CLINICAL STUDY PROTOCOL

NCT Number: NCT03268811

Study Title: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Subjects with Short Bowel Syndrome Who Completed SHP633-302

Study Number: SHP633-305

Protocol Version and Date:

Amendment 4: 06 Nov 2020

Clinical Trial Protocol: SHP633-305

TITLE:	A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Subjects with Short Bowel Syndrome Who Completed SHP633-302
NUMBER:	SHP633-305
PHASE:	3 Extension
DRUG:	Teduglutide
IND:	058213
OTHER NO.:	NA
INDICATION:	Short bowel syndrome
SPONSOR:	Shire Human Genetic Therapies, Inc. Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-Chrome, Chuo-ku, Osaka-Shi Osaka Japan
PROTOCOL HISTORY:	Amendment 4: 06 Nov 2020 Amendment 3: 20 Jul 2018 Amendment 2: 24 Jan 2018 Amendment 1: 26 May 2017 Original Protocol: 22 July 2016

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** 12-Nov-2020 | 00:13 JST
[redacted], MD PhD [redacted], Clinical Science	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-305.

Title: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Subjects with Short Bowel Syndrome Who Completed SHP633-302

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 Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **06 Nov 2020**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Sponsor Name Changed to include both Shire Human Genetic Therapies, Inc. (USA) and Takeda Pharmaceutical Company Limited The Sponsor name was updated to align more accurately with legal entities responsible for study.		Signature Page
Changed name of sponsor protocol signatory to [redacted], MD, PhD.		Signature Page
Transferred back the role of in-country clinical caretaker from IQVIA Services Japan K.K to the sponsor. The sponsor is now responsible for notifying the relevant regulatory authorities of related, unexpected serious adverse events (SAEs).		Emergency Contact Information Section 8.2.7
Changed name of Shire medical monitor to [redacted], MD, PhD, MPH. (Protocol Administrative Amendment dated 27 Mar 2020)		Emergency Contact Information
Changed the fax number for SAE reporting. The priority should be given to reporting SAEs via email, and if not possible, to reporting by fax. (Clarification Memo dated 04 Feb 2019)		Emergency Contact Information
Updated the end of the planned study period to December 2021.		Synopsis
Expanded the timing to perform a colonoscopy/sigmoidoscopy at the end of a teduglutide treatment cycle (CxW24). Subjects who received 2 treatment cycles (48 weeks of teduglutide exposure) will undergo a colonoscopy/sigmoidoscopy before the next cycle of teduglutide treatment. Colonoscopy/sigmoidoscopy performed after the Visit CxW24 (±4 days) window and before the next cycle of teduglutide treatment will **not** be considered a protocol deviation. All other visit procedures must adhere to the (±4 days) visit window. (Clarification Memos dated 08 Jun 2020 and 11 Jun 2020)		Table 3, Section 7.2.9.2
Specified that the SHP633-305 study will continue as a post-marketing study if teduglutide is approved for marketing.		Section 3.2
Clarified that the output diaries should be recorded for subjects during a teduglutide treatment period within 1 week of implementing a change in the PS prescription.		Section 7.2.10.2
Added a new section entitled “Changes to Study Procedures Due to a Pandemic”. The purpose of these changes is to maintain the subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic.		Section 7.3
Clarified the definition of an overdose as the administration of the investigational product at a dose or frequency greater than 0.05 mg/kg subcutaneous once daily. An overdose occurs if any of the following criteria are met: • More than 0.05 mg/kg is given at any one time • Consecutive doses are spaced less than 12 hours apart		Section 8.1.7

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **06 Nov 2020**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
• Any more than 0.05 mg/kg in one day (a day is defined as beginning at 12:00 AM and ending at 11:59 PM) (Clarification Memo dated 12 Jun 2019)		
Changed the data monitoring committee meeting frequency. The DMC members will review the data approximately every 6 months (previously 3 months) during the study treatment periods (date of the first subject's first dose to date of the last subject's last dose). (Protocol Administrative Amendment dated 02 Sep 2020)		Section 9.4
Updated the contact information for the monitoring personnel within Japan with the Takeda Pharmaceutical Company Limited address, removed the name and contact information for [redacted] who is no longer on the program, and updated [redacted] phone number.		Appendix 4

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 AEs as Required by Protocol within 24 hours to IQVIA Services Japan K.K. using the details below.

Pharmacovigilance SAE Reporting:

Email (preferred method): [redacted]

or

FAX: [redacted] (Japan domestic line only)

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 between 8:00 to 20:00 US Eastern Standard Time, the investigator may contact the Shire medical monitor:

[redacted], MD, PhD, MPH
[redacted]
Shire Medical Monitor
Mobile: [redacted]
Email: [redacted]

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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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
COVID-19	coronavirus disease 2019
CTCAE	common terminology criteria for adverse events
DILI	drug-induced liver injury
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase 4
EC	ethics committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLP-2	glucagon-like peptide 2
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor-1
INR	international normalized ratio
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NTT	no-teduglutide treatment
PDA	patent ductus arteriosus
PS	parenteral support
PT/INR	prothrombin time/international normalized ratio
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2}$	elimination half-life

ULN	upper limit of normal
US(A)	United States

STUDY SYNOPSIS

Protocol number: SHP633-305 **Drug:** Teduglutide

Title of the study: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Subjects with Short Bowel Syndrome Who Completed SHP633-302

Number of subjects (total and for each treatment arm):

Approximately 7 subjects who completed Study SHP633-302 are expected to enroll in this extension study. This study will enroll up to as many subjects who complete Study SHP633-302.

Investigator(s): Multicenter study

Site(s) and Region(s):

Approximately 5 investigational sites in Japan will participate in this extension study.

Study period (planned): **Clinical phase:** 3 Extension

August 2017 – Dec 2021

Objectives:

Primary: To evaluate the long-term safety and tolerability of teduglutide treatment in Japanese pediatric subjects with short bowel syndrome (SBS) who completed Study SHP633-302.

Secondary: To evaluate long-term efficacy of teduglutide treatment in Japanese pediatric subjects with SBS who completed Study SHP633-302.

Rationale:

This extension study is needed to evaluate long-term safety and efficacy of teduglutide treatment in Japanese children with SBS. It also provides the opportunity to offer additional teduglutide treatment to subjects who completed Study SHP633-302.

Investigational product, dose, and mode of administration:

Teduglutide 0.05 mg/kg subcutaneous (SC) once daily injection will be administered to eligible pediatric subjects who previously received teduglutide 0.05 mg/kg once daily in Study SHP633-302. There is no active comparator or reference product.

Methodology:

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in Japanese pediatric subjects who completed Study SHP633-302 (core study). The study population will include 2 cohorts based on age of subjects at the time of entry in the core study: infants 4-<12 months corrected gestational age and children 1-15 years of age.

Once informed consent (and if applicable, informed assent) has been obtained, demographics, updates to medical history and short bowel syndrome history will be obtained at screening. The first visit after screening (either a no-teduglutide treatment [NTT] visit or a pretreatment visit), must occur within 12 weeks of screening. Subjects not receiving teduglutide treatment (ie, in an NTT period), will be seen approximately every 12 weeks to collect safety and parenteral support (PS) requirements. At any point after screening, including during an NTT period, subjects who meet at least one teduglutide treatment inclusion criteria may proceed immediately to a pretreatment visit if the investigator and the subject (and/or parent/guardian, as applicable), agree to proceed with teduglutide therapy.

At the pretreatment visit, eligibility for teduglutide treatment is confirmed. Subjects who meet *at least one* of the teduglutide treatment inclusion criteria and *none* of the teduglutide treatment exclusion criteria will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up period, during which no teduglutide is administered. During the 28-week cycle, clinic visits will occur at Day 1 and Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after each adjustment in PS during the teduglutide treatment period (between Weeks 1-24), and weekly during the follow-up period (between Weeks 24 and 28). Safety and PS requirements will be evaluated at every visit. A subject may "escape" the follow-up period between cycle Week 24 and Week 28 and proceed immediately to another

pretreatment visit if the subject meets at least one follow-up period escape criteria.
Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit (or another pretreatment visit, if needed) within 12 weeks. A subject may participate in multiple treatment cycles and NTT periods depending on his or her clinical trajectory.

At all site and phone visits, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithm (developed with SBS expert input and provided in Appendix 2 and Appendix 3 of the protocol) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines and weaning algorithms, however, is not considered a protocol deviation.

Study Design Flow Chart

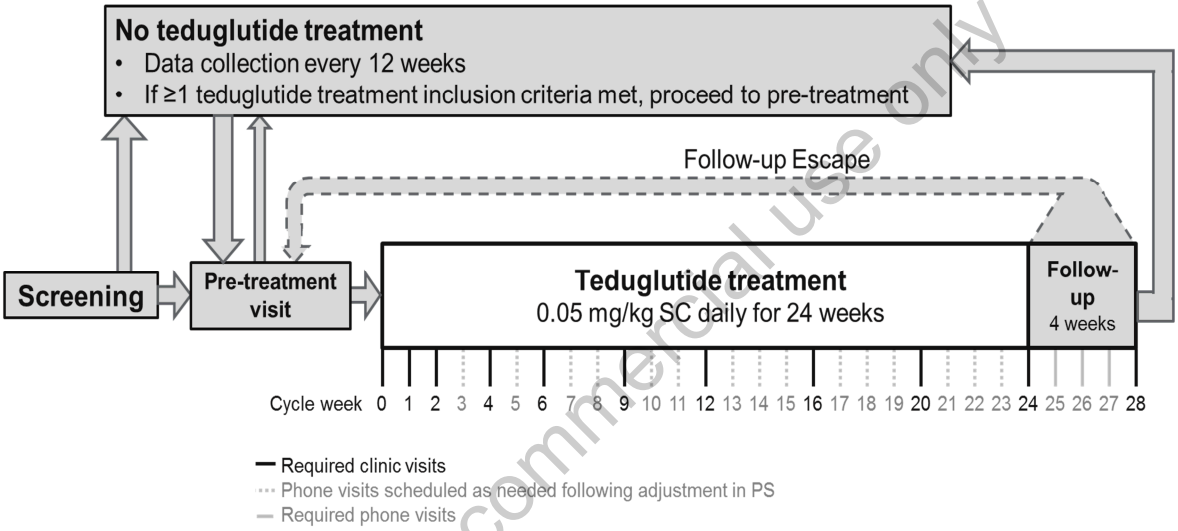


Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Subjects eligible for teduglutide will enter a 28-week treatment cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at Day 1 (Week 0) and Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between Weeks 2 and 24 (**dashed grey lines**). At Week 24, subjects enter a 4-week follow-up period, where teduglutide is not received, during which phone visits will be performed weekly (**solid grey lines**). If at least 1 escape criterion is met at Week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.
PS=parenteral support; SC=subcutaneous

Study Inclusion Criteria:

The subject will be considered eligible for the study if they meet *all* of the study inclusion criteria. Teduglutide treatment eligibility does not impact study eligibility.

1. Informed consent by a parent or guardian prior to any study-related procedures.
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures.
3. Subject completed Study SHP633-302.
4. Subject (and/or parent/guardian) understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Study Exclusion Criteria: There are no exclusion criteria for this study.

Teduglutide Eligibility Criteria: Subjects are eligible for teduglutide treatment if *at least 1* of the teduglutide treatment inclusion criteria, and *none* of the teduglutide treatment exclusion criteria, are met. In addition, the investigator and the subject (and/or parent/guardian, as applicable) must agree to proceed with treatment.

***Teduglutide Treatment Inclusion Criteria*:**

1. Increasing PS requirements following teduglutide discontinuation.
2. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
3. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
4. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
5. Severe diarrhea related to teduglutide discontinuation.

Teduglutide Treatment Exclusion Criteria:

1. Body weight <5 kg at the pretreatment visit.
2. Unresected gastrointestinal (GI) polyp, known polyposis condition, premalignant change, or malignancy, in the GI tract.
3. History of cancer in the previous 5 years except surgically curative skin cancers.
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle.
6. Clinically significant intestinal stricture or obstruction.
7. Clinically significant, active or recurrent pancreatic or biliary disease.
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pretreatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 ×ULN
    c. Alanine aminotransferase (ALT) ≥7 ×ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pretreatment visit.
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation.

