Phone: [redacted]
Email: [redacted]
Fax: [redacted]

In-country Clinical Caretaker:
IQVIA Services Japan K.K.
4-10-18 Takanawa, Minato-ku
Tokyo, 108-0074, Japan

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

The product quality includes quality of the drug delivery device combination product. As such device defects should be reported according to the instructions in this section. The reporting of product quality occurrences, when the product does not meet specifications, includes the reporting of device defects.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
Ex-US	[redacted]

Telephone numbers (provided for reference, if needed):

Shire, Lexington, MA (USA)
[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase, equivalent to SGPT
AST	aspartate aminotransferase, equivalent to SGOT
AUC	area under the plasma concentration-time curve
AUC_{0-t}	AUC from zero to the last measurable concentration
BUN	blood urea nitrogen
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EGD	esophagogastroduodenoscopy
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
ICF	informed consent form
ICMJE	International Committee of Medicinal Journal Editors
ICH	International Committee on Harmonisation
IBD	inflammatory bowel disease
I/O	oral fluid intake and urine output
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN/IV	parenteral nutrition/intravenous
PNALD	parenteral nutrition-associated liver disease
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2}$	terminal-phase half-life
t_{max}	time to C_{max}
ULN	upper limit of normal
US	United States
V/F	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP633-306	**Drug:** Teduglutide
Title of the study: A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 5 Japanese subjects will be dosed.	
Investigator(s): Multicenter study.	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 sites in Japan.	
Study period (planned): 2017-2020	**Clinical phase:** 3

Objectives:

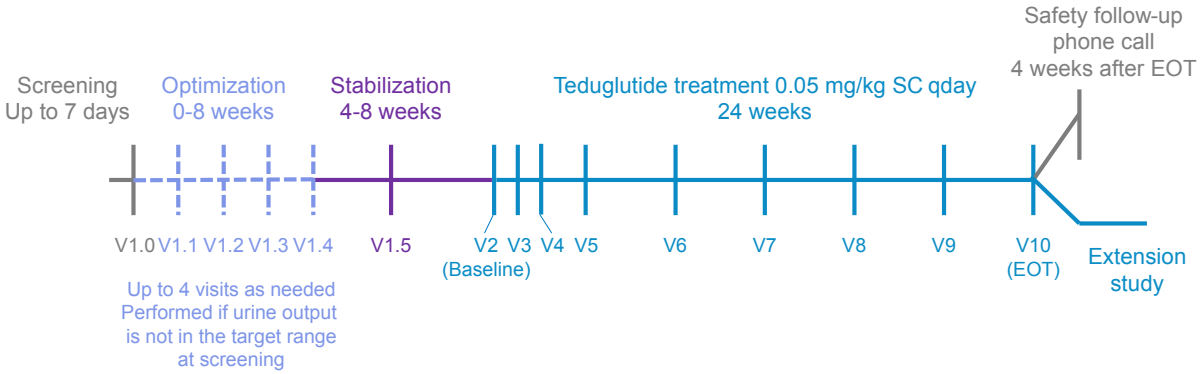
The objectives of this clinical study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of teduglutide in Japanese subjects with short bowel syndrome (SBS) who are dependent on parenteral nutrition/intravenous (PN/IV) over a 24-week treatment period.

Investigational product, dose, and mode of administration:

Teduglutide 0.05 mg/kg subcutaneously (SC) once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.

Methodology:

This is an open-label, multicenter study, consisting of a conditional PN/IV optimization period, a mandatory PN/IV stabilization period, and a 24-week treatment period.



SC=subcutaneous; qday=once daily; EOT=end of treatment

If at screening, a subject does not have an optimized PN/IV volume, defined as a 48-hour urine output between 2 and 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/IV volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/IV volume will be documented.

All subjects will then enter the stabilization period, during which the target PN/IV volume will be maintained for at least 4 consecutive weeks (8 weeks maximum).

Following the stabilization period, subjects will enter a 24 week dosing period, during which all subjects will receive teduglutide 0.05 mg/kg SC once daily. At each site visit during the treatment phase, efficacy (adjustments to PN/IV) and safety will be monitored.

Subjects will have blood samples taken for teduglutide PK analysis at predose, at 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at the baseline visit (Visit 2). Subjects also will have blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at Week 4 (Visit 5) or Week 12 (Visit 7) of the treatment period.

All subjects who complete the study may participate in a long-term extension study in which subjects will continue to receive teduglutide. Subjects who do not enroll in the extension study or who discontinue the study prematurely at any time will receive a follow-up phone call 4 weeks after the last dose of study drug.

Inclusion and Exclusion Criteria:
Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Ability to voluntarily provide written, signed, and informed consent to participate in the study.
2. Male or female 16 years of age or older at the time of signing informed consent.
3. Intestinal failure due to SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/IV dependence at the time of informed consent.
4. Parenteral nutrition requirement of at least 3 times per week during the week before the screening visit and during the 2 weeks prior to the baseline visit.
5. Stable PN/IV requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment. Stability is defined as:
    a. Actual PN/IV usage is similar to prescribed PN/IV.
    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ±25% of the respective 48-hour I/O volumes at the last optimization visit.
    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours at the last optimization visit, the stabilization visit, and the baseline visit.
6. For subjects with a history of Crohn's disease, clinical remission for at least 12 weeks prior to the baseline visit as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
7. Females of childbearing potential must agree to comply with the contraceptive requirements of the protocol.
8. An understanding, ability, and willingness to fully comply with study procedures and restrictions.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Participation in a clinical study using an experimental drug within 30 days or 5.5 half-lives, whichever is longer, prior to screening, or concurrent participation in any other clinical study.
2. Use of GLP-2 or human growth hormone or analogs of these hormones within the past 6 months.
3. Use of octreotide, GLP-1 analogs, dipeptidyl peptidase-IV inhibitors, or enteral glutamine within 30 days.
4. Previous use of teduglutide.
5. Subjects with active inflammatory bowel disease (IBD) or subjects with IBD who received a change in immunosuppressant therapy (eg, azathioprine, anti-TNFs) within the past 6 months.
6. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, familial adenomatous polyposis, etc.
7. Chronic intestinal pseudo-obstruction or severe dysmotility.
8. Clinically significant intestinal stenosis or obstruction, or evidence of such on upper gastrointestinal (GI) series with small bowel follow-through, within the past 6 months.

