## Table 1-2: Schedule of Events for Subjects Not Receiving Teduglutide

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

FOBT = fecal occult blood testing; NTT = no-teduglutide treatment; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; TED = teduglutide

[a] The first NTx visit following the screening visit must occur within 2 to 12 weeks of screening.

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

[c] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pretreatment visit if the investigator, subject, and parent or guardian agree to proceed with teduglutide therapy (Table 1-3).

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

[f] Intake diaries will collect actual PS volume and hours per day, completed daily for a minimum of 2 weeks prior to each study visit (see Section 7.2.11.2). Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit (see Section 7.2.11.3 for more detail).

[f] 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.

[g] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. CRP will not be measured in subjects <10 kg.

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

[i] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[j] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[k] Lack of collection of serum samples will not constitute a protocol deviation. Stored serum samples should be omitted for subjects weighing less than 15 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 1-3: Schedule of Events for Subjects While Receiving Teduglutide

| Period | Pre-treatment | Teduglutide Treatment | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **Px[a]** | **Cx D1** | **Cx W1** | **Cx W2** | Phone contact is required approximately 1 week after PS adjustment | **Cx W4** | Phone contact is required approximately 1 week after PS adjustment | **Cx W6** | Phone contact is required approximately 1 week after PS adjustment | **Cx W9** | Phone contact is required approximately 1 week after PS adjustment | **Cx W12** | Phone contact is required approximately 1 week after PS adjustment | **Cx W16** | Phone contact is required approximately 1 week after PS adjustment | **Cx W20** | Phone contact is required approximately 1 week after PS adjustment | **CxW24 (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]** | -21 to 0 | | **±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 |
| PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales | | 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 |

## Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

| Period | Pre-treatment | Teduglutide Treatment | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serum sample[m] | X | | | | | | | | | | | | | | | | X | | |
| Evaluate escape criteria[n] | | | | | | | | | | | | | | | | | X[p] | X | X |
| Dispense study drug[o] | | X | X | X | | X | | X | | X | | X | | X | | X | | | |

EOS = end of study; EOT = end of treatment; ET = early termination; FOBT = fecal occult blood test; FOCBP = female of child-bearing potential; FU = follow-up; GI = gastrointestinal; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; SBS = Short Bowel Syndrome; SC = subcutaneous; Scr = Screening; TED = teduglutide; Tx = treatment

[a] If the first pretreatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.

[b] Phone visits are required approximately 1 week after adjustments 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] The investigator may combine the CxW28 visit with the next pretreatment visit if at least one escape criterion is met at the CxW28 visit, and the pretreatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Table 1-1) will take place in lieu of 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 labs 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] Intake diaries will collect actual PS volume and hours per day. Intake diaries should be completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pretreatment visit), for 1 week following PS adjustment, and daily during the 4-week follow-up period. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PS prescription. See Section 7.2.11 for more detail.

[h] 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.

[i] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Clinical chemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety labs performed between clinic visits may be performed locally. Unscheduled lab results will not be captured in the eCRFs. If abnormal results are considered an adverse event, an AE form will be completed. Collect PT/INR 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 labs, but lack of urinalysis will not constitute a protocol deviation. CRP will not be measured in subjects <10 kg.

[j] Samples collected on CxD1 must be drawn prior to first administration of teduglutide. Samples collected while subjects are receiving teduglutide (CxW12 and CxW24) must be drawn at least 14 hours after dosing.

[k] The teduglutide-naïve subjects age 12 and older will undergo colonoscopy/sigmoidoscopy at the pretreatment visit if one has not been performed within 1 year. Subjects of any age with newly positive FOBT 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 FOBT 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 FOBTs at CxW12 is at the discretion of the investigator. Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy/sigmoidoscopy. See Section 7.2.9 for details.

[l] A serum pregnancy test is performed on all FOCBP at the teduglutide pretreatment visit (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered 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.

[m] Lack of collection of serum samples will not constitute a protocol deviation. Stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.

**Table 8-1: CTCAE Criteria for Adverse Events that May Lead to Dose Interruption**

| | | |
|---|---|---|
| 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) |

Source: Common Terminology Criteria for Adverse Events, version 4.03, 14 June 2010

ULN=upper limit of normal

[a] In the setting of clinically acute and symptomatic pancreatitis



### 8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

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

- 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. International normalized ratio 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 [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 Shire medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

# 4 STUDY POPULATION

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

## 4.1 Study Inclusion Eligibility Criteria

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

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, subject informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 or SHP633-301 studies (including subjects in the standard of care treatment arms). Subjects are considered to have completed SHP633-301 if they completed study assessments through week 24.
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

## 4.2 Study Exclusion Eligibility Criteria

There are no exclusion criteria for this study.

## 4.3 Teduglutide Eligibility Criteria

Subjects are eligible for teduglutide treatment if at least 1 (≥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 or legal guardian, as appropriate) must agree to proceed with treatment.