11. Participation in a clinical study using an experimental drug (other than glutamine or intravenous lipid emulsions) within 3 months or 5.5 half-lives of experimental drug administration, whichever is longer, prior to the pretreatment visit and for the duration of the 28-week cycle.
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pretreatment visit.
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
15. Known history of alcohol or other substance abuse within 1 year prior to the pretreatment visit.
16. Pregnant or lactating female subjects.
17. Sexually active female subjects of childbearing potential unwilling to use approved contraception throughout the study period and for 30 days following the last dose of investigational product.
18. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Follow-up Period Escape Criteria: At the discretion of the investigator, the follow-up period may be interrupted or omitted and the subject may proceed directly to the pretreatment visit, if *at least 1* of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.
5. The subject escaped during the follow-up period of a previous teduglutide treatment cycle within SHP633-305.

Maximum duration of subject involvement in the study:

A subject will be considered enrolled in the study once the subject (and/or parent/guardian, as applicable) has provided signed consent/assent, and meets all of the study inclusion criteria. Subjects may participate in multiple NTT periods and/or multiple 28-week treatment cycles. The study will continue until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued. The subject's maximum duration of participation is expected to be approximately 3 years. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the end of study (EOS) visit.

- **Planned duration of no teduglutide treatment periods**: variable, depending on disease course
- **Planned duration of the teduglutide pretreatment visit:** 1 to 21 days
- **Planned teduglutide treatment cycle duration**: 28 weeks. Each cycle consists of 24 weeks of teduglutide treatment followed by a 4-week follow-up period

Subject Population:

The **safety population** will consist of all enrolled subjects. The safety population will be used for both safety and efficacy analysis.

Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (Week 24 or end of treatment [EOT]), and at each study visit, relative to the baseline of the core study (SHP633-302). The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, blood pressure
- Laboratory safety data (ie, biochemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing, including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and body mass index

Statistical Methods:

Data will be analyzed and presented by subject cohorts according to the subjects' age at the time of entry in the core study: infants 4-<12 months corrected gestational age and children 1-15 years of age.

Efficacy Analysis

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages. The derivations of the weekly PS volume will be described in the study statistical analysis plan in detail.

Safety Analysis

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. Adverse events will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Sample Size Justification

As this is an extension study, the maximum number of subjects will be determined by completion of Study SHP633-302.

STUDY SCHEDULES

Table 1 Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
		EOS/ET
Visit Type	**Site**	**Site**
Informed consent/assent[a]	X	
Study eligibility	X	
Demographics, medical history[b], SBS history[c]	X	
Dispense intake and output diaries	X	
Evaluate teduglutide treatment inclusion criteria[d]	X	
Adverse events	X	X
Concomitant medications and procedures	X	X
Physical examination and vital signs, including weight		X
Height and head circumference[e]		X
Review intake and output diaries[f]		X
Record PS prescriptions, and adjust as needed[g]	X	X
Safety laboratory tests[h]		X
Antibodies to teduglutide		X
Fecal occult blood testing[i]		(X)
Colonoscopy/sigmoidoscopy[j]		(X)
Pregnancy testing[k]		(X)

EOS=end of study; EN=enteral nutrition; ET=early termination; GI=gastrointestinal; PS=parenteral support; SBS=short bowel syndrome

[a] In general, subjects (and/or parent or guardian, as applicable) should sign consent (and informed assent, if applicable) to participate in Study SHP633-305 within 7 days after completion of Study SHP633-302.

[b] Updates to the medical history will be collected, consisting of adverse events that were ongoing at the time of completion of SHP633-302, and events that occurred during the period between completion of SHP633-302 and informed consent/assent to SHP-633-305.

[c] If the subject has any changes to the SBS history that had been collected at the baseline of the SHP633-302, then the updated SBS history will be collected.

[d] If one or more teduglutide treatment eligibility criteria are satisfied, the first pretreatment visit assessments may begin immediately and can be combined with the SHP633-302 Week 28 (EOS) assessments if performed within 7 days of the SHP633-302 EOS visit.

[e] Head circumference will be measured in subjects 36 months of age and younger.

[f] The intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of PS and EN stability before the EOS/ET visit.

[g] Parenteral support prescription will be collected at the screening visit. PS adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2 and Appendix 3.

[h] Safety laboratory assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety lab tests, but lack of urinalysis will not constitute a protocol deviation.

[i] Fecal occult blood test should be performed on an annual basis, approximately every 48-60 weeks at a minimum.

[j] The need for colonoscopy/sigmoidoscopy in response to a positive fecal occult blood test during a no-teduglutide treatment period is at the discretion of the investigator, but all subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of investigational product exposure).

[k] Pregnancy testing is required for female subjects of childbearing potential at an ET visit if the subject has not had a pregnancy test at least 30 days after investigational product discontinuation.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

Table 2 Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	**NTx**
Visit Type	**Site**
Visit Frequency	**Every 12 weeks**
Window (days)[a]	**±7**
Dispense intake and output diaries	X
Evaluate teduglutide treatment inclusion criteria[b]	X
Adverse events	X
Concomitant medications and procedures	X
Physical examination and vital signs, including weight	X
Height and head circumference[c]	X
Review intake and output diaries[d]	X
Record PS prescriptions, and adjust as needed[e]	X
Safety laboratory tests[f]	X
Antibodies to teduglutide[g]	(X)
Fecal occult blood testing[h]	Annually
Colonoscopy/sigmoidoscopy[i]	(X)
Serum sample[j]	Every 24 weeks

EN=enteral nutrition; GI=gastrointestinal; NTx=no treatment; PS=parenteral support

[a] Window is relative to the first NTx visit in the current no-teduglutide treatment period.

[b] Subjects who meet at least one teduglutide treatment inclusion criteria, may proceed to the pretreatment visit if the investigator and the subject (and/or parent/guardian, as applicable) agree to proceed with teduglutide therapy.

[c] Head circumference will be measured in subjects 36 months of age and younger.

[d] The intake diary should be completed daily for a minimum of 2 weeks prior to each NTx visit. The output diary should be completed daily over a 48-hour period of PS and EN stability before each NTx visit.

[e] PS adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2 and Appendix 3.

[f] Safety laboratory assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety lab tests, but lack of urinalysis will not constitute a protocol deviation.

[g] Subjects who have been treated previously and test positive for antibodies specific to teduglutide should have follow-up samples collected every 12 weeks until a negative result is obtained or the study ends.

[h] Fecal occult blood test should be performed on an annual basis, approximately every 48-60 weeks at a minimum.

[i] The need for colonoscopy/sigmoidoscopy in response to a positive fecal occult blood testing during a no-teduglutide treatment period is at the discretion of the investigator, but all subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of investigational product exposure).

[j] Lack of collection of serum samples will not constitute a protocol deviation. Saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

Table 3 Schedule of Events for Subjects While Receiving Teduglutide

Period	**Pretreatment**	**Teduglutide Treatment**															**Follow-up**	
Visit Number	**Px**[a]	**Cx D1**	**Cx W1**	**Cx W2**	Phone visit is required approximately 1 week after PS adjustment	**Cx W4**	Phone visit is required approximately 1 week after PS adjustment	**Cx W6**	Phone visit is required approximately 1 week after PS adjustment	**Cx W9**	Phone visit is required approximately 1 week after PS adjustment	**Cx W12**	Phone visit is required approximately 1 week after PS adjustment	**Cx W16**	Phone visit is required approximately 1 week after PS adjustment	**Cx W20**	Phone visit is required approximately 1 week after PS adjustment	**Cx W24 (EOT)**	**CxW25 CxW26 CxW27**	**CxW28**[c]
Visit Type	**Site**	**Site**	**Site**	**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**	**Phone**[b]	**Site**
Cycle Day	**-21 to 0**	**1**	**8**	**15**		**29**		**43**		**64**		**85**		**113**		**141**		**169**	**176 183 190**	**197**
Window (days)[d]			**±2**	**±2**		**±2**		**±2**		**±4**		**±4**		**±4**		**±4**		**±4**	**±2**	**±2**
Evaluate teduglutide eligibility (inclusion and exclusion) criteria	X	X[e]																		
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X		X		X		X
Adverse events	X	X	X	X		X		X		X		X		X		X		X	X	X
Concomitant medications and procedures	X	X	X	X		X		X		X		X		X		X		X	X	X
Physical examination and vital signs, including weight	X	X	X	X		X		X		X		X		X		X		X		X
Height and head circumference[f]	X	X										X						X		
Review intake and output diaries[g]	X	X	X	X		X		X		X		X		X		X		X	X	X
Record PS Rx, and adjust as needed[h]	X	X	X	X		X		X		X		X		X		X		X	X	X
Safety laboratory tests[i]	X[i]	X	X	X		X		X		X		X		X		X		X	(X)	X
Antibodies to teduglutide[j]		X										X						X		X
Fecal occult blood testing	X											X						X		
Colonoscopy/ sigmoidoscopy[k]	(X)											(X)						(X)		
Pregnancy testing[l]	X	X				X				X		X		X		X		X		X
Serum sample[m]	X																	X		

Table 3 Schedule of Events for Subjects While Receiving Teduglutide

Period	Pretreatment	Teduglutide Treatment														Follow-up	
Visit Number	Px[a]	Cx D1	Cx W1	Cx W2	Phone call to adjust approximately 1 week after PS adjustment	Cx W4	Phone call to adjust approximately 1 week after PS adjustment	Cx W6	Phone call to adjust approximately 1 week after PS adjustment	Cx W9	Phone call to adjust approximately 1 week after PS adjustment	Cx W12	Phone call to adjust approximately 1 week after PS adjustment	Cx W16	Phone call to adjust approximately 1 week after PS adjustment	Cx W20	Phone call to adjust approximately 1 week after PS adjustment	Cx W24 (EOT)	CxW25 CxW26 CxW27	CxW28[c]
Visit Type	Site	Site	Site	Site		Site		Site		Site		Site		Site		Site		Site	Phone[b]	Site
Cycle Day	-21 to 0	1	8	15		29		43		64		85		113		141		169	176 183 190	197
Window (days)[d]			±2	±2		±2		±2		±4		±4		±4		±4		±4	±2	±2
Evaluate escape criteria[n]																		X[o]	X	X
Review study drug administration diary[p]			X	X		X		X		X		X		X		X		X		
Dispense investigational product and study drug administration diary		X	X	X		X		X		X		X		X		X				
Confirm administration proficiency		X[q]																		

Cx=cycle x; D1=Day 1 of teduglutide treatment cycle; EN=enteral nutrition; ET=early termination; EOS=end of study; EOT=end of treatment; GI=gastrointestinal; PS=parenteral support; PT/INR=prothrombin time/international normalized ratio; Rx=prescription; Px=pretreatment; SC=subcutaneous; W=week

[a] The first pretreatment visit may be combined with the screening visit and Study SHP633-302 EOS visit (Week 28), if the pretreatment visit assessments occur within 7 days of the SHP633-302 EOS assessments. If subjects proceed directly from screening to a pretreatment visit, the first pretreatment visit must occur within 12 weeks of screening.

[b] Phone visits are required approximately 1 week after an adjustment in PS. The assessments to be performed at phone visits are the same as those described for CxW25-27 (except for evaluation of escape criteria).

[c] Whenever possible, subjects who withdraw early from the study during a teduglutide treatment cycle should complete the EOT visit and 4-week follow-up period (CxW25-27) and then proceed to the ET visit in Table 1. The ET visit will take place in lieu of the CxW28 visit. The investigator may combine the CxW28 visit with a pretreatment visit if at least 1 escape criterion is met at the CxW28 visit.

[d] Visit windows are relative to the CxD1 visit.

[e] Eligibility will need to be re-confirmed prior to the first dose in the cycle. Negative urine pregnancy test is required prior to the first dose of teduglutide, but results of other lab tests obtained at the CxD1 visit are not required to determine teduglutide treatment eligibility.

[f] Head circumference will be measured in subjects 36 months of age and younger.

[g] The intake diary should be completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pretreatment visit), for 1 week after PS adjustment, and daily during the 4-week follow-up period. The output diary should be completed daily over a 48-hour period of PS and EN stability before each clinic or phone visit and within 1 week of implementing a change in the PS prescription. See Section 7.2.10.2 for more detail.