9. Major GI surgical intervention, including bowel lengthening procedures, within the past 3 months (insertion of feeding tube or endoscopic procedure is allowed).
10. Unstable cardiac disease, (eg, congestive heart failure, cyanotic disease, or congenital heart disease).
11. Moderate or severe renal impairment, defined as creatinine clearance <50 ml/min.
12. Currently diagnosed with cancer or a history of any cancer except surgically curative skin cancer within the past 5 years.
13. Severe hepatobiliary disease including:
    a. Total bilirubin level ≥2 times the upper limit of normal (ULN).
    b. Aspartate aminotransferase (AST) ≥5 times ULN.
    c. Alanine aminotransferase (ALT) ≥5 times ULN.
14. Active clinically significant pancreatic disease, including clinical signs of pancreatitis associated with elevations in serum amylase or lipase ≥2 times ULN.
15. More than 4 SBS-related or PN/IV -related hospital admissions (eg, central line-associated bloodstream infection, bowel obstruction, severe fluid/electrolyte disturbances) within the past 12 months.
16. Unscheduled hospitalization within 30 days prior to screening.
17. Pregnant or lactating female.
18. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevent completion of the study, or interfere with analysis of the study results.

Maximum Duration of Subject Involvement in the Study:

Subjects will undergo up to a 7 day screening period, a conditional PN/IV support optimization period (up to 8 weeks), and a stabilization period (up to 8 weeks) prior to receiving teduglutide treatment. Thus, the screening, optimization period, and stabilization period could last up to 17 weeks in total.

Following the optimization and stabilization periods, the subjects will receive the study drug for 24 weeks.

Endpoints:

Efficacy

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at end of treatment (EOT).
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who are able to completely wean off of PN/IV support.

Pharmacokinetics

The following parameters will be derived: area under the plasma concentration–time curve from zero to the last measurable concentration (AUC_{0-t}); maximum plasma concentration (C_{max}); time to C_{max} (t_{max}); terminal-phase half-life ($t_{1/2}$); apparent clearance (CL/F); and apparent volume of distribution (V/F).

Safety

Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide, and changes in 48-hour urine output, body weight and body mass index will be evaluated. An abdominal ultrasound, esophagogastroduodenoscopy, and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the treatment period. Esophagogastroduodenoscopy will be repeated at the end of the treatment period for subjects with risk factors for gastric cancer. For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the Stabilization Period, prior to the baseline visit.

Statistical Methods:

Efficacy

The absolute and relative change in weekly PN/IV volume, days per week of PN/IV support, and plasma citrulline, from baseline to each scheduled visit, as well as at EOT, will be summarized using descriptive statistics.

The number and percentage of subjects who demonstrate a response at Week 20 and again at Week 24 will be summarized. A response is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume. The number and percentage of subjects who demonstrate at least a 20% reduction from baseline in weekly PN/IV volume at each visit will also be summarized.

The number and percentage of subjects who completely wean off PN/IV support by Week 24/EOT will be summarized. A subject will be considered to have achieved independence from PN/IV (completely weaned off PN/IV) if the investigator prescribes no PN/IV at week 24/EOT and there is no use of PN/IV recorded in the subject diary during the 2 weeks prior to the last dosing visit.

Pharmacokinetics

Teduglutide plasma concentrations will be summarized using descriptive statistics (number, mean and standard deviation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using non-compartmental analysis as appropriate and summarized using descriptive statistics (number, mean, standard deviation, geometric mean, and CV%, minimum, median, and maximum).

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as AEs that started or worsened on or after the date and time of the first dose of study dose. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity, relationship to treatment, and for AEs leading to discontinuation, and death. In addition, SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour oral intake and urine output, vital signs, body weight, and body mass index, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

STUDY SCHEDULES

Table 1 Schedule of Evaluations and Procedures – Optimization/Stabilization

Procedures	Screening (up to 7-days)	PN/IV Optimization Period (8-week maximum)				PN/IV Stabilization Period[a] 4-8 weeks
		Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:	**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X[b]					
Eligibility criteria	X					
Medical history, demographics	X					
Crohn's disease assessment	X					
Physical examination[c]	X	X	X	X	X	X
Record PN/IV use and adjust prescription as indicated	X[d]	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Abdominal ultrasound[e]						X
Upper GI contrast series with small bowel follow-through[f]						X
Esophagogastroduodenoscopy[e]						X
Colonoscopy/sigmoidoscopy[g]						X
Prior/Concomitant medication/procedures[h]	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Height	X					
Body weight	X	X	X	X	X	X[i]
12-lead ECG[j]	X					
Safety laboratory tests	X	X	X	X	X	X
Urine pregnancy test[k]	X					
Interim safety evaluation	[X][l]	[X][l]	[X][l]	[X][l]	[X][l]	
Dispense diary[m]	X	X	X	X	X	X

Table 1 Schedule of Evaluations and Procedures – Optimization/Stabilization

Procedures	**Screening** (up to 7-days)	**PN/IV Optimization Period** (8-week maximum) **Week 2** (± 3 days)	**Week 4** (± 3 days)	**Week 6** (± 3 days)	**Week 8** (± 3 days)	**PN/IV Stabilization Period**[a] 4-8 weeks
Visit Number:	**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Review Diary [m]	X	X	X	X	X	X

ECG=electrocardiogram; GI=gastrointestinal; ICF=informed consent form; PN/IV =parenteral nutrition/intraveous; V=visit

[a] The baseline visit must occur 4-8 weeks after the last optimization visit (or screening visit if no optimization is needed). The stabilization visit must occur during this 4-8 week interval, and must occur at least 7 days apart from the preceding visit (screening or optimization visit) and subsequent visit (baseline).

[b] No study-related procedures are to be performed unless the ICF has been signed.

[c] A full physical examination is to be performed at screening. Focused physical exams may be performed at all other visits

[d] PN/IV evaluation is to confirm weekly volume for inclusion criteria.

[e] Abdominal ultrasound and esophagogastroduodenoscopy should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[f] Upper GI contrast series with small bowel follow-through is required for subjects with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[g] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in subjects with any colon remnant including rectal stump evaluation. Colonoscopy/sigmoidoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy documented within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[h] At screening, information on all medications taken in the previous 14 days will be collected.

[i] The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This is the first of 2 body weight measurements that will be used to determine drug volume.

[j] A 12-lead ECG will be performed at the study center after the subject has been resting for at least 5 minutes.

[k] For women of childbearing potential.

[l] Interim safety evaluations will be performed 5 to 7 days after implementing a change to the subject's PN/IV. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[m] Subjects will record their PN/IV support daily throughout the study. Prior to each clinic and safety visit, subjects will also record all enteral fluid intake and urine output over a 48-hour period.