## 4.4 Teduglutide Treatment Inclusion Criteria

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least 1 of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.

| | |
|---|---|
| NTT | no-teduglutide treatment |
| PDA | patent ductus arteriosus |
| PedsQL | Pediatric Quality of Life inventory |
| PS | parenteral support |
| PT/INR | prothrombin time/international normalized ratio |
| QD | once daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBS | short bowel syndrome |
| SC | subcutaneous |
| SOC | standard of care |
| $t_{1/2}$ | elimination half-life |
| TESAE | treatment-emergent serious adverse event |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| WHO-DD | World Health Organization – Drug Dictionary |

If a subject meets 1 of the follow-up period escape criteria between cycle week 24 and 28, the subject may "escape" the follow-up period early and proceed immediately to another pretreatment visit. Following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit or another pretreatment visit within approximately 12 weeks.

At all site visits and telephone contacts, 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 (developed with SBS expert input and provided in the protocol) for decisions regarding PS support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation. (Appendix 2).

**Study Design Flow Chart**

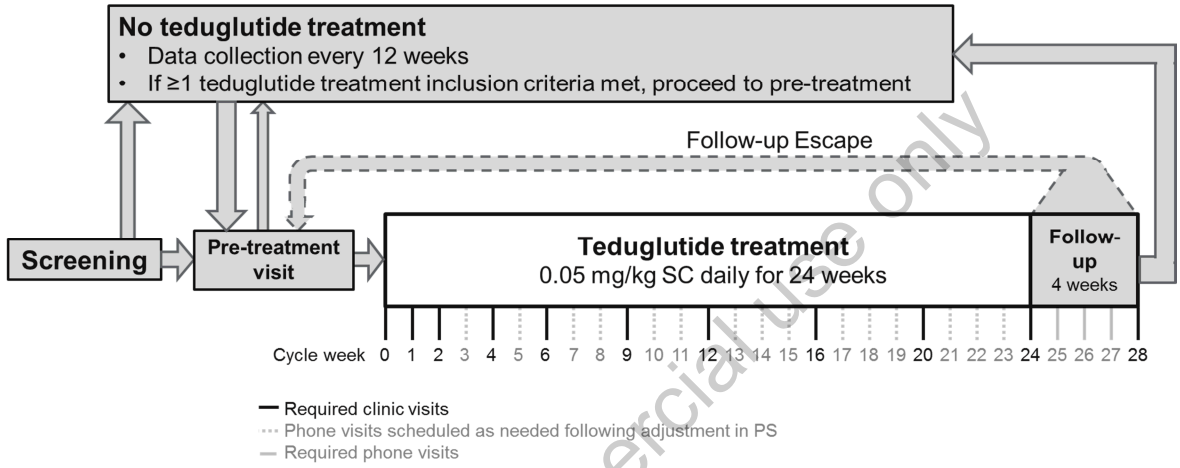


Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**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**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met at week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

**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. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 or SHP633-301 studies (including subjects in the standard of care treatment arms). Subjects are considered to have completed SHP633-301 if they completed study assessments through week 24.
3. Subject 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 one (≥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 or legal guardian, as appropriate) must agree to proceed with treatment.

# 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 pediatric subjects who completed the TED-C14-006 or SHP633-301 studies (the "core studies"). At the time of entry into TED-C14-006, subjects were less than 18 years of age, were dependent on parenteral nutrition to provide at least 30% of their caloric or fluid needs and had not been able to significantly reduce PS for at least 3 months prior to enrollment. During TED-C14-006, some subjects elected to receive standard of care instead of teduglutide treatment. Subjects who elected to receive teduglutide were randomized to 0.025 mg/kg or 0.05 mg/kg once daily (QD) dosing in a double-blinded manner.

At the time of entry into SHP633-304, subjects were 4 to 12 months corrected gestational age, were dependent on parenteral nutrition to provide at least 35% of their caloric or fluid needs, and had not been able to significantly reduce PS for at least 1 month prior to enrollment. During SHP633-301, subjects were randomized to receive standard of care or teduglutide 0.05 mg/kg SC QD.

Approximately 65 subjects who complete the core studies are expected to enroll in this extension study. All subjects who completed either core study, including those who received standard of care, may be eligible to enter SHP633-304. To be eligible to receive teduglutide treatment within SHP633-304, subjects must meet ≥1 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 period”), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. At any point during a no-teduglutide treatment period, subjects who meet ≥1 *teduglutide treatment inclusion* may proceed directly to the pretreatment visit if the investigator, subject, and parent 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

Analysis suggested that pediatric patients, ages 1 to 17 years old, are likely to require the same dose as used in adults, namely 0.05 mg/kg/day (Mouksassi et al., 2009). In this extension study, all subjects who enter a teduglutide treatment cycle will receive 0.05 mg/kg SC QD.

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 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 (O'Keefe et al., 2006).

Further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 (approximately 15% lower than healthy subjects in the same age group). Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state ($AUC_{ss}$) and maximum concentration at steady state ($C_{max,ss}$). Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in infants (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The clinical package in conjunction with $C_{max}$ was considered to support teduglutide dose of 0.05 mg/kg since $AUC_{ss}$ was previously shown not to correlate with efficacy. Thus, the 0.05 mg/kg dose is proposed for testing in all age groups.

Duration of Treatment

The duration of teduglutide treatment in this study mirrors that of the TED-C14-006 and SHP633-301 studies, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period. The follow-up period is a mechanism to evaluate whether continued teduglutide is needed. If a subject deteriorates during the follow-up period, the subject may be evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorate or stop improving at any time after the end of the follow-up period will also be assessed for additional treatment.