Table 3 Schedule of Events for Subjects While Receiving Teduglutide

Period	Pretreatment	Teduglutide Treatment														Follow-up	
Visit Number	Px[a]	Cx D1	Cx W1	Cx W2	Home call approximately 1 week after previous visit	Cx W4	Home call approximately 1 week after previous visit	Cx W6	Home call approximately 1 week after previous visit	Cx W9	Home call approximately 1 week after previous visit	Cx W12	Home call approximately 1 week after previous visit	Cx W16	Home call approximately 1 week after previous visit	Cx W20	Home call approximately 1 week after previous visit	Cx W24 (EOT)	CxW25 CxW26 CxW27	CxW28[c]
Visit Type	Site	Site	Site	Site		Site		Site		Site		Site		Site		Site		Site	Phone[b]	Site
Cycle Day	-21 to 0	1	8	15		29		43		64		85		113		141		169	176 183 190	197
Window (days)[d]			±2	±2		±2		±2		±4		±4		±4		±4		±4	±2	±2

[h] PS adjustments should be made after review of the intake and output diaries and the safety lab data according to the nutritional support adjustment guidelines and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[i] Safety laboratory assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central laboratory. Biochemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety lab tests performed between clinic visits may be performed at the investigational site laboratory. Unscheduled results processed by the investigational site laboratory will not be captured in the eCRFs, but if abnormal results are considered an adverse event, an AE form will be completed. PT/INR will be collected at the pretreatment visit. Additional collection will occur if a potential drug-induced liver injury signal is observed. Urine specimen collection should be attempted as part of the safety lab tests, but lack of urinalysis will not constitute a protocol deviation.

[j] Blood samples collected on CxD1 must be drawn prior to first administration of teduglutide. Samples collected while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[k] Subjects of any age with newly positive fecal occult blood test results at the pretreatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy prior to receiving teduglutide. If newly positive fecal occult blood test results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy/sigmoidoscopy will be performed. The need for colonoscopy/sigmoidoscopy in response to positive fecal occult blood tests at CxW12 is at the discretion of the investigator. Subjects who have received the equivalent of 2 treatment cycles (48 weeks of investigational product exposure) will undergo colonoscopy/sigmoidoscopy before the next cycle of teduglutide treatment. Colonoscopy/sigmoidoscopy performed after the Visit CxW24 (±4 days) window and before the next cycle of teduglutide treatment will not be considered a protocol deviation (all other visit procedures must adhere to the (±4 days) visit window).

[l] Serum pregnancy test at the pretreatment visit, urine pregnancy tests at all other visits as per protocol schedule.

[m] If the subject met a follow-up period escape criterion, the serum sample will not be collected at the pretreatment visit. Lack of collection of serum samples will not constitute a protocol deviation. Saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.

[n] If escape criteria are met, the subject may proceed directly to another pretreatment visit at the discretion of the investigator.

[o] Escape criteria will be assessed for subjects who escaped during the follow-up period of a previous teduglutide treatment cycle at CxW24. The investigator may combine the CxW24 visit with the next pretreatment visit if at least 1 escape criterion is met at the CxW24 visit. In order to combine assessments, the pretreatment assessments must occur within 7 days of the CxW24 visit.

[p] The study drug administration diary should be completed daily between CxD1 and CxW24 by the subject or parent/guardian/study site staff. See Section 6.2.2 for dosing adjustment.

[q] The study physician must observe the parent/guardian administer the study drug in compliance with the study drug administration checklist at the beginning of each teduglutide treatment cycle before the parent/guardian is allowed to administer the drug without direct observation by the physician. Refer to Section 6.2.2.1.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

Table 3 Schedule of Events for Subjects While Receiving Teduglutide

Period	Pretreatment	Teduglutide Treatment														Follow-up	
Visit Number	Px[a]	Cx D1	Cx W1	Cx W2	Phone call to schedule approximately 1 week appt.	Cx W4	Phone call to schedule approximately 1 week appt.	Cx W6	Phone call to schedule approximately 1 week appt.	Cx W9	Phone call to schedule approximately 1 week appt.	Cx W12	Phone call to schedule approximately 1 week appt.	Cx W16	Phone call to schedule approximately 1 week appt.	Cx W20	Phone call to schedule approximately 1 week appt.	Cx W24 (EOT)	CxW25 CxW26 CxW27	CxW28[c]
Visit Type	Site	Site	Site	Site		Site		Site		Site		Site		Site		Site		Site	Phone[b]	Site
Cycle Day	-21 to 0	1	8	15		29		43		64		85		113		141		169	176 183 190	197
Window (days)[d]			±2	±2		±2		±2		±4		±4		±4		±4		±4	±2	±2

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal disease that results in major surgical resections of the small intestine. In children, most cases of short bowel syndrome begin in infancy. Based on national surveys, it is estimated that the number of patients with SBS who are dependent on parenteral support (PS) is less than 1000 in Japan (Kitajima et al., 2013; Takagi et al., 1995; Takehara, 2001). Among the 195 SBS subjects in the 2011 survey, 99 (51%) developed SBS at <1 years old. Common causes of SBS in children include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis (Duro et al., 2008; Squires et al., 2012). Similar to adults, new-onset SBS in older children usually stems from Crohn's disease, trauma, or cancer. The diminished absorptive capacity for fluids and nutrients often results in dependence on PS (parenteral nutrition or intravenous fluids) to maintain energy, fluid, and electrolyte homeostasis.

After resection or congenital loss, the small intestine is capable of remarkable adaptation. Mechanisms for adaptation include up-regulation of nutrient transporters, increased villus height and crypt depth, dilation, and delayed intestinal transit. The main principle of management of SBS is to provide the minimal necessary PS to maintain energy, fluid, and electrolyte homeostasis while maximizing enteral feeding to promote intestinal adaptation. In infants, rapid linear growth of the intestines during the first year of life dramatically complements the aforementioned adaptive responses. About 30% of infants who develop SBS during the neonatal period become independent of PS requirements within 12 months of the initial insult, and an additional 10% wean off PS within 24 months. After this time, linear intestinal growth slows. About 60% of children with SBS are able to become independent of PS within 5 years (Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, many children remain dependent on PS.

For this reason, research in the pediatric arena is focused on children with PS-dependent SBS. Given intestinal adaption in younger children, the unmet medical need is the greatest in children who are 1 year of age and older.

Complications of long-term PS include liver disease, catheter-related blood stream infections, central line-associated venous thrombosis, and dwindling central venous access. Sepsis is the leading cause of death in these patients, and quality of life is poor. Accelerating the adaptive process is an urgent goal for all patients with SBS who are dependent on PS.

1.2 Product Background and Clinical Information

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption (Drucker and Yusta, 2014). Chief among these is hormones glucagon-like peptide-2 (GLP-2), which is secreted from L-type enteroendocrine cells that reside in the distal ileum and colon. Resection of these regions may impair the adaptive response by limiting endogenous production of GLP-2.

In the United States (US) and the European Union (EU), a GLP-2 analog called teduglutide is approved for the treatment of SBS in adult patients who are dependent on PS. On 29 June 2016, the European Commission approved teduglutide for the treatment of children with SBS who are dependent on PS. There are no other approved pharmacological therapies that promote intestinal adaptation in children with SBS.

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 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$) of approximately 2 hours in healthy adults and 1.3 hours in SBS adults 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 (Tappenden et al., 2013; Thymann et al., 2014).

Teduglutide was designated as an orphan drug indicated for SBS in Japan on 20 Nov 2014.

Adult Studies

Four Phase 3 studies have been completed in adult SBS subjects in US/EU countries. A completed adult study (CL0600-004) and its extension (CL0600-005) together evaluated safety and tolerability of daily teduglutide dosing for up to 12 months in SBS subjects who were dependent on PS. Study CL0600-004, a double-blind, placebo-controlled study in which 83 subjects were enrolled and 67 dosed with teduglutide, assessed the effects of teduglutide (0.05 and 0.10 mg/kg/day) on reductions in PS. There was a statistically significant difference favoring the 0.05 mg/kg/day group over placebo (p=0.007) by using a graded response at the end of the study. At Week 24, the weekly reduction of PS volume was similar in the 2 active groups (2.5 L each). The extension study, CL0600-005, assessed the long-term safety of teduglutide (0.05 mg/kg/day and 0.10 mg/kg/day) and the proportion of responders in the CL0600-004 study that maintained their response at the end of a further 28 weeks of treatment. The extension study also assessed the effects of teduglutide at 28 weeks on those subjects previously receiving placebo in Study CL0600-004.

Results from the extension study supported the clinical benefits of the 0.05 mg/kg/day teduglutide treatment in the initial Phase 3 study, which included significant reductions in PS. Seventy-five percent of the subjects who previously responded to teduglutide treatment in Study CL0600-004 maintained this response or experienced further improved benefit from teduglutide treatment. More than 60% of the subjects previously receiving placebo in Study CL0600-004 achieved a clinical response after switching to teduglutide treatment for 6 months. Most of the adverse events (AEs) reflected the underlying disease and were not treatment related.

Study CL0600-020 was a randomized, double-blind, placebo-controlled study in which subjects were randomized to teduglutide 0.05 mg/kg/day or placebo on a 1:1 ratio. The first stage of the study included a screening and optimization period and a stabilization period that demonstrated stable administration of PS volume for a minimum of 4 weeks up to a maximum of 8 weeks.

The second stage was a dosing period of 24 weeks. Subjects on 0.05 mg/kg/day teduglutide achieved a higher responder rate (defined as a 20% to 100% reduction from baseline in PS volume at Weeks 20 and 24) than the placebo-treated subjects (27/43 subjects [62.8%] versus 13/43 subjects [30.2%], respectively). This difference was clinically and statistically significant in both the intent-to-treat ($p=0.002$) and per protocol ($p <0.001$) populations. Generally, the incidence of treatment-emergent AEs was distributed similarly across all treatment groups. The treatment-emergent AEs with a higher incidence in the teduglutide group were mainly of GI origin.

A long-term, open-label extension study (CL0600-021) assessed safety and efficacy for up to 24 additional months (ie, up to 30 months of exposure for subjects who received teduglutide in Study CL0600-020). Overall, 30 of 43 subjects who received teduglutide in Study CL0600-020 and entered Study CL0600-021 completed a total of 30 months of treatment with teduglutide. Of these, 28 subjects (93%) achieved a 20% or greater reduction of PS resulting in a PS volume reduction of 7.55 L/week, corresponding to a mean reduction of 65.6% relative to baseline prior to exposure to teduglutide at the beginning of Study CL0600-020. Parenteral support use was reduced by at least one day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with teduglutide. The mean reduction in PS volume was 3.11 L/week from baseline at the start of Study CL0600-021 (a 28% reduction). Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of PS. Of the 12 subjects entering Study CL0600-021 directly, 6 completed 24 months of treatment with teduglutide. The mean reduction in PS volume was 4.0 L/week (a 39.4% reduction from baseline at the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of PS.

Pediatric Studies

One Phase 3 study, TED-C13-003, was completed in pediatric SBS subjects in US/EU countries. In this study, teduglutide was administered to 3 cohorts of children from age 1 through 17. Thirty-seven children received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional children were enrolled in an observational standard of care cohort.

There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to standard of care and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PS volume at Week 12 of 37%, including complete independence from PS in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PS volume at Week 12 of 39%, including complete independence from PS in 3 subjects, and a reduction of 4.18 hours per day infusion time.

Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent AEs related to teduglutide were reported. No discontinuations from study were due to AEs.

Subjects who completed Study TED-C13-003 will be followed in a long-term retrospective and prospective extension study.

A second Phase 3 pediatric study (TED-C14-006) was recently completed in the US and EU in which pediatric subjects through 17 years received 24 weeks of teduglutide treatment followed by a 4-week follow-up period. Subjects who completed this study are followed in a long-term prospective study.

SHP633-302 is an ongoing open-label Japanese study where subjects receive 0.05 mg/kg/day teduglutide treatment once daily. Subjects participate in a 2-week minimum screening period, a 24-week teduglutide treatment, and a 4-week follow-up period. Subjects who complete Study SHP633-302 will be asked to enroll in the SHP633-305 extension study.