Table 2 Schedule of Evaluations and Procedures – Treatment Period

Procedures	Baseline	Dosing Week 1	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 /EOT[a] (or ET[b])	Follow-up Call Week 28[a]
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7	± 7
Eligibility criteria	X									
Crohn's disease assessment[c]	X									
Physical examination[d]	X	X	X	X	X	X	X	X	X	
Record PN/IV use and adjust prescription as indicated	X[e]		X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X
EGD									X[f]	
Colonoscopy/ Sigmoidoscopy									X	
Concomitant medication /procedures	X	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	
Body weight	X[g]		X	X	X	X	X	X	X	
12-lead ECG[h]	X			X					X	
Safety laboratory tests	X		X	X	X	X	X	X	X	
Citrulline[i]	X			X	X		X		X	
Antibodies to teduglutide[j]	X					X			X	
PK sampling	X[k]			(X)[k]		(X)[k]				
Urine pregnancy test[l]	X		X	X	X	X	X	X	X	
Drug dispensing	X		X	X	X	X	X	X		
Teduglutide dosing[m]	X	X	X	X	X	X	X	X	X[n]	
Confirm administration proficiency	X[o] X[o] X[o]			X		X			X[p]	
Interim safety evaluation[q]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	
Dispense Diary[r]	X	X	X	X	X	X	X	X	X[p]	
Review Diary[r]	X		X	X	X	X	X	X	X	
Compliance[s]		X	X	X	X	X	X	X	X	

Table 2 Schedule of Evaluations and Procedures – Treatment Period

Procedures	Baseline	Dosing Week 1	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 /EOT[a] (or ET[b])	Follow-up Call Week 28[a]
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**

(X) = Possible PK sampling time point; [X] = Possible interim safety evaluation time point; 48-hour I/O=48-hour fluid intake/urine output; ECG=electrocardiogram; EGD=esophagogastroduodenoscopy; EOT=end of treatment; ET=early termination; PK=pharmacokinetic; PN/IV=parenteral nutrition/intraveous; V=visit

[a] The follow-up period for this protocol is 4 weeks from the last dose of investigational product. Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks after the last dose to query for SAEs, AEs, and concomitant treatments.

[b] Subjects with an ET visit should have all applicable Week 24 (Visit 10) assessments. Call sponsor for guidance.

[c] Subjects with active Crohn's disease are excluded from the study participation, therefore endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease.

[d] A full physical examination is to be performed at baseline and Week 24 (Visit 10); a brief examination will be performed at all other dosing weeks with a clinic visit.

[e] The PN/IV evaluation is to confirm weekly volume for inclusion criteria.

[f] Esophagogastroduodenoscopy at Visit 10 is required for subjects with risk factors for gastric cancer (see Section 7.2.3).

[g] The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This is the second of 2 body weight measurements that will be used to determine drug volume.

[h] A 12-lead ECG will be performed at the study center after the subject has been resting for at least 5 minutes.

[i] Blood sample for measuring citrulline should be drawn from peripheral venous access, if this is not possible, sample may be drawn from a central line.

[j] Blood sample for antibody testing is to be collected at baseline (Visit 2) prior to first investigational product administration. Blood samples for antibody testing at Week 12 (Visit 7) and Week 24 (Visit 10) must be collected prior to that day's dose, and more than 14 hours after the prior day's dose.

[k] Samples for PK analysis will be collected pre-dose and at 15, 30 minutes post-dose and at 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose at Visit 2. Additional PK samples will be collected predose, and 1 and 2 hours post-dose at Week 4 (Visit 5) or Week 12 (Visit 7). The site of teduglutide administration prior (arm, thigh, or abdomen) and the person administering the injection (subject or physician) must be specified. Blood sample for measuring PK must be drawn from peripheral venous access.

[l] For women of childbearing potential.

[m] Teduglutide is dosed once daily during the treatment period. The first dose of study drug must be administered by the study physician.

[n] Dosing will continue if the subject enters the extension study, but will stop at the Week 24 visit if the subject doesn't enter the extension study.

[o] The study physician must observe the subject administering the study drug in compliance with the study drug administration checklist at least twice before the subject is allowed to administer the drug without direct observation by the physician. Refer to Section 6.2.2.1.

[p] For subjects entering the extension study only.

[q] Interim safety evaluations will be performed 5 to 7 days after any change to the subject's PN/IV has been implemented. These measures include 48-hour oral fluid intake, 48-hour urine output, hemoglobin, hematocrit, serum blood urea nitrogen, creatinine, and urine sodium, and may be performed at the investigational site laboratory.

[r] Subjects will record their PN/IV support and teduglutide dosing daily throughout the study. Prior to each clinic and safety visit, subjects will also record all enteral fluid intake and urine output over a 48-hour period.

[s] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare, serious, disabling, socially incapacitating and potentially life-threatening condition which is the leading cause of intestinal failure (Nightingale and Woodward 2006; Pironi et al. 2015). Intestinal failure from SBS results from surgical resection or congenital defects and is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth. Patients with SBS are highly prone to malnutrition, diarrhea, dehydration, and an inability to maintain weight due to the reduced intestinal capacity to absorb macronutrients, water, and electrolytes (Dudrick et al. 1991; Nightingale 1999; Rombeau and Rolandelli 1987; Shanbhogue and Molenaar 1994; Vanderhoof and Langnas 1997; Wilmore et al. 1997). Additional potential consequences of SBS include dehydration, electrolyte disturbances, malabsorption of nutrients, gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhea, diarrhea, small bowel bacterial overgrowth and weight loss (Nightingale and Woodward 2006; O'keefe et al. 2006).

Following resection, intestinal adaptation may occur in adults during the first 1 to 2 years postsurgery. The adaptive response characterized by mucosal hyperplasia, increased mucosal blood flow, improved segmental absorption and increased hepatobiliary secretions (O'keefe et al. 2006). These morphologic and functional changes are coordinated by the release of glucagon-like peptide 2 (GLP-2) from L-type enteroendocrine cells. In response to lumenal nutrients reaching the distal ileum and colon, L-cells secrete GLP-2, which regulates gastrointestinal secretions, motility, and the local production of additional hormones, cytokines, and growth factors.

The clinical care of SBS is mainly supportive and focuses on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, antidiarrheal and antisecretory agents. Despite intestinal adaptation following resection, many SBS develop intestinal failure, characterized by the requirement for chronic use of parenteral nutrition/intravenous (PN/IV) to maintain hydration, electrolyte balance, and/or nutritional needs.

Although PN/IV can meet basic nutrition and fluid requirements, it does not improve the body's ability to absorb nutrients. Parenteral nutrition dependence is associated with shortened life span (Messing et al. 1999; Scolapio et al. 1999), life threatening complications (eg, sepsis, blood clots, or liver damage), as well as reduced quality of life (Delegge et al. 2007; Jackson and Buchman 2005; Jeppesen 2006). The development of parenteral nutrition-associated liver disease (PNALD) predisposes patients to sepsis, increased mortality rates, and the potential to develop irreversible liver damage (Tazuke and Teitelbaum 2009). The American Gastroenterological Association Medical Position Statement on Short Bowel Syndrome recommends that management of PNALD should include reducion of toxic Parenteral nutrition constituents such as phytosterols, a component of soy-based lipid emulsions (American Gastroenterological Association 2003).