Rationale: During the teduglutide treatment cycle, visit frequency is similar to frequencies performed in TED-C13-003, TED-C14-006, and SHP633-301 to ensure sufficient safety monitoring and weaning of PS. During the no-teduglutide treatment, visits occur 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.

# 5 CONCOMITANT TREATMENT

## 5.1 Concomitant Medications and Procedures

Concomitant treatment refers to all treatment taken between the dates of informed consent and EOS, inclusive. Concomitant medications and procedures will be assessed at each site visit, and include all non-study 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.

### 5.1.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

### 5.1.2 Prohibited Treatment

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. Down-titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

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

**Table 5-1: 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 |

- Record PS prescription and adjust as needed
- Safety Laboratory Tests (ie, clinical chemistry, hematology, and urinalysis)
- PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales
- Antibodies to teduglutide, if and when required
- Fecal occult blood testing, as indicated (Section 7.2.9.1)
- Colonoscopy/sigmoidoscopy, as indicated (see Section 7.2.9.2)
- Serum sample, as indicated

Teduglutide treatment may be considered at any time during the NTT period. If the investigator and the subject (and parent or legal guardian, as appropriate) agrees to proceed with treatment if the subject is eligible, the subject may proceed to the pretreatment visit immediately to determine eligibility.

### 7.1.3 Visits for Subjects Receiving Teduglutide

#### 7.1.3.1 Pretreatment Visit

Subjects who meet at least 1 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, subject and parent 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.

The pretreatment visit may also be combined with screening visit, and if the pretreatment visit assessments occur within 7 days of the TED-C14-006 or SHP633-301 EOS visit, both sets of assessments can be combined. A subject must have 2 weeks of intake diary data collected, prior to the first dose administration (CxD1) during any teduglutide treatment cycle. In general, pretreatment assessments may occur over a period of up to 21 days. The teduglutide pretreatment visit (Px) assessments and procedures will be performed as in Table 1-3 and as described below:

- Evaluate teduglutide eligibility (treatment inclusion/exclusion criteria)
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant procedures
- Fecal occult blood testing
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed

- Safety Laboratory Tests
  (In addition to clinical chemistry, hematology, and urinalysis, labs at this visit include prothrombin time [PT] international normalized ratio [INR]. Subsequent prothrombin time/international normalized ratio [PT/INR] measurement is only required to evaluate for suspected drug-induced liver injury [DILI]).
- Serum pregnancy testing, if applicable (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory)
- Serum sample

#### 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 1-3 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. Visit windows are calculated based upon the date of first investigational product administration (Visit CxD1).

**Visit CxD1**

Assessments and procedures at this visit will be performed as outlined Table 1-3 and as described below.

Two weeks of intake diary data are required before drug is administered at CxD1.

- Confirm teduglutide treatment eligibility
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing (urine), if applicable
- Dispense study drug

- Study drug dispensation (except for CxW24)
- Adverse events, concomitant medications and concomitant GI procedures

In addition, at CxW12 and CxW24 Visits **ONLY**, the following procedures will be performed:

- Height and head circumference
- Antibodies to teduglutide
- Fecal occult blood testing (FOBT)
- GI-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Quality of life measurements

At CxW24 **ONLY**, 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.

#### 7.1.3.4 Phone Visits

Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period. Phone visit assessments and procedures are outlined in Table 1-3 and described below:

- Review intake and output diaries
- Safety laboratory tests (clinical chemistry and urinalysis)
- Record PS and EN prescriptions, and adjust as needed
- Obtain AEs, concomitant medications, and concomitant GI procedures
- Evaluate escape criteria

### 7.1.4 Teduglutide Follow-up Period

The safety follow-up period for this protocol is 4 weeks (Weeks 25 – 28 of the cycle). Phone visits will occur on cycle weeks 25, 26, and 27 for all subjects. Phone visit assessments and procedures at weeks 25-27 will be the same as for telephone visits performed during the teduglutide treatment period. In addition, subjects will be evaluated for follow-up period escape criteria. If escape criteria are met at any time during the follow-up period, the subject may proceed directly to another pre-treatment visit at the investigator's discretion.

At cycle week 28 (CxW28), subjects will return to the study site. In addition to the assessments performed at weeks 25-27, the following procedures will be performed at **CxW28 ONLY:**

- Physical examination and vital signs, including weight
- Antibodies to teduglutide
- Pregnancy testing (urine)
- Evaluate escape criteria

#### 7.1.4.1 Study Completion/Early Termination Visit (EOS/ET Visit)

All subjects will return to the study site for the end of study/early termination visit (EOS/ET). Assessments and procedures at this visit will be performed as outlined in Table 1-1 and as

described here. If a subject discontinues the study prematurely, the assessments for the EOS/ET Visit are to be performed as completely as possible.

- Adverse events, concomitant medications and concomitant GI procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS and EN prescriptions, and adjust as needed
- Safety laboratory tests
- Fecal occult blood testing, as indicated
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated.
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing, as needed

## 7.2 Study Evaluations and Procedures

### 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 TED-C14-006
- Events that occurred during the period between completion of TED-C14-006 and informed consent to SHP-633-304
- Gestational age at birth and parental heights.

This medical history information will supplement the medical history information collected at the start of the TED-C14-006 core study. If the subject has any changes to the SBS history collected at the baseline visit of the TED-C14-006 study, that information (updated SBS history) will be collected.