Additional information is provided in the investigator's brochure.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in Japanese pediatric subjects with SBS who completed Study SHP633-302. In addition to evaluating the long-term safety and durability of efficacy after 24 weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in Japanese pediatric subjects with SBS who completed Study SHP633-302.

2.2.2 Secondary Objectives

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide treatment in Japanese pediatric subjects with SBS who completed Study SHP633-302.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in Japanese pediatric subjects who completed Study SHP633-302 (core study). The study population will include 2 cohorts based on age of subjects at the time of entry in the core study: infants 4-<12 months corrected gestational age and children 1-15 years of age. At the time of entry into Study SHP633-302, subjects were dependent on parenteral nutrition to provide at least 30% of their caloric and/or fluid/electrolyte needs, and had not been able to significantly reduce PS for at least 3 months prior to enrollment. During the core study, subjects were to receive 0.05 mg/kg once daily of teduglutide. Study SHP633-302 will also be referred to as the core study throughout this protocol.

Approximately 7 subjects who complete the core study are expected to enroll in this extension study. To be eligible to additional teduglutide treatment, subjects must meet at least one of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria.

Additional Teduglutide Treatment:

Subjects not receiving teduglutide treatment (ie, in a "no-teduglutide treatment [NTT] period"), will be seen approximately every 12 weeks for safety and PS requirements. At any point during an NTT period, subjects who meet *at least one* teduglutide treatment inclusion criterion may proceed directly to the pretreatment visit if the investigator and the subject (and/or parent/guardian, as applicable) agree to proceed with teduglutide therapy.

Rationale: Some pediatric subjects may have a durable beneficial effect after 24 weeks of teduglutide treatment and thus long-term follow-up without additional teduglutide treatment may be appropriate. However, there may be some pediatric subjects who deteriorate or stop improving after discontinuation of teduglutide treatment. In these pediatric subjects, additional teduglutide treatment may be beneficial.

Dose Selection:

In this extension study to SHP633-302, eligible subjects will be able to receive daily doses of teduglutide 0.05 mg/kg once daily for 24-week periods.

Rationale: Teduglutide is approved for adult use in the US and EU, and for pediatric use in the EU, at a dose of 0.05 mg/kg subcutaneous (SC) once daily. The completed pediatric studies (TED-C13-003 and TED-C14-006) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population pharmacokinetic modeling and simulations were conducted to determine the effective dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as the pediatric study (TED-C13-003) and suggested that the dose in pediatric subjects is likely to be same as the dose in adults (refer to the investigator's brochure for more information).

Duration of Treatment:

The duration of teduglutide treatment periods in this study mirrors that of Study SHP633-302, consisting of 24 weeks of teduglutide treatment, followed by 4-week follow-up periods. The follow-up periods are a mechanism to evaluate whether continued teduglutide is needed. If a subject deteriorates during a follow-up period, the subject may be evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorate or stop improving at any time during an NTT period may be immediately assessed for eligibility to additional treatment.

Rationale: During the teduglutide treatment cycle, visit frequency is similar to frequencies performed in TED-C13-003 and SHP633-302, to ensure sufficient safety monitoring and weaning of PS. During NTT, visits occur approximately every 12 weeks, a frequency that is consistent with standard medical practices. To minimize risk to subjects, those who have deteriorated quickly after treatment interruption (ie, escaped from a prior follow-up period) may be evaluated immediately for eligibility for additional treatment when they reach the Week 24 visit.

Measures and Parameters:

Following the review and signing of the informed consent (and informed assent, if applicable), screening visit procedures will begin, including demographics and updates to medical history and short bowel syndrome history. Subjects who meet at least one of the teduglutide treatment inclusion criteria may proceed to the pretreatment visit.

After the pretreatment visit, subjects who meet *at least one* of the teduglutide treatment inclusion criteria, and meet *none* of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up (no treatment) period (Figure 1). During the 28-week cycle, clinic visits will occur at Day 1 and Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1 and 24), and weekly during the teduglutide follow-up period (between weeks 24 and 28).

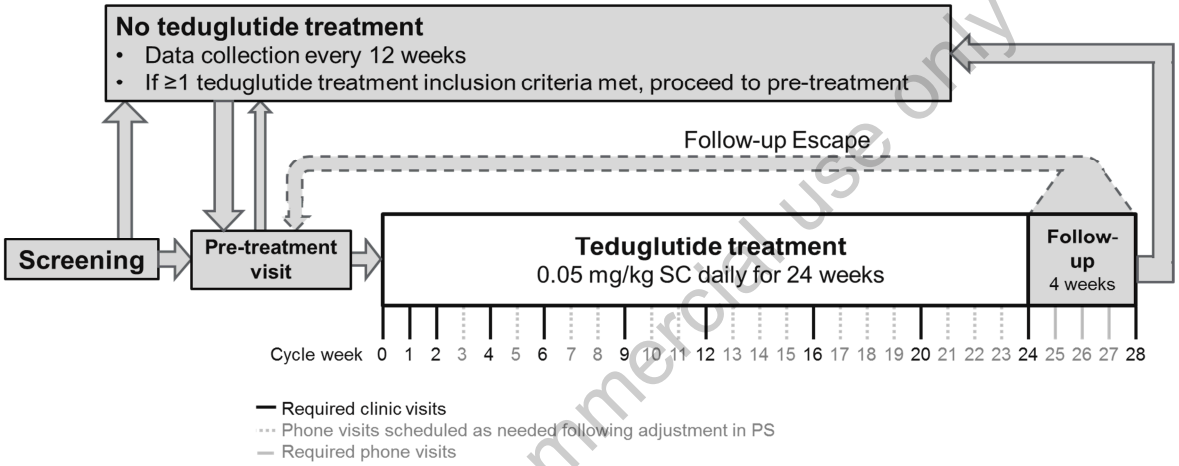
At all site and phone visits, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithm (developed with SBS expert input and provided in Appendix 2 and Appendix 3, respectively) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines (Appendix 2 and Appendix 3), however, is not considered a protocol deviation.

Rationale: Measures of long term safety will include AEs, growth parameters, safety laboratory tests, and anti-drug antibodies. Measure of long term efficacy will include durability of effect as measured by reduction in PS. A reduction in PS volume of at least 20% at end of treatment (EOT) was used as the primary endpoint in pivotal Phase 3 adult clinical trials and the completed Phase 3 pediatric study (TED-C13-003), and will be used as an endpoint in this extension study. In previous clinical studies, a reduction of this magnitude was associated with a reduction in the

number of days per week of PS. Reduction in volume and time of PS due to improved enteral absorption may provide a pediatric subject with opportunities for more age-appropriate activities including oral rehabilitation.

Teduglutide has been found to have a targeted intestinotrophic effect. Taking into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests, including fecal occult blood testing and colonoscopy/sigmoidoscopy, which are commonly part of the routine care of these subjects, will be performed to ensure safety. This study captures long-term safety data on polyps and other colonic mucosal changes in teduglutide-exposed subjects using the surveillance strategy proposed in Section 7.2.9.

Figure 1 Study Design Flow Chart



PS=parenteral support; SC=subcutaneous
Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Subjects eligible for teduglutide will enter a 28-week cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at Day 1 (Week 0) and Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between Weeks 2 and 24 (**dashed grey lines**). At Week 24, subjects enter a 4-week follow-up period, where teduglutide is not received, during which phone visits will be performed weekly (**solid grey lines**). If at least 1 escape criterion is met at Week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

3.2 Duration and Study Completion Definition

A subject will be considered enrolled in the study once the subject (and/or parent/guardian, as applicable) has provided signed consent (and informed assent, if applicable), and meets all of the inclusion criteria at screening. The study will continue until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the end of study (EOS) visit. If teduglutide is approved for marketing, this study will be continued as a post-marketing study. This protocol will continuously be used. "Clinical Study" mentioned in the protocol will be read as "Post-marketing Study" as appropriate.

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 will be conducted at approximately 5 investigational sites in Japan.

4 STUDY POPULATION

Each subject (and/or parent or guardian, as applicable) must review and sign the informed consent/assent before any study-related procedures specified in the protocol are performed. Teduglutide treatment eligibility does not impact study eligibility.

4.1 Study Eligibility Criteria

4.1.1 Study Inclusion Eligibility Criteria

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

1. Informed consent by a parent or guardian prior to any study-related procedures.
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board [IRB]) by the subject prior to any study-related procedures.
3. Subject completed Study SHP633-302.
4. Subject (and/or parent/guardian) understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.1.2 Study Exclusion Eligibility Criteria

There are no exclusion criteria for this study.

4.2 Teduglutide Eligibility Criteria

Subjects are eligible for teduglutide treatment if *at least 1* of the teduglutide treatment inclusion criteria, and *none* of the teduglutide treatment exclusion criteria, are met. In addition, the investigator and the subject (and/or parent/guardian, as applicable) must agree to proceed with treatment.

4.2.1 Teduglutide Treatment Inclusion Criteria

1. Increasing PS requirements following teduglutide discontinuation.
2. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
3. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
4. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
5. Severe diarrhea related to teduglutide discontinuation.

4.2.2 Teduglutide Treatment Exclusion Criteria

1. Body weight <5 kg at the pretreatment visit.
2. Unresected GI polyp, known polyposis condition, premalignant change, or malignancy, in the GI tract.

3. History of cancer in the previous 5 years except surgically curative skin cancers.
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle.
6. Clinically significant intestinal stricture or obstruction.
7. Clinically significant, active or recurrent pancreatic or biliary disease.
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pretreatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 ×ULN
    c. Alanine aminotransferase (ALT) ≥7 ×ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pretreatment visit.
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine or intravenous lipid emulsions) within 3 months or 5.5 half-lives of experimental drug administration, whichever is longer, prior to the pretreatment visit and for the duration of the 28-week cycle.
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or DPP-4 inhibitors within 3 months prior to the pretreatment visit.
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
15. Known history of alcohol or other substance abuse within 1 year prior to the pretreatment visit.
16. Pregnant or lactating female subjects.
17. Sexually active female subjects of childbearing potential unwilling to use approved contraception throughout the study period and for 30 days following the last dose of investigational product.
18. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

4.3 Follow-up Period Escape Criteria

At the discretion of the investigator, the follow-up period may be interrupted or omitted and the subject may proceed directly to the pretreatment visit, if *at least 1* of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.
5. The subject escaped during the follow-up period of a previous teduglutide treatment cycle within SHP633-305.

4.4 Reproductive Potential

4.4.1 Female Contraception

To be eligible for treatment with teduglutide, sexually active females of childbearing potential must use an acceptable form of contraception. Females of childbearing potential must be advised to use 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 acceptable contraception, as defined below, if they become sexually active during the period of the study and for 30 days following the last dose of investigational product.

Female children and adolescent subjects should be either:

- Premenarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of childbearing potential with a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the teduglutide pretreatment visit and a negative urine β-HCG pregnancy test prior to enrollment. Females of childbearing potential must agree to abstain from sexual activity (ie, true abstinence*) that could result in pregnancy or 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.

*Note: True abstinence: Abstention of sexual activity that is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

4.5 Discontinuation of Subjects

4.5.1 Permanent Discontinuation of Investigational Product

If the investigational product is discontinued prematurely during a teduglutide treatment cycle and the subject wishes to remain in the study, the evaluations listed for the EOT visit are to be performed. A 4-week follow-up period will ensue, consisting of weekly phone visits (CxW25 to CxW27) and the week 28 clinic visit (CxW28) shown in Table 3. The subject would then enter an NTT period.

Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. In all cases, the reason for permanent discontinuation must be recorded in the electronic case report form (eCRF) and in the subject's medical records, as described in Section 4.5.3. The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor, when possible.

4.5.2 Study Withdrawal

At any time during the study, the investigator or sponsor may withdraw a subject, or a subject may withdraw from the study, for any reason, without prejudice to their future medical care by the physician or at the institution.

If a subject withdraws from the study during a teduglutide cycle, the evaluations listed for the EOT visit are to be performed as completely as possible. Whenever possible, the subject will then be asked to return 4 weeks later for the early termination (ET) visit, and will be contacted weekly by phone during the interim period between EOT and ET for safety follow-up.

If a subject withdraws from the study during an NTT period, the evaluations listed for the ET visit are to be performed as completely as possible.

Subjects who withdraw from the study will not be replaced.