The severity of SBS is illustrated by the shortened life-span in patients with moderate to severe disease (Messing et al. 1999). In SBS, survival can be impacted by the underlying condition, by severe clinical manifestations of malabsorption, and treatment-associated life-threatening complications (O'keefe et al. 2006). With current medical management practices, the overall 10 year survival in SBS patients is 52%, and is significantly lower in patients who remain chronically PN/IV -dependent compared to patients who wean off PN/IV (40.7% versus 67%) (Amiot et al. 2013).

In addition, the symptoms of SBS and the inconveniences and complications in relation to PN/IV support may cause potential restrictions in the lifestyle of these patients leading to significant impairment of their quality of life (Jeppesen et al. 1999; Baxter et al. 2006; Winkler and Smith 2014). The impact of SBS and PN/IV on quality of life may be significant with patients, on average, moving their bowels at least 10 times a day, with multiple ostomy bag changes per day, and having a typical output of 2 to 3 liters of watery diarrhea per day. Patients may be on PN/IV 10 to 15 hours a day for up to 7 days a week. Sleep is disrupted and patients typically cannot work.

1.2 Product Background and Clinical Information

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours in healthy subjects and 1.3 hours in adult SBS subjects compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines.

Results of the pivotal study, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/IV support in adult subjects with SBS. In this study the responder rate (defined as at least a 20% reduction from baseline in weekly PN/IV volume at Week 20 and Week 24) was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/IV volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/IV volume reduction, gaining additional days off per week, and achieving complete weaning of PN/IV. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in CL0600-020 and continued treatment in CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/IV support and 18/30 (60.0%) had a reduction in their PN/IV requirement of at least 3 days per week. It was encouraging that efficacy was also observed for subjects who initiated treatment in CL0600-021 (ie, those who received placebo or were not treated in CL0600-020).

After only 6 months of treatment, 37.1% of subjects who had received placebo in CL0600-020 had at least a 20% reduction in weekly PN/IV volume, which increased to 55.2% by Month 24. Two of these subjects completely weaned off of their PN/IV support. In subjects who had not been treated in CL0600-020, 50.0% had at least a 20% reduction in weekly PN/IV volume after 6 months of treatment, which increased to 66.7% by Month 24. One of these subjects completely weaned off of their PN/IV support. Overall, a total of 13 subjects achieved enteral autonomy (independence of PN/IV support), and 25/65 (38.5%) subjects demonstrated a reduction of ≥3 days/week in their PN/IV by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect. The results of this study support the efficacy of long-term treatment with teduglutide in PN/IV -dependent SBS subjects.

Teduglutide (0.05 mg/kg/day) is currently indicated for the treatment of adult patients with SBS. The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (REVESTIVE®) on 30 Aug 2012. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS. A New Drug Application for teduglutide (GATTEX®) was approved by the United States (US) Food and Drug Administration (FDA) on 21 Dec 2012. Teduglutide is currently approved in >30 countries.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the EU and the US. The clinical profile and medical issues related to SBS and PN/IV in Japan are similar to those in the EU and US. Therefore, there is an unmet medical need for Japanese patients with PN/IV -dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

2.2 Study Objectives

The objectives of this clinical study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of teduglutide in Japanese subjects with SBS who are dependent on PN/IV over a 24-week treatment period.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is an open-label, multicenter study, consisting of a conditional PN/IV optimization period, a mandatory PN/IV stabilization period, and a 24-week treatment period. A schematic representation of the study design is presented in Figure 1.

3.1.1 Optimization and Stabilization Periods

If at screening, a subject does not have an optimized PN/IV volume, defined as a 48-hour urine output between 2 and 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/IV volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/IV volume will be documented. For subjects who don't have an optimization period, the "last optimization visit" is the screening visit.

All subjects will then enter the stabilization period, during which the target PN/IV volume will be maintained for at least 4 consecutive weeks (8 weeks maximum). Those subjects who fail to stabilize will not proceed further and will not be included in the treatment period. Appendix 2 provides details of the optimization procedure. Schedules of evaluations for the optimization/stabilization period can be found in Table 1.

3.1.2 Treatment Period

Following the stabilization period, subjects will enter a 24-week dosing period, during which all subjects will receive teduglutide 0.05 mg/kg SC once daily. At each site visit during the treatment phase, efficacy (adjustments to PN/IV) and safety will be monitored.

Subjects will have blood samples taken for teduglutide PK analysis at predose, at 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at the baseline visit (Visit 2). Subjects will also have blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at Week 4 (Visit 5) or Week 12 (Visit 7) of the treatment period.

All subjects who complete the study may participate in a long-term extension study in which eligible subjects will continue to receive teduglutide.

Schedules of evaluations for the Treatment Period can be found in Table 2. Procedures to adjust or reduce PN/IV volume during the Treatment Period is provided in Appendix 3, and should be followed carefully throughout the study.

3.2 Study Duration

Subjects will undergo up to a 7 day screening period, a conditional PN/IV support optimization period (up to 8 weeks), and a stabilization period (up to 8 weeks) prior to receiving teduglutide treatment. Thus, the screening, optimization period, and stabilization period could last up to 17 weeks in total.

Following the optimization and stabilization periods, and appropriate training on study drug administration, the subjects will receive the study drug for 24 weeks.

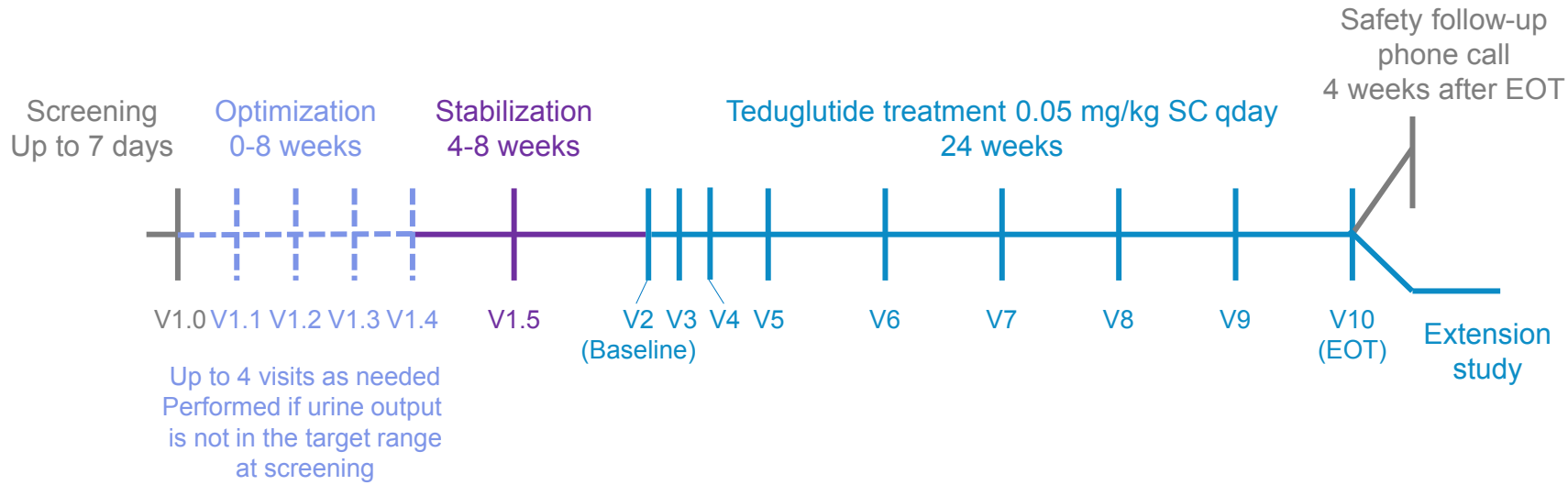
Subjects who do not enroll in the extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks after the last dose of study drug.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact (last safety contact), whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