### 7.2.2 Physical Examination

Physical examinations will be performed according to the study schedules. Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

### 7.2.3 Vital Signs, Body Weight, Height, Head Circumference and Body Mass Index (BMI)

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study).

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Height (or length) and head circumference (for subjects ≤36 months of age) will be measured at selected visits. A height z-score, weight z-score, BMI, and BMI z-score will be calculated by the sponsor using the site-provided height and weight data collected at each site visit

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 to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1-1, Table 1-2, and Table 1-3) Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. Safety labs performed after PS adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an AE (see Section 8.1). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant labs should be reported as AEs.

complete. The scales include self-reports for pediatric subjects and adolescents aged 5 to 18 years and proxy-reports from parents of pediatric subjects aged 2 to 18 years.

Field trials have shown that the internal consistency reliability of the PedsQL was excellent, with alphas for the generic core scales in both self- and proxy-report greater than the 0.70 standard, and alphas for the full 23-item scale approaching 0.90 for self- and proxy-report. Missing data were minimal. Item response distributions were across the full scale range, with no floor effects, and minimal ceiling effects.

The validity of the PedsQL Generic Core Scales was demonstrated through known group comparisons, and correlations with other measures of disease burden. The PedsQL self- and proxy-report distinguished between pediatric subjects with and without a chronic health condition, and within the group of pediatric subjects with a chronic condition, between those who did or did not have an overnight hospital visit in the last 12 months. Further, both child self-report and parent proxy-report correlated significantly with the number of days the child was too ill to pursue normal activities, needed someone to care for him or her, missed school in the last month, the number of days the parent missed from work in the last month, and parent-report of problems pursuing their normal work routine and concentrating at work. The PedsQL Generic Core Scales are also responsive to clinical change, as demonstrated in field trials.

#### 7.2.13.1 Pediatric Quality of Life Generic Core Scale (PedsQL™), Acute version

The PedsQL Generic Core Scale is designed to measures health-related quality of life (HRQoL) in pediatric subjects and adolescents (2-18 years of age). The developmentally appropriate PedsQL Generic Core Scale will be completed by either the parent or legal guardian and subject as indicated in Table 7-2 at the time points as outlined in Table 1-1, Table 1-2 and Table 1-3.

**Table 7-2: Developmentally Appropriate PedsQL™ Generic Core Scales**

| Report | Completed by |
|---|---|
| Parent Report for Toddlers (ages 2-4) | Parent or Legal Guardian |
| Child Self Report and Parent Proxy-Report for Young Pediatric subjects (ages 5-7) | Subject and Parent or Legal Guardian |
| Child Self Report and Parent Proxy-Report for Pediatric subjects (ages 8-12) | Subject and Parent or Legal Guardian |
| Child Self Report and Parent Proxy-Report for Teens (ages 13-18) | Subject and Parent or Legal Guardian |

Abbreviations: PedsQL=Pediatric Quality of Life Inventory

The Parent Report for Toddlers (ages 2-4) of the PedsQL Generic Core Scale is composed of 21 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (3 items).

The Child and Parent Reports of the PedsQL Generic Core Scale for Young Pediatric subjects (ages 5-7), Pediatric subjects (ages 8-12), and Teens (ages 13-18) are composed of 23 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (5 items).

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

In consideration of whether a treatment-emergent adverse event (TEAE) might lead to dose interruption (Section 8.4.1) or early termination of the study (Section 8.5), severe TEAEs will also be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grading criteria (US Department of Health and Human Services et al., 2010).

### 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 study drug 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.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Drug Safety Department 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 Sponsor 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 discontinued immediately.

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 SAEs and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events and Non-serious AEs as Required by the 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 the 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 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 given in one day (a day is defined as beginning at 12:00 AM and ending at 11:59 PM)

- 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 pre-existing 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 1 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 subject signs the informed consent until the defined follow-up period stated in Section 7.1.4, and must be reported to the Shire Global Drug Safety Department and the Sponsor 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 the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.



### 8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

### 8.2.6 Fatal Outcome

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

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

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

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, 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 include the following:

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

For AEs of special interest, the sponsor 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 the seriousness criteria.

## 8.4 Dose Interruption of Individual Subjects

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted.

Attempts should be made to contact the sponsor/designee prior to dose interruption. Reasons for dosage interruptions may include but are not limited to hospitalization, AEs, a lapse in investigational product delivery, etc. The length of the dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

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

- An AE of special interest (see Section 8.3)
- An AE that is of NCI CTCAE severity Grade 3 or 4 and related to teduglutide
- Intestinal obstruction
- Biliary obstruction related to teduglutide
- Pancreatic duct obstruction related to teduglutide
- Heart failure with severe fluid overload related to teduglutide

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

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to study drug. 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.
- Confirmed DILI related to teduglutide (see Section 8.4.2)
- Any malignancy.

### 8.4.1 Dose Interruption Criteria Based on Adverse Event Severity and Relationship to Investigational Product

The investigational product must be interrupted if the subject experienced an AE that is of severity ≥Grade 3 per the NCI CTCAE and is reported as related to the investigational product.