4.5.3 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 parent/guardian
- Withdrawal by subject
- Lack of efficacy
- Other

If the reason is not known, the subject must be followed-up to establish whether the reason was an AE and, if so, the AE must be reported in accordance with the procedures described in Section 8.1.

4.5.4 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 (site or phone visit). At least one 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 CONCOMITANT TREATMENT

5.1 Concomitant Medications and Procedures

Concomitant treatment refers to all treatment taken between the dates of informed consent/assent and EOS, inclusive. Concomitant medications and procedures will be assessed at each site visit, and include all nonstudy treatments (medications, herbal treatments, vitamins, invasive, and diagnostic procedures). Concomitant treatment information must be recorded on the appropriate eCRF page. Details of medication changes and/or dosages will be recorded on the eCRF. See also nutritional support in Section 7.2.10.1.

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.

5.1.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.1.2 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 4):

Table 4 Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Native/synthetic glucagon-like peptide-2 (not-including teduglutide)	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy used to treat inflammatory bowel disease (eg, antitumor necrosis factor)	6 months

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 or 1.25 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 SHP633 investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product(s)

6.2.1 Allocation of Subjects to Treatment

This is an open-label study where subjects may receive teduglutide 0.05 mg/kg/day as described in Section 6.2.2. Subjects will retain their assigned subject number from Study SHP633-302. Assessment of need for teduglutide treatment should be guided by the teduglutide treatment inclusion criteria. If the investigator and the subject (and/or parent/guardian, as applicable) agree to proceed with treatment, a formal evaluation of teduglutide inclusion and exclusion criteria will be performed at the pretreatment visit (Table 3).

6.2.2 Dosing

If teduglutide treatment eligibility is established at the pretreatment visit and again confirmed at the Cycle Day 1 (CxD1) visit, the subject will start a teduglutide treatment period, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily. The initial dose will be calculated based on body weight measured at the teduglutide pretreatment visit, and adjusted as needed, based on body weight measured at Week 12 (CxW12). No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. 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. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

At the end of each 24-week teduglutide treatment period, subjects will be evaluated for the need for additional teduglutide treatment. During the 4-week follow-up, the investigator will assess the subject via weekly phone visits. At Week 24 or any time during the follow-up period, if escape criteria are met, the subject may proceed directly to another pretreatment visit to assess treatment eligibility for another cycle (Section 4.3). Following the completion of the 4-week follow-up, the subject will continue in the study off teduglutide until teduglutide treatment eligibility criteria are again met. Additional 28-week cycles may be repeated if treatment eligibility is established each time.

If the investigational product is discontinued prematurely during a teduglutide treatment cycle and the subject wishes to remain in the study, the evaluations listed for the EOT visit are to be performed. A 4-week follow-up period will ensue, consisting of weekly phone visits (CxW25 to CxW27) and the week 28 clinic visit (CxW28) shown in Table 3. The subject would then enter an NTT period and could be evaluated for subsequent teduglutide treatment eligibility according to the study schedules.

6.2.2.1 Administration by Parent/Guardian

The processes for training the parent/guardian to administer teduglutide and for providing oversight of study drug administration are described in the Site Training Guide. Before a parent/guardian is permitted to administer teduglutide, the study physician must observe the parent/guardian 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. It is expected that most parents/guardians of subjects enrolled in study SHP633-305 will have already been deemed proficient to administer teduglutide in study SHP633-302. Those who have already demonstrated proficiency need only to be observed once by a study physician at the beginning of each teduglutide treatment cycle (CxD1 visit, see Table 3) as long as they continue to prepare and administer teduglutide in compliance with the study drug administration checklist. If a parent/guardian fails to administer teduglutide in compliance with the checklist, they must perform this procedure correctly on 2 consecutive observations by the study physician in order to be deemed proficient to administer the study drug unsupervised. Refer to the Site Training Guide for details regarding this training. This process ensures that the parent/guardian continues to administer the study drug correctly and safely throughout the dosing period.

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

Eligibility for teduglutide to be administered by a parent/guardian 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 Parent/Guardian:

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

Criteria to Discontinue Teduglutide Administration by the Parent/Guardian:

- The parent/guardian 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 administered by their parent/guardian. In addition to discontinuing administration of teduglutide by the parent/guardian, if a subject sustains an adverse drug reaction where the symptoms are considered intolerable, dose interruption or study drug discontinuation should be considered (see Section 8.4).
- In the study physician's judgment, it is inappropriate for the parent/guardian to continue administration of the study drug for any other reason.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

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

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 and 8°C until dispensed to a subject. The prefilled sterile water for injection syringes will be stored at a temperature between 2 and 25°C. Once dispensed/supplied to a subject, the investigational product can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25°C). A parent/guardian will be instructed to keep the subject's 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.

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 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 his/her treatment assignment. 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

Subject compliance with investigational product dosing will be monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject, the subject's parent or guardian, or study site staff if they have 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 AEs, a lapse in investigational product delivery, etc.

Compliance with study drug is calculated from subject diaries. Of those subjects eligible for teduglutide treatment, 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, Table 2, and Table 3) and must be referred to in conjunction with the instructions provided in this section.

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/assent from the subject and/or parent/guardian, as applicable. In general, consent/assent to participate in Study SHP633-305 should be obtained within 7 days after completion of Study SHP633-302. The first visit after screening (either an NTT visit or a pretreatment visit), must occur within 12 weeks of screening.

The screening visit (Scr) assessments and procedures, beginning with informed consent/assent, will be performed as outlined in Table 1.

7.1.2 Visits for Subjects Not Receiving Teduglutide

While outside of the 28-week teduglutide-treatment cycle, subjects will be followed approximately every 12 weeks for safety and efficacy assessments. No-teduglutide treatment visits are numbered sequentially (NT1, NT2, etc.), even if interrupted by the treatment cycles. When subjects proceed from screening to the first NTT visit, the first NTT visit must occur within 12 weeks of screening. Assessments will be performed as outlined in Table 2.

7.1.3 Visits for Subjects Receiving Teduglutide

7.1.3.1 Pretreatment Visit

Subjects who meet at least one of the teduglutide treatment inclusion criteria during the screening visit or during the NTT period may proceed to the pretreatment visit immediately if the investigator and the subject (and/or parent/guardian, as applicable) agree to proceed with teduglutide therapy. Similarly, subjects who meet escape criteria at cycle Week 24 or during the teduglutide follow-up period may proceed to the pretreatment visit immediately. Pretreatment visits cannot occur consecutively and must be scheduled at least 12 weeks apart.

The first pretreatment visit may be combined with the screening visit and the Study SHP633-302 EOS visit (Week 28), if the pretreatment visit assessments occur within 7 days of the SHP633-302 EOS assessments. If subjects proceed directly from screening to a pretreatment visit, the first pretreatment visit must occur within 12 weeks of screening.

In general, pretreatment assessments should occur within 21 days. The teduglutide pretreatment visit (Px) assessments and procedures will be performed as outlined in Table 3.

7.1.3.2 Teduglutide Treatment Period (CxD1-CxW24)

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments and procedures listed for visits CxD1-CxW24 in Table 3 shall be completed. Cycles are numbered sequentially, such that the first visit of the first cycle is C1D1, and the first visit of the second cycle is C2D1, etc. Every effort should be made to complete 2 weeks of intake diary entries prior to each clinic visit and to complete 48 hours of output diary entries during a period of PS stability prior to each clinic visit.

Following the CxD1 visit, subjects will return for clinic visits on Cycle Weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24/EOT. Assessments and procedures at these visits will be performed as outlined in Table 3.

At the CxW24 visit, a serum sample is collected and stored for future analysis. This sample will not be used for genetic testing and lack of collection will not constitute a protocol deviation. Saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.

Escape criteria are also evaluated at CxW24. The investigator may combine the CxW24 assessments with the next pretreatment visit assessments if at least 1 escape criterion is met at the CxW24 visit and the pretreatment assessments occur within 7 days of the CxW24 visit.

7.1.3.3 Phone Visits

Phone visits are required approximately 1 week after an adjustment in PS during the teduglutide treatment period and weekly during the 4-week follow up period. Phone visit assessments and procedures are outlined in Table 3.

7.1.4 Teduglutide Follow-up Period

The safety follow-up period is 4 weeks (Weeks 25–28 of the cycle). During this period, phone visits will occur on Cycle Weeks 25, 26, and 27, and a clinic visit will occur at Week 28. Follow-up period assessments and procedures are outlined in Table 3.

If escape criteria are met at any time during the follow-up period, the subject may proceed directly to another pretreatment visit at the investigator's discretion. The investigator may combine the CxW24 or CxW28 visit with the next pretreatment visit if at least 1 escape criterion is met at the CxW24 or CxW28 visit, and the pretreatment assessments occur within 7 days of the CxW24 or CxW28 visit.

7.1.5 Study Completion/Early Termination Visit (EOS/ET Visit)

All subjects will return to the study site for the EOS/ET. Assessments and procedures at this visit will be performed as outlined in Table 1. If a subject discontinues the study prematurely, the assessments for the EOS/ET Visit are to be performed as completely as possible.

7.2 Study Evaluations and Procedures

All evaluations and procedures will be performed as outlined in the study schedules (Table 1, Table 2, and Table 3).

7.2.1 Demographics, Medical History, and SBS History

Demographics, medical history, and SBS history will be obtained at screening. Medical history for purposes of this extension study will consist of the following:

- Adverse events that were ongoing at the time of completion of Study SHP633-302.
- Events that occurred during the period between completion of Study SHP633-302 and informed consent/assent to Study SHP633-305.

Updates to medical history will supplement the medical history information collected at the start of the SHP633-302 core study. If the subject has any changes to the SBS history collected at the baseline visit of Study SHP633-302, that information (updated SBS history) will be collected.

7.2.2 Physical Examination (Including Height, Weight, and Head Circumference)

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/assent) should be recorded on the appropriate AE page of the eCRF.

Subjects should be weighed on the same scale at each study visit. Height (or length [cm]) and head circumference (for subjects ≤36 months of age [cm]) will be measured at selected visits.

Body mass index (BMI) and z-scores for weight, height (or length), head circumference, and BMI will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.3 Vital Signs

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 extremity, and in the same position throughout the study, whenever possible).

New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

7.2.4 Clinical Laboratory Tests

Safety laboratory tests are to be performed at site visits with results processed by a central laboratory. They consist of biochemistry, hematology, coagulation, and urinalysis and will be performed as outlined in the study schedules. 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.

During the teduglutide treatment period, subjects will also have safety lab tests within approximately 5-7 days after a PS adjustment. Safety lab tests performed after PS adjustment and between site visits will consist of biochemistry and urinalysis to be performed at the investigational site laboratory. Urine specimen collection should be attempted as part of the safety lab tests, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant lab tests results should be reported as AEs (see Section 8.1).

All laboratory testing will be processed at the investigational site and performed according to the study schedules. Tests include the following (Table 5):

Table 5 List of Laboratory Tests

Hematology:	**Biochemistry:**
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Platelet count	Alanine aminotransferase
Red blood cell (RBC) count	Amylase
RBC morphology, if needed	Aspartate aminotransferase
White blood cell count with differential	Bicarbonate
	Bilirubin (total, direct and indirect)
Coagulation:	Blood urea nitrogen
Prothrombin time/International normalized ratio	Calcium (total)
	Chloride
Urinalysis:	Cholesterol
Blood	C-reactive protein
Glucose	Creatinine
Leukocytes	Estimated glomerular filtration rate
pH	(Schwartz formula)
Protein	Gamma-glutamyl transferase
Specific gravity	Glucose
Microscopic analysis	Lipase
	Magnesium
Pregnancy tests (females of childbearing potential):	Phosphorus
Serum β-HCG (pretreatment)	Potassium
Urine β-HCG (all other visits)	Sodium
	Triglycerides
	Uric acid

7.2.5 Serum Sampling

Serum samples will be collected and stored for future analysis at the following times:

- At the pretreatment visit. If the subject arrived at the pretreatment visit by meeting an escape criterion, the serum sample will not be repeated at the pretreatment visit, because it will have been collected recently at the CxW24 visit.
- At the CxW24 (EOT) visit
- During NTT: Approximately every 24 weeks

The serum sample will not be used for genetic testing. Lack of collection will not constitute a protocol deviation. Saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their sample and/or extracted material destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

7.2.6 Antibody Assessment

Blood samples will be drawn for the analysis of antibodies to teduglutide according to the study schedules. Blood samples for antibodies may be drawn from a central line or peripheral access. The sample drawn on CxD1 must be drawn prior to administration of the first dose of teduglutide. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing. Subjects who test positive for antibodies to teduglutide will also be tested for neutralizing antibody. Subjects who have been previously treated with teduglutide, and who test positive for antibodies to teduglutide, will have follow-up blood draws for antibodies to teduglutide every 12 weeks until a negative result is obtained or the study ends.