This study is planned to be conducted in approximately 5 sites in Japan.

Figure 1 Study Schematic



SC=subcutaneous; qday=once daily; EOT=end of treatment

4 STUDY POPULATION

At least 5 Japanese subjects with PN/IV-dependent SBS will be dosed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Ability to voluntarily provide written, signed, and informed consent to participate in the study.
2. Male or female 16 years of age or older at the time of signing informed consent.
3. Intestinal failure due to SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/IV dependence at the time of informed consent.
4. Parenteral nutrition requirement of at least 3 times per week during the week before the screening visit and during the 2 weeks prior to the baseline visit.
5. Stable PN/IV requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment. Stability is defined as:
    a. Actual PN/IV usage is similar to prescribed PN/IV.
    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ±25% of the respective 48-hour I/O volumes at the last optimization visit.
    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours at the last optimization visit, the stabilization visit, and the baseline visit.
6. For subjects with a history of Crohn's disease, clinical remission for at least 12 weeks prior to the baseline visit as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
7. Females of childbearing potential must agree to comply with the contraceptive requirements of the protocol.
8. An understanding, ability, and willingness to fully comply with study procedures and restrictions.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Participation in a clinical study using an experimental drug within 30 days or 5.5 half-lives, whichever is longer, prior to screening, or concurrent participation in any other clinical study.
2. Use of GLP-2 or human growth hormone or analogs of these hormones within the past 6 months.
3. Use of octreotide, GLP-1 analogs, dipeptidyl peptidase-IV inhibitors, or enteral glutamine within 30 days.
4. Previous use of teduglutide.
5. Subjects with active inflammatory bowel disease (IBD) or subjects with IBD who received a change in immunosuppressant therapy (eg, azathioprine, anti-TNFs) within the past 6 months.
6. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, familial adenomatous polyposis, etc.
7. Chronic intestinal pseudo-obstruction or severe dysmotility.
8. Clinically significant intestinal stenosis or obstruction, or evidence of such on upper GI series with small bowel follow-through, within the past 6 months.
9. Major GI surgical intervention, including bowel lengthening procedures, within the past 3 months (insertion of feeding tube or endoscopic procedure is allowed).
10. Unstable cardiac disease, (eg, congestive heart failure, cyanotic disease, or congenital heart disease).
11. Moderate or severe renal impairment, defined as creatinine clearance <50 ml/min.
12. Currently diagnosed with cancer or a history of any cancer except surgically curative skin cancer within the past 5 years.
13. Severe hepatobiliary disease including:
    a. Total bilirubin level ≥2 times the upper limit of normal (ULN).
    b. Aspartate aminotransferase (AST) ≥5 times ULN.
    c. Alanine aminotransferase (ALT) ≥5 times ULN.
14. Active clinically significant pancreatic disease, including clinical signs of pancreatitis associated with elevations in serum amylase or lipase ≥2 times ULN.
15. More than 4 SBS-related or PN/IV-related hospital admissions (eg, central line-associated bloodstream infection, bowel obstruction, severe fluid/electrolyte disturbances) within the past 12 months.
16. Unscheduled hospitalization within 30 days prior to screening.
17. Pregnant or lactating female.
18. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevent completion of the study, or interfere with analysis of the study results.

4.3 Reproductive Potential

To be eligible for treatment with teduglutide, sexually active females of childbearing potential must use a medically acceptable form of contraception. Females of childbearing potential must be advised to use medically acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use medically acceptable contraception if they become sexually active during the period of the study and for 30 days following the last dose of investigational product.

Females of childbearing potential must have a negative urine β-HCG pregnancy test at all visits where it is tested to participate in the study (see Section 8.1.6 for information about reporting a pregnancy).

Females of childbearing potential must agree to use medically acceptable methods of contraception at all times during the study and for 30 days following the last dose of investigational product.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Visit 10 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also receive a follow-up phone call 4 weeks after the last dose of study drug unless the subject has withdrawn consent. Comments (spontaneous or elicited) or complaints pertaining to study drug discontinuation made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks after the last dose of study drug.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF.

If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.
Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by subject
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 14 days prior to the Screening Visit (Visit 1.0) (or pharmacokinetic equivalent of 5 half lives, whichever is longer must be recorded on the appropriate eCRF page. Any diagnostic, surgical or other therapeutic treatments received by a subject within 14 days prior to the Screening Visit (Visit 1.0) will also be recorded on the eCRF.

5.2 Concomitant Treatment

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins),-must be recorded from screening and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, digoxin), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index, are given.

5.2.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.2.2 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the baseline visit (Table 3):

Table 3 Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Baseline Visit
Teduglutide	Any
Glucagon-like peptide-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, dipeptidyl peptidase 4 inhibitors, GLP-1 analogs, and enteral glutamine[a]	30 days

[a] Enteral glutamine refers to L-glutamine powder for oral solution, such as Nutrestore® or Endari™, administered in quantities of 5 g or more per dose or more than 10 g per day. The use of elemental formulas that contain glutamine, such as Elental®, is allowed.

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 5 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product

6.2.1 Allocation of Subjects to Treatment

All subjects will receive teduglutide 0.05 mg/kg once daily.

6.2.2 Dosing

Teduglutide 0.05 mg/kg once daily will be administered daily by subcutaneous (SC) injection into either thigh or arm or 1 of the 4 quadrants of the abdomen (in subjects without a stoma). Each day, the injection site should be rotated. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

Any subject who achieves complete independence from PN/IV support at any time during the treatment period will continue to receive teduglutide treatment.

6.2.2.1 Subject Administration

The first dose of teduglutide will be administered by a study physician.

The processes for training the subject to self-administer teduglutide and for providing oversight of study drug administration are described in the Site Training Guide. Before a subject is permitted to administer teduglutide, the study physician must observe the subject administering the study drug at least twice in compliance with the teduglutide administration checklist. The checklist is included as an appendix to the Site Training Guide.