In consideration of whether a TEAE might lead to dose interruption, severe TEAEs will also be graded according to the NCI CTCAE severity grading criteria (US Department of Health and Human Services et al., 2010). All such TEAEs should be discussed with the Sponsor Medical Monitor or designee as soon as possible. The length of the dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

## 9.8 Safety Analyses

### 9.8.1 Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, and blood pressure
- Laboratory safety data (ie, clinical chemistry, 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, incidence, and percentage of AEs will be calculated overall, by System Organ Class (SOC) and by preferred term. SAEs 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 (WHO-DD) 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/procedural 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, body weight, and fluid balance variables, 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 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.

## 9.9 Other Analyses

### 9.9.1 Health-related Quality of Life Analyses

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
  - Food and Drink Limits
  - Diarrhea

### 9.9.2 Qualitative Interviews

A final report will be developed for the qualitative interviews and will be included in the CSR of the study.

**Table 8-1: CTCAE Criteria for Adverse Events that May Lead to Dose Interruption**

| Adverse Events | Grade 3 Description | Grade 4 Description |
|---|---|---|
| Alkaline Phosphatase increased | >5.0 to 20.0x ULN | >20.0x ULN |
| 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) |

Source: Common Terminology Criteria for Adverse Events, version 4.03, 14 June 2010

ULN=upper limit of normal

[a] In the setting of clinically acute and symptomatic pancreatitis



### 8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

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

- 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%)

| Abbreviation | Definition |
|---|---|
| IWRS | interactive web-based response system |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NA | North America |
| NCI | National Cancer Institute |
| NDA | new drug application |
| NTT | no-teduglutide treatment |
| PedsQL | Pediatric Quality of Life inventory |
| PS | parenteral support |
| PT/INR | prothrombin time/international normalized ratio |
| QD | once daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBS | short bowel syndrome |
| SC | subcutaneous |
| SOC | standard of care |
| $t_{1/2}$ | elimination half-life |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| WHO-DD | World Health Organization – Drug Dictionary |

**Table 7-3: Developmentally Appropriate PedsQL™ Generic Core Scales**

| Report | Completed by |
|---|---|
| Parent Report for Toddlers (ages 2-4) | Parent or Legal Guardian |
| Child Self Report and Parent Proxy-Report for Young Pediatric subjects (ages 5-7) | Subject and Parent or Legal Guardian |
| Child Self Report and Parent Proxy-Report for Pediatric subjects (ages 8-12) | Subject and Parent or Legal Guardian |
| Child Self Report and Parent Proxy-Report for Teens (ages 13-18)[a] | Subject and Parent or Legal Guardian |

Abbreviations: PedsQL=Pediatric Quality of Life Inventory

[a] The Child Self Report and Parent Proxy-Report for Teens (ages 13-18) will also be completed for subjects older than 18 years of age.

The Parent Report for Toddlers (ages 2-4) of the PedsQL Generic Core Scale is composed of 21 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (3 items).

The Child and Parent Reports of the PedsQL Generic Core Scale for Young Pediatric subjects (ages 5-7), Pediatric subjects (ages 8-12), and Teens (ages 13-18) are composed of 23 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (5 items).

#### 7.2.12.2 Pediatric Quality of Life Family Impact Module (PedsQL™), Acute Version

The PedsQL Family Impact Module is a parent-report multidimensional instrument that will be completed by the parent or legal guardian, as outlined in Table 1-1, Table 1-2, and Table 1-3.

The PedsQL Family Impact Module is a specific module of the PedsQL that is used to measure the impact of pediatric chronic health conditions on parents and the family (Varni et al., 2004). The 36-item PedsQL Family Impact Module consists of 6 scales measuring parent self-reported functioning as follows: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items; worries about treatment and disease), 5) Communication (3 items), 6) Worry (5 items). Two additional scales measure parent-reported family functioning as follows: 1) Daily Activities (3 items), and 2) Family Relationships (5 items). The PedsQL Family Impact Module should take the parent or legal guardian approximately 5 to 10 minutes to complete.

#### 7.2.12.3 PedsQL Gastrointestinal Symptoms Module (PedsQL™), Acute Version

The PedsQL Gastrointestinal Symptom Module is a disease-specific 58-item module, comprised of 10 different symptom scales that assess gastrointestinal symptom-related quality of life: food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in poop, and diarrhea. The PedsQL Gastrointestinal Symptoms Module was designed to allow the selection and scoring of individual scales from the Module. The scales of Food and Drink Limits (6 items) and Diarrhea (7 items) were identified as clinically relevant and appropriate for the symptoms experienced in this pediatric study population, and therefore, are the only scales used in this study.

## Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

| Period | Pre-treatment | Teduglutide Treatment | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **Px[a]** | **Cx D1** | **Cx W1** | **Cx W2** | Phone contact is required approximately 1 week after PS adjustment | **Cx W4** | Phone contact is required approximately 1 week after PS adjustment | **Cx W6** | Phone contact is required approximately 1 week after PS adjustment | **Cx W9** | Phone contact is required approximately 1 week after PS adjustment | **Cx W12** | Phone contact is required approximately 1 week after PS adjustment | **Cx W16** | Phone contact is required approximately 1 week after PS adjustment | **Cx W20** | Phone contact is required approximately 1 week after PS adjustment | **CxW24 (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]** | -21 to 0 | | **±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 GI procedures[f] | 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[g] | X | X | | | | | | | | | | X | | | | | | X | | |
| Review intake and output diaries[h] | X | X | X | X | | X | | X | | X | | X | | X | | X | | X | X | X |
| Record PS Rx and adjust as needed[i] | X | X | X | X | | X | | X | | X | | X | | X | | X | | X | X | X |
| Safety laboratory tests[j] | X[j] | X | X | X | | X | | X | | X | | X | | X | | X | | X | (X) | X |
| PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales | | X | | | | | | | | | | X | | | | | | X | | |
| Antibodies to teduglutide[k] | | X | | | | | | | | | | X | | | | | | X | | X |
| Fecal occult blood testing | X | | | | | | | | | | | X | | | | | | X | | |
| Colonoscopy/ sigmoidoscopy[l] | (X) | | | | | | | | | | | (X) | | | | | | (X) | | |
| Pregnancy testing[m] | X | X | | | | X | | | | X | | X | | X | | X | | X | | X |

## Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

| Period | Pre-treatment | Teduglutide Treatment | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serum sample[n] | X | | | | | | | | | | | | | | | | X | | |
| Evaluate escape criteria[o] | | | | | | | | | | | | | | | | | | X | X |
| Dispense study drug[p] | | X | X | X | | X | | X | | X | | X | | X | | X | | | |

EOS = end of study; EOT = end of treatment; ET = early termination; FOBT = fecal occult blood test; FOCBP = female of child-bearing potential; FU = follow-up; GI = gastrointestinal; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; SBS = Short Bowel Syndrome; SC = subcutaneous; Scr = Screening; TED = teduglutide; Tx = treatment.

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

[a] If the first pre-treatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.

[b] Phone visits are required approximately 1 week after adjustments 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] The investigator may combine the CxW28 visit with the next pre-treatment visit if at least one escape criterion is met at the CxW28 visit, and the pre-treatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Table 1-1) will take place in lieu of 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 labs obtained at the CxD1 visit are not required to determine teduglutide treatment eligibility.

[f] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

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

[h] Intake diaries will collect actual PS volume and hours per day. Intake diaries should be completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pre-treatment visit), for 1 week following PS adjustment, and daily during the 4-week follow-up period. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PS prescription. See Section 7.2.11 for more detail.

[i] 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.

[j] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Clinical chemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety labs performed between clinic visits may be performed locally. Unscheduled lab results will not be captured in the eCRFs. If abnormal results are considered an adverse event, an AE form will be completed. Collect PT/INR at the pre-treatment 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 labs, but lack of urinalysis will not constitute a protocol deviation.

[k] Samples collected on CxD1 must be drawn prior to first administration of teduglutide. Samples collected while subjects are receiving teduglutide (CxW12 and CxW24) must be drawn at least 14 hours after dosing.

[l] The teduglutide-naïve subjects age 12 and older will undergo colonoscopy/sigmoidoscopy at the pre-treatment visit if one has not been performed within 1 year. Subjects of any age with newly positive FOBT results at the pre-treatment 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 FOBT 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 FOBTs at CxW12 is at the discretion of the investigator. Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo

### 8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

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

- 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. International normalized ratio 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 [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 Sponsor medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

## 8.5 Early Termination of the Clinical Study

The data monitoring committee (DMC) may recommend stopping the study if any of the following conditions are met:

- ≥2 subjects develop the same event of CTCAE severity Grade 3 that is reported as related to the investigational product

  or

- 1 subject develops an event of CTCAE severity Grade 4 that is reported as related to the investigational product.

and 28, the subject may "escape" the follow-up period early and proceed immediately to another pretreatment visit. Following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit or another pretreatment visit within approximately 12 weeks.

At all site visits and telephone contacts, 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 (developed with SBS expert input and provided in the protocol) for decisions regarding PS support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation. (Appendix 2).

**Study Design Flow Chart**

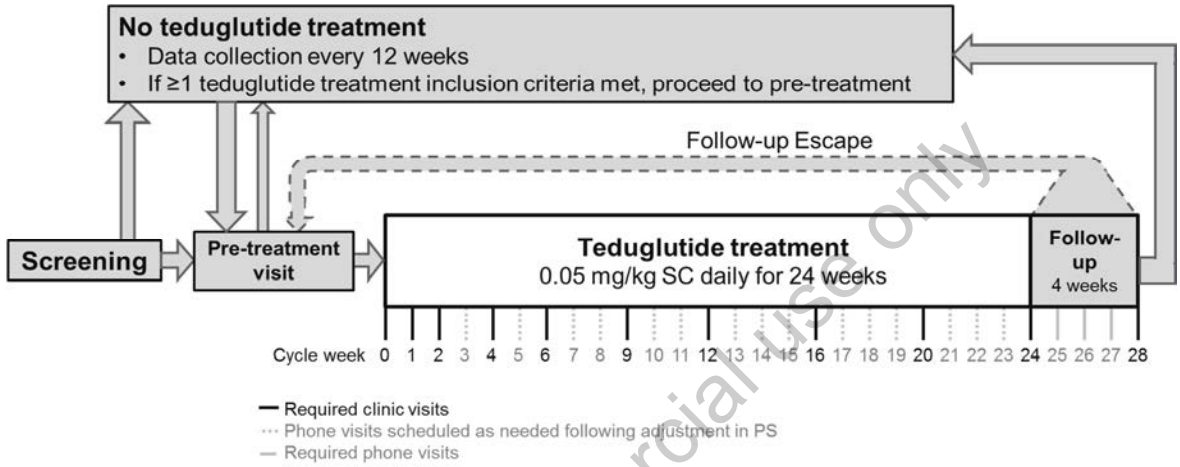


Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**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**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met at week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

**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. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 or SHP633-301 studies (including subjects in the standard of care treatment arms). Subjects are considered to have completed SHP633-301 if they completed study assessments through week 24.
3. Subject 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 one (≥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 or legal guardian, as appropriate) must agree to proceed with treatment.