7.2.7 Pregnancy Testing

A serum pregnancy test will be performed on all female subjects of child bearing potential (Section 4.4.1) at the teduglutide pretreatment visit. Urine pregnancy tests will be performed at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

7.2.8 Volume of Blood

During this study, efforts will be made based on Japanese manufacturer or laboratory regulations and guidelines to minimize the amount of blood drawn from all pediatric subjects enrolled in this study.

The amount of blood to be drawn may vary according to instructions provided by the manufacturer or laboratory for an individual assessment.

When more than one blood assessment is to be done at the same time point, the assessments should be combined if they require the same type of tube.

7.2.9 Gastrointestinal-specific Testing

7.2.9.1 Fecal Occult Blood Testing

Fecal occult blood testing must be performed on all subjects at the pretreatment visit, Week 12, and Week 24 of the teduglutide cycle. During NTT periods, fecal occult blood testing must be performed on a roughly annual basis (approximately every 48-60 weeks). Actions to be taken in response to a positive fecal occult blood testing are described below.

7.2.9.2 Colonoscopy or Sigmoidoscopy

Subjects of any age with newly positive fecal occult blood testing results at the pretreatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy prior to receiving teduglutide. If newly positive fecal occult blood test results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy/sigmoidoscopy will be performed. The need for colonoscopy/sigmoidoscopy in response to positive fecal occult blood tests at any other point during the study, or to reevaluate persistently positive fecal occult blood tests is at the discretion of the investigator.

Subjects who have received the equivalent of 2 treatment cycles (48 weeks of investigational product exposure) will undergo colonoscopy/sigmoidoscopy before the next cycle of teduglutide treatment. While receiving additional teduglutide treatment, subjects will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed.

Upper endoscopy may be performed along with any colonoscopy/sigmoidoscopy at the investigator's discretion. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Subjects with unresected GI polyps, polyposis conditions, pre-malignant change or malignancy in the GI tract will be excluded from teduglutide treatment.

7.2.10 Other Study Procedures

7.2.10.1 Nutritional Support

Nutritional support includes PS, EN, and other food and fluids. Reductions to PS will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Intake and output diaries will include data to be considered in the adjustment of each subject's nutritional support. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2 and Appendix 3, respectively.

7.2.10.2 Diaries

Study Drug Administration Diary:

A study drug administration diary will record administration of teduglutide. This diary should be completed by the subject, parent/guardian, or study site staff) daily during the teduglutide treatment period (between visits CxD1 and CxW24).

Intake Diary:

An intake diary will be used to record administration of PS. Every effort should be made to complete the intake diary for 2 weeks prior to each scheduled site visit (except at pretreatment visit), for 1 week following PS adjustment during the teduglutide treatment period (CxD1 to CxW24), and daily during the 4-week follow-up period (CxW24 to CxW28). The subject, parent/guardian, or study site staff will record:

- Volume and infusion duration.
- Site personnel will determine the actual PS daily calories based on diary entries.

Output Diary:

Urine and stool output should be recorded in the output diary over a 48-hour period of PS stability before every clinic visit; in addition, output should be recorded for subjects during a teduglutide treatment period within 1 week of implementing a change in the PS prescription.

Urine data:

- Toilet-trained subjects (who do not wear diapers)
  Measure and record all urine output in mL or cc.
- Nontoilet-trained subjects (who wear diapers)
  Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc.
- At the discretion of the investigator, the parent may be asked to collect the first void after the daily PS infusion to measure specific gravity.

Stool data (includes diapers with mixed urine and stool):

- Toilet-trained subjects (who do not wear diapers)
  Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see output diary).
- Nontoilet-trained subjects (who wear diapers)
  Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (see output diary). Stool volume will be calculated using the formula: 1 g (scale weight) = 1 mL or 1 cc.

All ostomy output volume should be recorded. Ostomy output will not be scored using the Bristol Stool Form Scale.

All available diary data will be reviewed by the investigator or their designee at each clinic and phone visit to assess clinical status and opportunity for PS reduction and advance in feeds.

7.3 Changes to Study Procedures Due to a Pandemic

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites that are impacted by a pandemic (eg, coronavirus disease 2019 [COVID-19] or other future similar unexpected public health concerns) that require physical distancing that may result in subjects missing their visits. This guidance takes references from the Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards, March 2020 and updated on 02 July 2020, the European Medicines Agency (EMA) Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic, Version 3 (28 April 2020), and the EMA Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, dated 26 June 2020.

Because a pandemic (eg, COVID-19) may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator, in consultation with the study team (and the medical team as needed), while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 (or other similar pandemic) may include the following:

- Informed Consent Form Procedure: If necessary, informed re-consent from a current study participant may be obtained via electronic informed consent capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site, based on local regulations or requirements.
- Clinic / Telephone Visits: In situations where a clinic visit is not completed due to a COVID-19 (or other similar pandemic) concern, a telephone visit may be conducted as an unscheduled safety assessment on subject well-being. The on-site visit will be recorded as "Not Done" with a free text comment referencing COVID-19 (or similar pandemic) and the telephone visit will be documented in the study records and recorded as an unscheduled visit in the eCRF, with a free text comment indicating "Telephone visit".
- Deviations from protocol-specified procedures, eg, missing visits, missing data, alternative visits, etc. will be recorded as related to a pandemic (eg, COVID-19 or other similar pandemic).
- Secure direct-to-patient delivery of the study drug from the investigational site to subjects may be implemented, as per investigational site and sponsor agreement.
- In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic or other similar pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to maintain patient safety and ensure data quality and integrity. Alternative monitoring approaches should be used only where allowed by applicable local regulations and permitted by the IRB/IEC.

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/assent is signed until the defined follow-up period stated in Section 7.1.4. This includes events occurring during the screening phase 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.

Note that the severity of AEs listed in Table 6 that may lead to dose interruption based on known or possible risks of teduglutide will also be evaluated using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria (Section 8.4.1).

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/assent 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 IQVIA Services Japan K. K. using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. 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 the pregnancy meets 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 according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. 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 the investigational product at a dose or frequency greater than 0.05 mg/kg subcutaneous once daily. An overdose occurs if any of the following criteria are met:
  - More than 0.05 mg/kg is given at any one time
  - Consecutive doses are spaced less than 12 hours apart
  - Any more than 0.05 mg/kg in one day (a day is defined as beginning at 12:00 AM and ending at 11:59 PM)
- 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.

All investigational product provided to pediatric subjects should be supervised by the parent/guardian.

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 IQVIA Services Japan K.K. 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 IQVIA Services Japan K.K. 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 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 email the completed form to IQVIA Services Japan K.K. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol From (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact section of the protocol and the form (sent under separate cover).

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/assent is obtained until the defined follow-up period stated in Section 7.1.4, and must be reported to IQVIA Services Japan K.K. and the CRO/Shire Medical Monitor 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 IQVIA Services Japan K.K. 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/assent 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 is responsible for notifying the relevant regulatory authorities and central IRBs/ethics committees (ECs), 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 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, IQVIA Services Japan K.K. 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.

8.4 Dose Interruption of Individual Subjects

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 interruptions may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Investigational product must be discontinued if any of the following events occur:

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to investigational product. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.

- An AE listed in (Table 6) that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to investigational product administration (see Section 8.4.1)
- Confirmed drug-induced liver injury (DILI) related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Known or Possible Risks of Teduglutide

The investigational product may be discontinued if the subject experiences an AE listed in Table 6 that is of severity ≥Grade 3 per the NCI CTCAE. All such AEs should be discussed with the medical monitor or designee as soon as possible. Teduglutide administration must be discontinued if the AE is considered related to the investigational product. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigators and the Data Monitoring Committee (DMC) should be guided by the descriptions of Grade 3 and 4 events, as they relate to known or possible risks associated with the administration of teduglutide (Table 6).

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	>5.0 to 20.0x ULN	>20.0x ULN

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Blood bilirubin increased	>3.0 to 10.0x ULN	>10.0x ULN
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Lipase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

ULN=upper limit of normal
[a] In the setting of clinically acute and symptomatic pancreatitis
Source: Common Terminology Criteria for Adverse Events, version 4.03, 14 June 2010

8.4.2 Dose Interruption Criteria Based on Drug-induced Liver Injury

Teduglutide administration for an individual subject may need to be discontinued if the subject has clinical and laboratory evidence of potential DILI, in the absence of an alternative explanation, as identified by the following criteria:

- Subjects with normal (or low) values of ALT and AST at baseline:
  - ALT or AST >8x ULN
  - ALT or AST >5x ULN for more than 2 weeks
  - ALT or AST >3x ULN and (total bilirubin >2x ULN or INR>1.5)
  - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Subjects with baseline elevations of values of ALT and/or AST over ULN:
  - ALT or AST >8x ULN
  - ALT or AST >5x ULN and >2x baseline value for more than 2 weeks
  - (ALT or AST >3x ULN and >2x baseline value) and (total bilirubin >2x ULN or INR>1.5)
  - ALT or AST >3x ULN and >2x baseline value with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. INR should be measured with this set of verification laboratory assessments and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and to evaluate the cause of liver injury.

This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin M [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

Additional evaluations may be performed at the discretion of the investigator in consultation with the medical monitor or designee.

Teduglutide administration must be discontinued if DILI is confirmed and deemed related to investigational product.

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

- At least 2 subjects develop the same event listed in Table 6 of severity CTCAE Grade 3

  or

- 1 subject develops an event listed in Table 6 of severity CTCAE Grade 4 which is attributable to investigational product or is not reasonably related to the underlying disease process

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigator or investigators' authorized site personnel must enter the information required by the protocol in 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 the investigator or qualified site personnel. When a data discrepancy warrants correction, the correction will be made by the investigator or authorized site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct. Original diary data should be entered into the eCRF and take precedence over data collected over the phone. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is enrolled, it is expected that the investigator or authorized site personnel will complete the eCRF entry in a timely manner following the subject's visit.

Unscheduled safety follow-up assessments (conducted after EOS) are not required to be collected.

9.2 Clinical Data Management

Training will occur at an investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

The required data will be captured in a validated clinical data management system that is compliant with the US FDA 21 CFR Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user.

Data will be entered into a clinical database as specified in the Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data will be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will 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.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Shire Global Drug Safety database.

9.3 Statistical Analysis Process

The 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.

Data will be analyzed and presented by subject cohorts according to the subjects' age at the time of entry in the core study: infants 4-<12 months corrected gestational age and children 1-15 years of age.

9.4 Planned Interim Analysis, and Data Monitoring Committee

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.

A DMC will be involved in the management of this study. The DMC members will review the data approximately every 6 months during the study treatment periods (date of the first subject's first dose to date of the last subject's last dose). The DMC review will include cumulative safety data (ie, AEs, laboratory assessments, physical examinations, etc.) through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Committee and the sponsor. Members of the Committee may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor (or designee), independent contractors hired by the sponsor (or designee), or members of regulatory agencies. The DMC may make recommendations to the sponsor (or designee) regarding stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped.

9.5 Sample Size Calculation and Power Considerations

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core study SHP633-302. The maximum number of subjects will be determined by the completion of Study SHP633-302.

9.6 Study Population

The safety population will include all enrolled subjects in the study. A subject will be considered enrolled in the study once the informed consent/assent has been obtained and the subject meets all of the study inclusion criteria at screening. Safety population will be used for both safety and efficacy analyses.

9.7 Efficacy Analyses

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages. The derivations of the weekly PS volume will be described in the study SAP in detail.