After the study physician certifies that the subject can safely administer the study drug, subsequent doses may be administered by the subject at home without direct supervision by the physician. However, at selected study visits during the dosing period (refer to Table 2), administration of the study drug must be performed under direct supervision by the study physician, and the teduglutide administration checklist must be completed again.

This ensures that the subject continues to administer the study drug correctly and safely throughout the dosing period.

If at any time a study physician suspects that the subject is no longer capable of administering the study drug safely and accurately, the subject should be re-assessed by a study physician using the teduglutide administration checklist. If the subject is deemed unable to administer the study drug, dosing must be performed by a study physician until the subject is re-trained and proficiency is confirmed using the teduglutide administration checklist.

Eligibility for teduglutide to be administered by a subject will be judged by a study physician using the following criteria. Refer to the checklist included as an appendix to the Site Training Guide.
Criteria to Initiate Teduglutide Administration by the Subject:

- The subject's condition is stable.
- The subject has been sufficiently trained and is able to administer teduglutide in compliance with the checklist.

Criteria to Discontinue Teduglutide Administration by the Subject:

- The subject is unable to administer teduglutide in compliance with the checklist.
- The subject's condition has deteriorated such that the study physician assesses it is inappropriate for the subject to have teduglutide self-administered. In addition to discontinuing administration of teduglutide by the subject, if a subject sustains an adverse drug reaction where the symptoms are considered intolerable, dose interruption or study drug discontinuation should be considered.
- In the study physician's judgment, it is inappropriate for the subject to continue administration of the study drug for any other reason.

6.2.3 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.3 Labeling, Packaging, Storage and Handling

6.3.1 Labeling and Packaging

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2 ^{o}C to 8^{o}C (35.6°F to 46.4°F) until dispensed to a subject. The prefilled sterile water for injection syringes will be stored at a temperature between 2°C to 25°C. Once dispensed/supplied to a subject, the investigational product and ancillary kits can be stored refrigerated up to a controlled room temperature (acceptable range of 2°C to 25^{o}C, or 35.6°F to77°F). The subject will be instructed to keep the investigational product and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the investigational product may be refrigerated. The study drug is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product and ancillary kits are maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures.

Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject if he/she has administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and adverse events (AEs), a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7 STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

Subjects who drop out of the study prior to the final visit should have all early termination procedures done whenever possible.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1.

Subjects may be rescreened no more than twice and only with prior sponsor medical approval. In the event of rescreening, a new subject number will be assigned. Subjects who are rescreened will be reconsented.

7.1.2 Optimization and Stabilization Periods

Subjects who are eligible for the study during the screening visit will proceed to the optimization or stabilization period depending on urine ouput evaluated at the screening visit. Assessments will be performed as outlined in Table 1.

During the optimization period, PN/IV adjustments will be made according to the algorithm in Appendix 2. Optimization visits will occur approximately every 2 weeks (for up to 8 weeks) until the subject achieves an optimized volume of PN/IV indicated by targeted urine output of 1.0 L/day to 2.0 L/day.

Once an optimal tolerated PN/IV volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/IV adjustments should take place during the stabilization period. Subjects who do not achieve stable PN/IV support during this period will not be eligibile to continue in the study.

7.1.3 Treatment Period

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments will be performed as outlined in Table 2.

7.1.4 Follow-up Period

Long-term safety and efficacy data will be obtained from subjects enrolling into the extension study at the Week 24 visit (Visit 10).

Subjects who do not enroll in the treatment extension study or who discontinue prematurely at any time during the study will receive a follow-up phone call 4 weeks (Week 28) after the last dose of study drug.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

7.2.1.1 Demographics and Medical History

Information on medical history and demographic data is to be recorded on the appropriate eCRF.

7.2.1.2 Clinical Assessment of Crohn's Disease Activity

Any subject with a history of Crohn's disease will have their clinical disease status assessed at screening and again at the baseline visit of the treatment period to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation. For all subjects, upper endoscopy and colonoscopy/sigmoidoscopy are required during the stabilization period if they have not been completed within 6 months prior to screening. For subjects with Crohn's disease, it may be necessary to perform upper endoscopy and colonoscopy prior to the baseline visit in subjects with clinical suspicion of active disease, even if these procedures had been completed within 6 months prior to screening. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant stenosis or stricture.

7.2.2 Efficacy Assessments

7.2.2.1 Subject Diaries

Diaries will be distributed to subjects at the time of informed consent and at clinic visits according to the study schedules. Subjects will record their PN/IV support daily throughout the study. Prior to each clinic and safety visit, subjects will also record all enteral fluid intake and urine output over a 48-hour period. Forty-eight hours of output data must be collected during Screening (Visit 1.0) in order to assess the need for the optimization period. Diaries may be completed by the subject or the subject's designee if the subject is physically unable to enter data on his/her own.

7.2.2.2 Prescribed Parenteral Nutrition

All attempts should be made to follow the PN/IV adjustment algorithm specified in the appendices. At the interim visits the PN/IV will be changed if the previous adjustment was not tolerated. Physician-directed changes in a subject's PN/IV volume must be followed by an interim safety visit 5 to 7 days after the adjustment has been implemented. If the subject has a AE that prevents him/her from adhering to study requirements, including the PN/IV adjustment algorithms, the subject may be withdrawn from the study.

The prescribed PN/IV weekly total volume and days per week will be recorded. Changes in parenteral support prescription that reflect changes in the subject's intestinal absorption are recorded.

Temporary adjustments to parenteral nutrition or IV fluids that last less than 72 hours may be recorded at the discretion of the investigator, but all parenteral support prescriptions that last more than 72 hours must be recorded. The PN/IV constituents are at the discretion of the physician; the identities of parenteral support constituents do not recorded.

7.2.2.3 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass. If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

7.2.3 Safety Assessments

7.2.3.1 Laboratory Evaluations

Safety laboratory tests are to be performed at site visits with results processed by a central laboratory. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/IV with lipids, within 3 hours of the clinic visit to permit consistent assessment.

Safety lab tests performed at interim safety visits after PN/IV adjustments will consist of hemoglobin, hematocrit, serum blood urea nitrogen, creatinine, and urine sodium, and may be performed at the investigational site laboratory.

The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved. New clinically significant lab tests results should be reported as AEs (see Section 8).

Tests include the following (Table 4):

Table 4 List of Laboratory Tests

Hematology:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Urinalysis:
- Blood
- Glucose
- Leucocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity
- Urine Sodium

Pregnancy tests (females of childbearing potential):
- Urine β-HCG

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bilirubin (total, direct and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- Citrulline (plasma)
- C-reactive protein
- Creatinine
- Creatinine clearance
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides
- Uric acid

7.2.3.2 Antibodies to Teduglutide

Blood samples for analyses of antibodies to teduglutide will be collected. Blood sample for antibody testing is to be collected at study site prior to first investigational product administration. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing.