***Teduglutide Treatment Inclusion Criteria*:**

## Table 1-2: Schedule of Events for Subjects Not Receiving Teduglutide

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

FOBT = fecal occult blood testing; NTT = no-teduglutide treatment; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; TED = teduglutide.

[a] The first NTx visit following the screening visit must occur within 2 to 12 weeks of screening.

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

[c] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pretreatment visit if the investigator, subject, and parent or guardian agree to proceed with teduglutide therapy (Table 1-3).

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

[f] Intake diaries will collect actual PS volume and hours per day, completed daily for a minimum of 2 weeks prior to each study visit (see Section 7.2.11.2). Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit (see Section 7.2.11.3 for more detail).

[f] 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.

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

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

[i] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[j] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[k] Lack of collection of serum samples will not constitute a protocol deviation.

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

## Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

| Period | Pre-treatment | Teduglutide Treatment | Follow-up |
|---|---|---|---|

[n] If escape criteria are met, the subject may proceed directly to another pretreatment visit at the discretion of the investigator.
[o] The first SC injection of teduglutide in treatment-naïve subjects will be administered under the supervision of the investigator/designee after which the subject will be observed for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF. See Section 6.2.3 for dose adjustment.
[p] 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.
Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

## 8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

- ≥2 subjects being administered investigational product develop the same event listed in Table 8-1 of severity CTCAE Grade 3

  or

- 1 subject develops an event listed in Table 8-1 of severity CTCAE Grade 4 which is attributable to investigational product or is not reasonably related to the underlying disease process.

d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
e. Severe diarrhea related to teduglutide discontinuation.

## 4.5 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 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 ligation
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, 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

# STUDY SYNOPSIS

| | |
|---|---|
| **Protocol number:** SHP633-304 | **Drug:** Teduglutide |
| **Title of the study:** A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome (SBS) Who Completed TED-C14-006 | |
| **Number of subjects (total and for each treatment arm):**<br>Approximately 34 subjects who completed the TED-C14-006 study, including subjects in the standard of care treatment arm, are expected to enroll in this extension study. This study will enroll up to as many subjects as complete the TED-C14-006 study. | |
| **Investigator(s):** Multicenter study | |
| **Site(s) and Region(s):**<br>Approximately 28 investigational sites in North America and Europe will participate in this extension study | |
| **Study period (planned):**<br>October 2016 – September 2019 | **Clinical phase:** 3 Extension |
| **Objectives:**<br>**Primary:** To evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS.<br>**Secondary:** To evaluate long-term efficacy of teduglutide treatment in pediatric subjects with SBS. | |
| **Rationale:**<br>This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with short bowel syndrome (SBS) who completed the TED-C14-006 study (the core study). 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, and will allow the study of first-time treatment of teduglutide-naïve subjects who participated in the standard of care (SOC) treatment arm in TED-C14-006. | |
| **Investigational product, dose, and mode of administration:**<br>This study will allow repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily (QD) injection for eligible pediatric subjects. There is no active comparator or reference product. | |
| **Methodology:**<br>This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 study (core study).<br><br>Once the informed consent (and if applicable, informed assent) have been reviewed and signed, demographics, medical history, and short bowel syndrome history will be obtained. Subjects not receiving teduglutide treatment (ie, in a no-teduglutide treatment [NTT] period), will be seen every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. The first NTT visit will occur approximately 12 weeks after the screening visit. At any point after screening, including during a NTT period, subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed **immediately** to the pre-treatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy.<br><br>After the pre-treatment visit, subjects who meet ≥1 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 period (during which no teduglutide is administered) (Figure 3-1). During the 28-week cycle, clinic visits will occur at 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 TED treatment period, between weeks 1-24, and weekly during the TED follow-up period, between weeks 24 and 28. Safety and PS requirements will be evaluated at every visit, and quality of life assessments will be made approximately every 12 weeks. If a subject has clinical deterioration and meets follow-up period escape criteria after stopping teduglutide, | |

***Teduglutide Treatment Inclusion Criteria*:**

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least one of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. 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 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 ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, 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.

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 SBS history. Subjects who meet ≥1 of the teduglutide treatment inclusion criteria may proceed to the pretreatment visit.

After the pretreatment visit, subjects who still meet ≥1 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 3-1). During the 28-week cycle, clinic visits will occur at 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 1-24), and weekly during the teduglutide follow-up period (between weeks 24 and 28).

Safety and PS requirements will be evaluated on a weekly basis, and quality of life assessments will be made approximately every 12 weeks. At all site visits and telephone contacts, 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 (developed with SBS expert input and provided in 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, however, is not considered a protocol deviation (Appendix 2).

Rationale: Measures of long-term safety will include AEs, growth parameters and anti-drug antibodies. Measure of long-term efficacy will include durability of effect as measured by reduction in PS and improvement in pediatric quality of life measures (PedsQL, PedsQL Family Impact Module). 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 and increases in enteral intake. 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. Quality of life assessments will be performed in this study to quantitate this effect.