Efficacy Endpoints:

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (Week 24 or EOT), and at each study visit, relative to the baseline of the core study (SHP633-302). The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

9.8 Safety Analyses

Safety Endpoints:

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, blood pressure
- Laboratory safety data (ie, biochemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing, including fecal occult blood testing and colonoscopy or sigmoidoscopy

- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and BMI

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events and percentage of AEs will be calculated overall, by System Organ Class and by preferred term. Serious adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized. Medical history (including surgical history) will be coded using MedDRA. The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

For clinical laboratory tests, vital signs, and body weight, descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the observed values and change from baseline at each scheduled visit.

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

Additional safety parameters and measures will include change in body weight, height (or length) and head circumference (up to 36 months of age). Derived variables will include height z-score, weight z-score, BMI, and BMI z-score. Descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the absolute values and change from baseline at each scheduled visit.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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 international government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor or designee 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 Public Posting of Study Information

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

10.1.3 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.

10.1.4 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/assent, 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 international 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 contract research organization, 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 Case Report Forms

Electronic case report forms will be supplied by the sponsor or designee 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 solely onto the eCRF.

All data transmitted to the sponsor or designee 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 will be 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/assent 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 Pharmaceuticals and Medical Devices 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 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 receives 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 or designee to obtain written informed consent from all subjects or parents/guardian, and assent from subjects where applicable, prior to any study-related procedures including screening assessments.

All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's parent or guardian, as applicable, is requested to sign and date the informed consent form/assent 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/assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's parent or guardian, as applicable. This document requires translation into the local language. Signed consent/assent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by the parent/guardian of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the blank consent form, and assent form where applicable, which was reviewed by the IRB/EC and which 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/assent 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

It is the responsibility of the investigator to submit this protocol, the informed consent/assent 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.

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/assent documents and amendments to the protocol unless there is a subject safety issue.

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

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; for multicenter studies, this 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 consent/assent to take part in the study is received, the sponsor and/or its representatives will review 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 IRBs/ECs 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 subject's 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.

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 current standards. Participation as an investigator does not confer any rights to authorship of publications.

11 REFERENCES

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12 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	22 Jul 2016	Global
Amendment 1	26 May 2017	Global
Amendment 2	24 Jan 2018	Global
Amendment 3	20 Jul 2018	Global
Amendment 4	06 Nov 2020	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date 20 Jul 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
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, Section 8.2.4, Section 8.2.7, Section 8.3
Changed name of Shire medical monitor to [redacted], MD, PhD, FAAP. (Protocol Administrative Amendment dated 15 Mar 2018)		Emergency Contact Information
Updated the approximate number of subjects to be enrolled in the SHP633-305 study from 5 to 7. This change reflects the addition of a minimum of 2 subjects to be enrolled in the core study (SHP633-302). Also added that the study population will include 2 cohorts based on age of subjects at the time of entry in the core study: infants 4-<12 months corrected gestational age and children 1-15 years of age.		Synopsis, Section 3.1
To minimize risk to subjects, a new escape criterion was added, allowing those who had escaped during the follow-up period of a previous teduglutide treatment cycle to omit the follow-up period during subsequent teduglutide treatment cycles. For subjects who previously escaped the follow-up period, CxW24 assessments can be combined with the next pretreatment visit assessments.		Synopsis, Table 3, Figure 1, Section 3.1, Section 4.3, Section 6.2.2, Section 7.1.3.1, Section 7.1.3.2, Section 7.1.4, Section 7.2.5
Modified teduglutide treatment exclusion criterion 1 on subject's body weight to accommodate younger children (exclude subjects if weight <5 kg).		Synopsis, Section 4.2.2
Specified that results for subjects enrolled as infants in the core study will be analyzed separately in the SHP633-305 study.		Synopsis, Section 3.1, Section 9.3
Specified that saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.		Table 2, Table 3, Section 7.1.3.2, Section 7.2.5
Updated the status of the clinical study TED-C14-006 which is now completed.		Section 1.2
Deleted text that was duplicated in the same paragraph.		Section 5.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **20 Jul 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Deleted the requirements for the first dose of teduglutide to be administered by a study physician and the subject to be observed for possible hypersensitivity reactions for at least 4 hours during their initial dosing visit. Subjects enrolled in the study have already received teduglutide in the core study. (Clarification memo #2 dated 17 May 2018)		Section 6.2.2.1
Clarified requirement for the study physician to observe the parent/guardian administering the study drug at least twice in compliance with the teduglutide administration checklist before permitting the parent/guardian to administer teduglutide. Parents/guardians who have already demonstrated proficiency need only to be observed once by a study physician at each CxD1 visit as long as they continue to prepare and administer teduglutide in compliance with the study drug administration checklist. If a parent/guardian fails to administer teduglutide in compliance with the checklist, they must perform this procedure correctly on 2 consecutive observations by the study physician in order to be deemed proficient to administer the study drug unsupervised. (Clarification memo #2 dated 17 May 2018)		Section 6.2.2.1
Clarified that compliance with study drug is calculated from subject diaries.		Section 6.5
Specified that blood pressure should be collected in the same extremity rather than in the same arm as blood pressure is not collected using the arm in small children.		Section 7.2.3
Added the contact information for the monitoring personnel.		Appendix 4
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

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **24 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated Emergency Contact Information.		Emergency Contact Information
Updated the product quality complaint section to address the drug delivery device.		Product Quality Complaints
Revised study drug administration language for clarity.		Section 6.2.2
As requested by PMDA, updated text to specify the process for training parent/guardian and measures to be taken to provide oversight on study drug administration.		Table 3, Section 6.2.2.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **24 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that the study drug administration diary can be completed by study site staff.		Table 3, Section 6.5, Section 7.2.10.2
Added direct bilirubin to the list of laboratory tests.		Table 5
Replaced the term "legally authorized representative" with guardian.		Throughout protocol.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **26 May 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The Pharmacovigilance SAE Reporting fax number and email address have been updated. A sentence has been removed from the emergency contact information to eliminate a redundancy with the information provided under the Pharmacovigilance SAE Reporting heading. The title of [redacted] MD PhD is now [redacted]; his email address has been changed and fax number removed as contact.		Protocol Signature Page Emergency Contact Information
The planned study period has been updated with the initiation in August 2017.		Synopsis
Clarification has been made that medical history and short bowel syndrome (SBS) history collected at entry of Study SHP633-305 are updates to the medical history and SBS history collected at the start of SHP633-302. The statement 'This period will be less than 7 days', referring to the period between completion of Study SHP633-302 and the signing of the informed consent/assent in Study SHP633-305, has been deleted as inconsistent with the protocol.		Synopsis Section 3.1 Section 7.2.1
Clarification has been made that during the no-teduglutide treatment period, visits will take place *approximately* every 12 weeks.		Synopsis Section 3.1 Figure 1 Section 7.1.2
Text was revised for consistency and clarity on the type of visits performed during the study: at the clinic and by phone. Phone contacts were renamed phone visits.		Synopsis Table 3 Section 3.1; Section 4.5.1; Section 4.5.4; Section 6.2.2; Section 7.2.10.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **26 May 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The text on the signing of informed consent and assent was revised for consistency throughout the protocol: subjects (and/or parent or legally authorized representative, as applicable) are to sign an informed consent (and informed assent, if applicable).		Synopsis Table 1 Section 3.2; Section 4; Section 5.1; Section 7.1.1; Section 7.2.1; Section 7.2.2; Section 8.2.4; Section 9.6
Teduglutide treatment exclusion criterion 11 has been revised to broaden experimental drug to any intravenous lipid emulsions (not only to Omegaven)		Synopsis Section 4.2.2
Teduglutide treatment exclusion criterion 17 has been revised for consistency with information on female contraception in Section 4.4.1 of the protocol. Use of approved contraception is throughout the study period and for 30 days following the last dose of investigational product.		Synopsis Section 4.2.2 Section 4.4.1
The timeframe for the study completion has been reworded to 'until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued'. It was previously 'until regulatory approval and commercial availability of teduglutide in Japan'.		Synopsis Section 3.2
Language on safety endpoints has been clarified.		Synopsis; Section 9.8
Clarification has been made that no results from gastro-intestinal procedures are to be recorded: 'GI procedures' was changed to 'procedures' in all study schedules tables (and the corresponding footnote deleted) and in Section 5.1 header. The statement on 'GI procedures' was deleted in Section 5.1.		Table 1; Table 2; Table 3 Section 5.1
Clarification has been made that parenteral support prescription is to be collected at the screening visit.		Table 1
The requirement for urine specimen collection has been revised so that a lack of urinalysis will not constitute a protocol deviation for any pediatric subjects (not only for subjects wearing diapers).		Table 1; Table 2; Table 3 Section 7.2.4
For consistency within the protocol, sigmoidoscopy has been added as the alternate to colonoscopy throughout the protocol.		Table 1; Table 2; Table 3 Section 3.1; Section 7.2.9.2
A new footnote (now footnote 'a') has been added to the pretreatment visit to clarify that it may be combined with the screening visit and Study SHP633-302 EOS visit (Week 28), if the pretreatment visit assessments occur within 7 days of the SHP633 302 EOS assessments; and that if subjects proceed directly from screening to a pretreatment visit, the first pretreatment visit must occur within 12 weeks of screening.		Table 3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **26 May 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Footnote 'c' (formerly 'a') in 'CxW28 visit' has been revised to clarify that when a subject withdraws from the study during the treatment period, the early termination visit will be performed in lieu of the CxW28 visit. Former footnote 'p' "The investigator may combine the CxW28 visit with a pretreatment visit if at least 1 escape criterion is met at the CxW28 visit." has been moved into footnote 'c'.		Table 3
Footnote 'g' in "Review intake and output diaries" has been clarified. It also specifies that completion of the intake diary is not required for 2 weeks prior to the pretreatment visit.		Table 3 Section 7.2.10.2
Clarification that unscheduled laboratory tests will be performed at the investigational site laboratory. Scheduled laboratory tests will be performed at the central laboratory.		Table 3 Section7.2.4
Former footnote 'k', stating that fecal occult blood testing should be performed on an annual basis (approximately every 48-60 weeks), has been removed from Table 3 as not relevant during the treatment period when fecal blood test is performed approximately every 12 weeks.		Table 3
Clarification on timing of blood collection for antibody testing at visit CxD1 has been added to footnote 'j'.		Table 3
Footnote 'l' (formerly 'm') has been revised to clarify that serum urine pregnancy tests will be performed as per protocol schedule.		Table 3
Clarifications have been made to the indication, product, and clinical background information.		Section 1.1; Section 1.2
The in-text citation for 'O'Keefe et al. 2006' has been deleted from the rationale for dose selection (it now refers to the investigator's brochure); and the corresponding full citation deleted from the list of references.		Section 3.1; Section 11
The definition of enrollment has been clarified; the timing when all of the study inclusion criteria must be met by a subject is at screening.		Section 3.2; Section 9.6
Clarifications have been made to discontinuation of treatment. A new header entitles Section 4.5.1 'Permanent Discontinuation of Investigational Product' has been added and includes the 2 paragraphs formerly under the Section 4.5 header with the following changes: the subjects cannot be evaluated for subsequent teduglutide treatment eligibility and 'withdrawal' has been replaced with 'permanent discontinuation'.		Section 4.5; Section 4.5.1
The last paragraph has been deleted for clarity. It was redundant with information presented in Sections 4.5.1 and 4.5.2 and not necessary here.		Section 4.5.3 (formerly Section 4.5.2)
Clarification has been made to the titration instructions for concomitant enteral medications with a narrow therapeutic index when given with teduglutide.		Section 5.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **26 May 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarification that biological therapy prohibited during teduglutide treatment and within 6 months prior to the pretreatment visit refers to biological therapy used to treat inflammatory bowel disease.		Section 5.1.2
Clarification has been made that all subjects may receive teduglutide 0.05 mg/kg/day as described in Section 6.2.2 Dosing.		Section 6.2.1
Clarification has been made on visit schedule when a subject prematurely discontinues investigational product during a teduglutide treatment cycle. Clarification that subjects, and/or any designated person who will be administering the investigational product, will be trained on investigational product preparation and administration before the first dose of teduglutide or the implementation of any change in ancillary kit components.		Section 6.2.2
Language on labelling of ancillary kits has been revised.		Section 6.3.1
Clarification has been made on handling of study drug, which is for single use only and should be used within 3 hours following reconstitution. 'Handling' was added to the section header for clarity.		Section 6.3.2
The text has been corrected for consistency with other sections of the protocol.		Section 7.1.3.1
Clarification that following the Cycle Day 1 visit, subjects will return to the clinic visits on Cycle Weeks 1 through 24.		Section 7.1.3.2
The Fahrenheit (°F) temperature scale is not used in Japan. The body temperature will only be recorded in the Celsius (°C) scale. Also, 'pulse (beats per minute)' has been changed to 'pulse rate' for translation purpose.		Section 7.2.3
Urine sodium has been removed from the list of urinalysis parameters to be tested. This parameter is not needed as safety parameter nor required for the decision to adjust a subject's nutritional support. Also, a typographical error for serum β-HCG testing has been corrected, it is performed at the pretreatment visit.		Table 5
'Specific' has been deleted from 'positive/specific anti-teduglutide antibodies' to eliminate the redundancy. By definition, positive samples must be specific (as assessed in the confirmatory assay), or otherwise considered negative.		Section 7.2.6