Anti-teduglutide antibody testing is a 3-step process. If a sample tests negative, no further testing is done. If a sample tests positive, further testing is done for teduglutide-specific antibodies. If teduglutide-specific antibodies are detected, the test is deemed "positive" and the titer derived, and neutralizing antibody testing is done. Subjects who test positive for teduglutide-specific antibodies may remain on treatment and blood samples for antibody testing will continue to be collected as per protocol schedule (Table 2).

Blood samples for anti-teduglutide antibody testing may be stored and then analyzed together periodically to streamline the testing procedure. However, if an investigator suspects that a subject is experiencing an AE that may be associated with the development of anti-drug antibodies, relevant samples will be tested for the presence of anti-drug antibodies upon request.

7.2.3.3 Physical Examinations

Physical examinations will be performed according to the study schedules to assess the subject's physical status. New clinically significant abnormalities that are detected or diagnosed after study evaluations have begun (after signing of the informed consent) should be recorded on the appropriate AE page of the eCRF. Complete physical exams are required at screening, baseline, and Week 24/ET. Focused physical exams may be performed at all other visits.

7.2.3.4 Vital Signs, Body Weight, and Height

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse rate, and body temperature (°C). Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Subjects should be weighed on the same scale at each study visit. Height will be measured at the screening visit.

7.2.3.5 Electrocardiograms

A 12-lead ECG will be performed at the study center after the subject has been resting for at least 5 minutes. Results will include general findings (normal, abnormal-not clinically significant, abnormal-clinically significant). If abnormal, the nature of the abnormality will be collected. Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the eCRF.

Electrocardiogram tracings should be printed, signed and dated by the investigator, and kept with the subject's source documents.

7.2.3.6 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below.

Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization if not completed within 6 months prior to screening) in subjects with any colon remnant including a rectal stump. This will be repeated at Visit 10 (or early termination). The date and result of colonoscopy are to be recorded in the eCRF.

Abdominal Ultrasound

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented).

Upper GI Contrast Series with Small Bowel Follow-through

Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy (EGD) will be performed on all subjects prior to teduglutide exposure (during the stabilization period if not completed within 6 months prior to screening). Esophagogastroduodenoscopy will be repeated at Week 24/Visit 10 (or ET) for subjects with any of the following risk factors:

- Age 40 or over at Week 24/Visit 10/ET
- History of H pylori gastritis
- History of atrophic gastritis
- History of intestinal metaplasia or dysplasia in the stomach

For subjects that do not have any of the above risk factors, EGD may be repeated at Visit 10/ET at the discretion of the investigator. The dates and results of all EGDs are to be recorded in the eCRF.

48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to study visits as required. The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring I/O, and to record these measurements into the diary. During the 48-hour measurements, the subject should maintain their usual oral fluid intake. 48-hour urine output measurements will also be collected prior to all interim safety visits.

7.2.4 Pharmacokinetic Assessments

The first dose of teduglutide will be administered by the study physician at the baseline visit (Visit 2). At this visit, subjects will have blood samples taken for teduglutide PK analysis:

- 0-hour (predose) draw: any time prior to the dose
- 15 minutes postdose: ±5 minutes
- 30 minutes postdose: ±5 minutes
- 1 hour postdose: ±10 minutes
- 2 hours postdose: ±10 minutes
- 3 hours postdose: ±10 minutes
- 4 hours postdose: ±30 minutes
- 6 hours postdose: ±30 minutes
- 8 hours postdose: ±30 minutes
- 10 hours postdose: ±30 minutes
- 12 hours postdose: ±30 minutes

Subjects also will have blood samples taken for teduglutide PK analysis at Week 4 (Visit 5) or Week 12 (Visit 7):

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose
- 1 hour postdose: ±10 minutes
- 2 hours postdose: ±10 minutes

Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) and the person administering the injection (physician or subject) must be recorded in the eCRF.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation [ICH] Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until until the defined follow-up period stated in Section 7.1.4. This includes events occurring during screening, optimization, and stabilization phases of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

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

Moderate: A type of AE that is usually alleviated with 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 subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related." The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to investigational product that are not resolved at EOT will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign can represent an AE if the change is clinically relevant or if, during treatment with investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the EOT with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values or vital signs which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant or female partner of male study participant must be reported within 24 hours to IQVIA Services Japan K.K. using the Shire Investigational and Marketed Products Pregnancy Report Form. In the event a subject becomes pregnant during the study, teduglutide administration must be immediately and permanently discontinued.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant using the Shire Investigational and Marketed Products Pregnancy Report Form. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification, and approximately 30 calendar days and 1 year postpartum, and report to IQVIA Services Japan K.K.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered serious adverse events (SAEs) and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events and Non-serious AEs as Required by Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that complications of the pregnancy meet serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor using SAE reporting form whether or not they result in an AE/SAE as described in Section 8.2, but such events are only recorded in the eCRF if they result in an AE. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).

- Overdose – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.

- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator's brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the sponsor or designee within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the sponsor or designee within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). The investigator must fax or e-mail the completed form to IQVIA Services Japan K.K. Applicable fax numbers and email addresses are found in the Emergency Contact Information.

8.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” 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 which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for preexisting conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent is obtained until the defined follow-up period stated in Section 7.1.4, and must be reported to the sponsor or designee within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the sponsor or designee within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or designee is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs.

In addition, the sponsor and/or designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the teduglutide program. The investigator is responsible for notifying the local Institutional Review Board (IRB) or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting for this study include the following:

- Growth of preexisting polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor or designee must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill seriousness criterion.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. It is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The data collected in this study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis

Interim analyses may be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.

9.5 Sample Size Calculation and Power Considerations

The sample size of the SHP633-306 study is based on patient prevalence and study design elements; no statistical estimation was involved. Possible medical institutes for SBS studies are limited, given the rarity of the disease and the very limited number of patients with SBS (<1000) in Japan. The applicant considers that 5 treated subjects in SHP633-306 should provide sufficient basic information concerning the efficacy, safety and tolerability as well as PK of teduglutide in the Japanese study population.

9.6 Study Population

The intent-to-treat (ITT) population will include all subjects who are deemed eligible for teduglutide treatment at the baseline visit (Visit 2).

The per protocol population will include all subjects in the ITT population who complete the Treatment Period without any major protocol violations that could potentially affect the efficacy conclusions of the study.

The safety population will include all subjects in the ITT population who receive at least 1 dose of study drug.

The pharmacokinetic population will include all subjects who receive at least 1 dose of teduglutide and have at least 1 evaluable post-dose pharmacokinetic concentration value.