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **26 May 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The estimated blood volume to be collected during the study has been removed because it may vary according to instructions provided by the manufacturer or laboratory for an individual assessment. Efforts will be made based on Japanese manufacturer or laboratory regulations and guidelines to minimize the amount of blood drawn from all pediatric subjects enrolled in this study.		Section 7.2.8
Performance of dipstick specific gravity tests by the subject at home on the first urine produced after the daily infusions of PS has been removed. It is now at the discretion of the investigator for all subjects, not just those in diapers. This change is to align with standard medical practice.		Section 7.2.10.2
Clarification has been made that only available diary data will be reviewed at each clinic and phone visit.		Section 7.2.10.2
The name of Shire Global Pharmacovigilance and Risk Management department has been changed to Shire Global Drug Safety.		Section 9.2
The incidence of adverse events has been deleted from the summarized data to be presented in the safety analysis for translation purpose. Percentage of adverse events will be summarized. Descriptive statistics will not be calculated for fluid balance variables.		Section 9.8

APPENDIX 2 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY

Nutritional support adjustment in volume and calories should be considered at all planned visits. Please consider the following clinical parameters identified as markers for adequate management of pediatric SBS. These parameters should be considered for managing nutritional support (PS and/or oral/enteral feeding) in terms of volume and calories during the treatment period:

- Growth trajectory, including weight, height (or length), and head circumference (for subjects up to 36 months of age)
- Other clinical evaluations
  - Serum electrolytes
  - Blood urea nitrogen /creatinine levels
  - Changes in stool frequency or volume, including mixed output
  - Stool consistency (ie, Bristol Stool Form Scale)
  - Urine specific gravity
- General consideration to possible clinical deterioration in SBS
  - Inability to maintain weight and growth velocity
  - Diarrhea (≥10 bowel movements per day, ≥80 mL/kg/day from an ostomy, or ≥75 mL/kg/day mixed output)
  - Colic/vomiting frequency increased
  - Electrolyte changes or imbalance
  - Skin breakdown
- Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.
- Nutritional support constituents may be adjusted at the discretion of the investigator.
- During the 48-hour intake/output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.
- If there is a change in EN or other food or fluid intake, the investigator should consider this when adjusting the PS/EN support in volume and calories.

APPENDIX 3 WEANING ALGORITHMS

Figure A-1 Weaning Algorithm for Subjects Who are NOT Toilet Trained and in Diapers

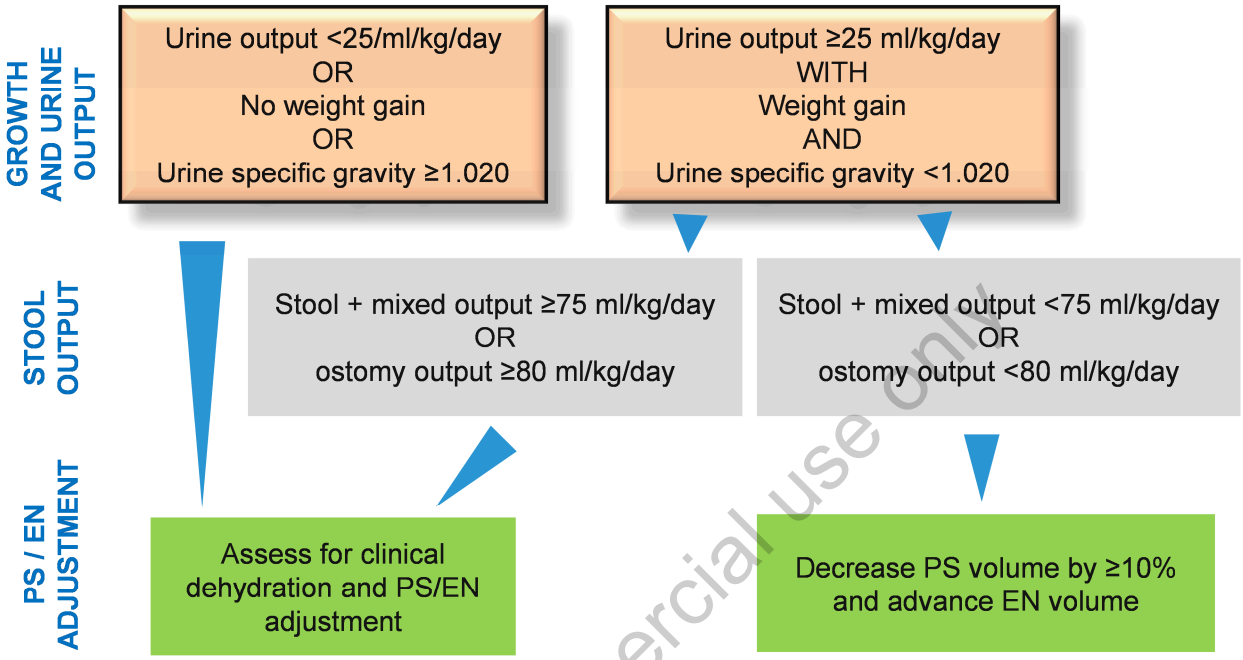


Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

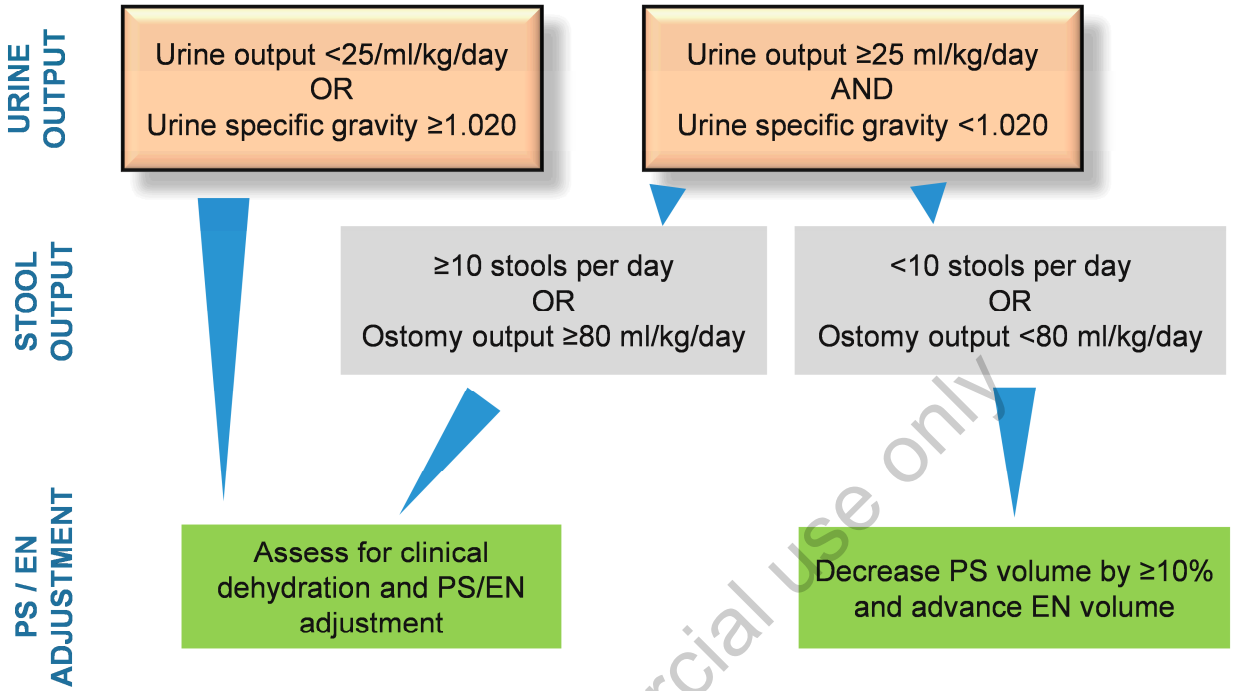
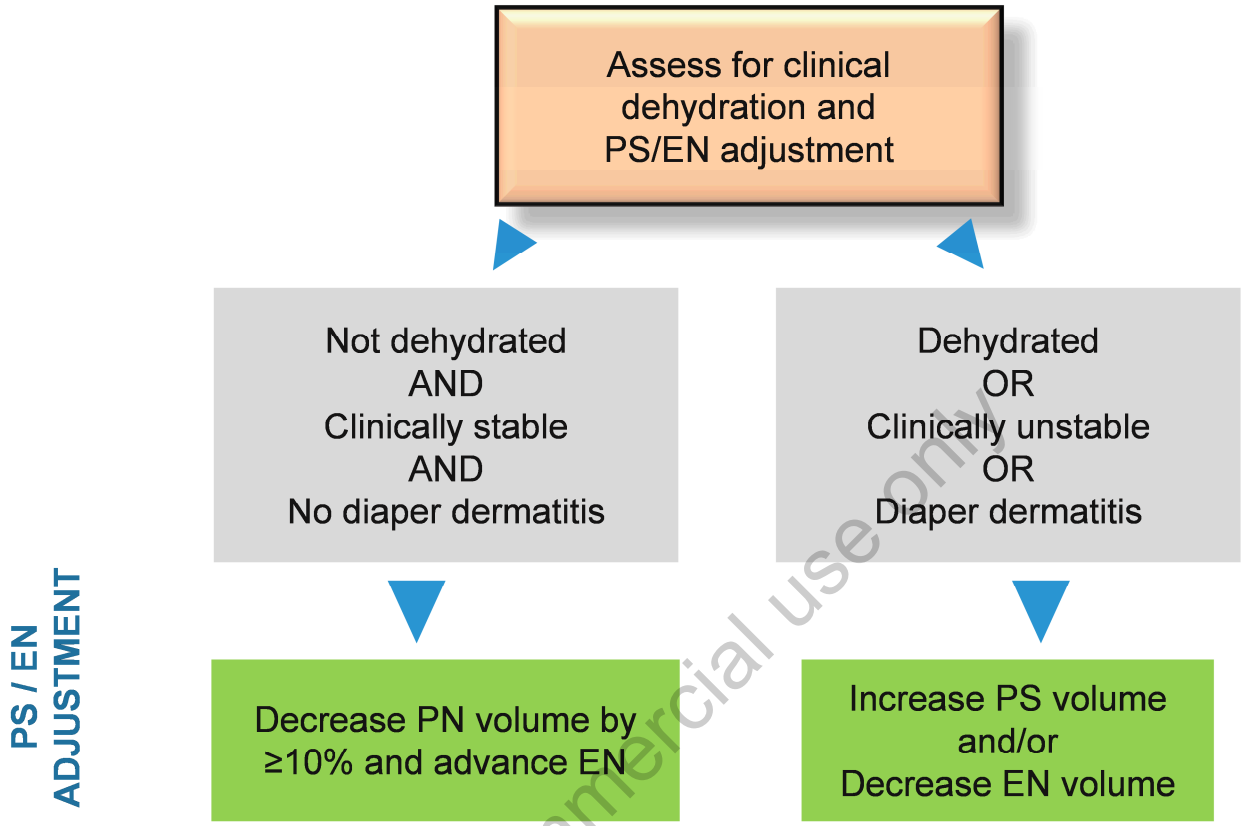


Figure A-3 Clinical Dehydration Assessment and PS/EN Adjustment



APPENDIX 4 MONITORING PERSONNEL

Takeda Pharmaceutical Company Limited
1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, Japan

Name: [redacted]
Contact info: TEL: [redacted]