9.7 Efficacy Analyses

The following efficacy endpoints will be analyzed:

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at end of treatment (EOT).
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who are able to completely wean off of PN/IV support.

The absolute and relative change in weekly PN/IV volume, days per week of PN/IV support, and plasma citrulline, from baseline to each scheduled visit, as well as at EOT, will be summarized using descriptive statistics.

The number and percentage of subjects who demonstrate a response at Week 20 and again at Week 24 will be summarized. A response is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume.

The number and percentage of subjects who demonstrate at least a 20% reduction from baseline in weekly PN/IV volume at each visit will also be summarized.

The number and percentage of subjects who completely wean off PN/IV support by Week 24/EOT will be summarized. A subject will be considered to have achieved independence from PN/IV (completely weaned off PN/IV) if the investigator prescribes no PN/IV at Week 24/EOT and there is no use of PN/IV recorded in the subject diary during the 2 weeks prior to the last dosing visit.

For efficacy analysis, the ITT population will be the primary analysis population; the per-protocol population will be used for secondary/sensitivity analysis.

9.8 Safety Analyses

The safety endpoints include AEs, 12-lead ECG, vital signs, laboratory safety data, antibodies to teduglutide, and 48-hour urine output, body weight, BMI and gastrointestinal-specific tests.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as AEs that started or worsened on or after the date and time of the first dose of study dose. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity, relationship to treatment, and for AEs leading to discontinuation, and death. In addition, SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, body mass index, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each time point.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

The safety population will be the analysis population for all the safety data analysis.

9.9 Pharmacokinetics Analyses

Teduglutide plasma concentrations will be summarized using the PK population with descriptive statistics (number, mean and standard deviation, minimum, median, and maximum) at nominal time points.

The following parameters will be derived: area under the plasma concentration–time curve from zero to the last measurable concentration (AUC_{0-t}); maximum plasma concentration (C_{max}); time to C_{max} (t_{max}); terminal-phase half-life ($t_{1/2}$); apparent clearance (CL/F); and apparent volume of distribution (V/F).

Pharmacokinetic parameters will be estimated using non-compartmental analysis as appropriate and summarized using descriptive statistics (number, mean, standard deviation, geometric mean, and CV%, minimum, median, and maximum).

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied, as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designe and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator. The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, original clinical laboratory reports, and imaging reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, European Medicines Agency [EMA], UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Original signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	23 Jan 2018	Global
Amendment 1	27 Sep 2018	Global

APPENDIX 2 PARENTERAL NUTRITION/INTRAVENOUS OPTIMIZATION

After signing the ICF, the investigator will determine if the subject's PN/IV volume produces an appropriate urine output target of 1.0 L/day to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/IV volume should be adjusted appropriately to reach the targeted urine output of between 1.0 L/day to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- <1.0 L/day, then PN/IV should be increased.
- >2.0 L/day, then PN/IV should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/IV volume should be documented. Keep in mind the following:

- During optimization, total weekly PN/IV volume should be adjusted in increments or decrements of 10-30% of the screening volume.
- Parenteral nutrition constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/IV volume:

1. **Screening and Optimization Visits:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.
2. **Interim Safety Evaluations:** If any PN/IV adjustments are made, the clinical effect and the health status of the subject will be assessed 5 to 7 days after the adjustment is implemented. Laboratory safety samples should be evaluated following a PN/IV adjustment (see Table A3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/IV should be increased if the decrease was not tolerated. No further reductions to PN/IV volume are made at the interim safety visit.
3. Maintain the PN/IV level until the next scheduled optimization visit.
4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/IV indicated by targeted urine output of 1.0 L/day to 2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/IV after 8 weeks, consult the sponsor's Medical Monitor.
5. **Parenteral Nutrition Stabilization:** Once an optimal tolerated PN/IV volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/IV adjustments should take place during this time period.

APPENDIX 3 PARENTERAL NUTRITION/INTRAVEOUS ADJUSTMENT DURING TREATMENT PERIOD

Points to keep in mind when adjusting PN/IV volume during dosing:

- There will be no PN/IV reduction attempts at baseline and Week 1.
- Parenteral nutrition/intravenous reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/IV will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- Parenteral nutrition/intraveous adjustments are targeted to be at least 10% but no more than 30% of **baseline** PN/IV level.
- Adjustments should be based on the actual PN/IV volume the subject infuses. Subjects should remain compliant with the PN/IV prescription during the length of the study.
- Parenteral nutrition/intravenous constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/IV adjustments are in Table A1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/IV volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2).
- Subjects who fail to maintain a PN/IV reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the sponsor's Medical Monitor.

Table A1 Parenteral Nutrition Adjustments at Scheduled Clinic Visits based on 48-hour Urinary Output

Urine Output	Parenteral Nutrition/Intravenous Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/IV by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2), increase PN/IV If not, maintain PN/IV.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/IV
At least a 10% increase over Baseline	Reduce PN/IV by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

L=liter; PN/IV=parenteral nutrition/intravenous (volume)

Table A2 Targeted Criteria for Hydration and Nourishment at all Clinic Visits and Interim Safety Visits

Hydration Assessment	Hydration Adequate
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/L or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal
Note: In combination with Table A1, any one of the above criteria determines dehydration.

Steps for adjusting PN/IV volume:

1. **DOSING WEEKS 2, 4, 8, 12, 16, and 20:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. Blood and urine samples will be collected to evaluate hydration and nutrition (see Table A2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **Parenteral Nutrition Changes:** Review Table A1 and Table A2 to take appropriate action.

3. **Interim Safety Evaluations:** If any PN/IV adjustments are made, the clinical effect and the health status of the subject will be assessed 5 to 7 days after the adjustment is implemented. Laboratory safety samples should be evaluated following a PN/IV adjustment (see Table A3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/IV should be increased if the decrease was not tolerated. No further reductions to PN/IV volume are made at the interim safety visit.

Table A3 Assessment of Tolerance of Pareneteral Nutrition/Intravenous Adjustments at Interim Safety Visits

Urine Output, Hydration and Nutrition	Parenteral Nutrition/Intravenous Action
Output less than Baseline	Increase PN/IV to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2)	Increase PN/IV to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2)	If possible, maintain PN/IV volume and increase nutrition. If not, increase PN/IV to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2)	Maintain PN/IV

L=liter; PN/IV=parenteral nutrition/intravenous (volume)
[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/IV is allowed.

4. Maintain the adjusted PN/IV level until the next scheduled visit.
5. Repeat steps 1 through 4 at each study visit as indicated per protocol.
    a. It is preferred that when the total weekly PN/IV needs have been reduced to a level that safely allows for a day or days off PN/IV, the physician should consider instituting a day(s) off PN/IV.
    b. If the total weekly PN/IV is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/IV completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.
    c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra IV fluid that will be included in the weekly PN/IV volume total.