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.

# 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 for this open-label study.

## 6.2 Administration of Investigational Product(s)

### 6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and return of investigational product. Please refer to the Study Manual for additional details regarding the IWRS.

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site, and site personnel will receive training.

### 6.2.2 Allocation of Subjects to Treatment

This is an open-label study. Subjects will retain their assigned subject number from the TED-C14-006 or SHP633-301 studies. Assessment of need for teduglutide treatment should be guided by the teduglutide treatment inclusion criteria. If the investigator, subject, and/or parent/guardian agree to proceed with treatment, a formal evaluation of teduglutide inclusion and exclusion criteria will be performed at the pretreatment visit (Table 1-3).

### 6.2.3 Dosing

If teduglutide treatment eligibility is established at the pretreatment visit and again, confirmed at the 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 QD into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

### Site Visits during Teduglutide Treatment Period

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 1-3 and as described below:

- Dispense/review intake and output diaries (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 nutritional stability prior to each clinic visit)
- Physical examination and vital signs, including weight
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Urine pregnancy testing for FOCBP (CxW4, CxW9, CxW12, CxW16, CxW20, CxW24)
- Study drug dispensation (except for CxW24)
- Adverse events, concomitant medications and concomitant procedures

In addition, at CxW12 and CxW24 Visits **ONLY**, the following procedures will be performed:

- Height and head circumference
- Antibodies to teduglutide
- Fecal occult blood testing (FOBT)
- GI-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Quality of life measurements

At CxW24 **ONLY**, 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.

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.

### Phone Visits

Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period. Phone visit assessments and procedures are outlined in Table 1-3 and described below:

- Review intake and output diaries
- Safety laboratory tests (clinical chemistry and urinalysis)
- Record PS prescription and adjust as needed

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Height (or length) and head circumference (for subjects ≤36 months of age) will be measured at selected visits. A height z-score, weight z-score, BMI, and BMI z-score will be calculated by the sponsor using the site-provided height and weight data collected at each site visit

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 to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1-1, Table 1-2, and Table 1-3) Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. Safety labs performed after PS adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results will not be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8.1). For pediatric subjects in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant labs should be reported as AEs.

The following clinical laboratory assessments will be performed according to the study schedules:

The following clinical laboratory assessments will be performed according to the study schedules:

**Table 7-1: List of Laboratory Tests**

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

**Coagulation**:
Prothrombin time/International normalized ratio

**Urinalysis**:
- Blood
- Glucose
- Leukocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity

**Pregnancy tests** (females of childbearing potential):
- Serum β-HCG (teduglutide pretreatment visit)
- Urine β-HCG (all other visits)

**Biochemistry**:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total, direct, and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein[a]
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides
- Uric acid

[a] C-reactive protein will not be measured in subjects <10 kg.



### 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

Stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.

#### 7.2.13.2 Pediatric Quality of Life Family Impact Module (PedsQL™), Acute version

The PedsQL Family Impact Module is a parent-report multidimensional instrument that will be completed by the parent or legal guardian, as outlined in Table 1-1, Table 1-2, and Table 1-3.

The PedsQL Family Impact Module is a specific module of the PedsQL that is used to measure the impact of pediatric chronic health conditions on parents and the family (Varni et al. 2004). The 36-item PedsQL Family Impact Module consists of 6 scales measuring parent self-reported functioning as follows: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items; worries about treatment and disease), 5) Communication (3 items), 6) Worry (5 items). Two additional scales measure parent-reported family functioning as follows: 1) Daily Activities (3 items), and 2) Family Relationships (5 items). The PedsQL Family Impact Module should take the parent or legal guardian approximately 5 to 10 minutes to complete.

#### 7.2.13.3 PedsQL Gastrointestinal Symptoms Module (PedsQL™), Acute version

The PedsQL Gastrointestinal Symptom Module is a disease-specific 58-item module, comprised of 10 different symptom scales that assess gastrointestinal symptom-related quality of life: food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in poop, and diarrhea. The PedsQL Gastrointestinal Symptoms Module was designed to allow the selection and scoring of individual scales from the Module. The scales of Food and Drink Limits (6 items) and Diarrhea (7 items) were identified as clinically relevant and appropriate for the symptoms experienced in this pediatric study population, and therefore, are the only scales used in this study. The scales will be completed by either the parent or legal guardian and subject as indicated in Table 7-2 at the time points outlined in Table 1-1, Table 1-2, and Table 1-3.

### 8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study in 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 the study, 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 end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

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

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

### 8.1.6 Pregnancy

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

- **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/legally-authorized representative/caregiver.

## 8.2 Serious Adverse Event Procedures

### 8.2.1 Reference Safety Information

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

### 8.2.2 Reporting Procedures

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

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Sponsor Medical Monitor 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 SAEs and Non-serious AEs as Required by Protocol and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Sponsor medical monitor or designee using the details specified in the emergency contact information section of the protocol.

### 8.2.3 Serious Adverse Event Definition

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

- Results in death

# 10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

## 10.1 Sponsor's Responsibilities

### 10.1.1 Good Clinical Practice Compliance

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

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

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

### 10.1.2 Indemnity/Liability and Insurance

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

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

### 10.1.3 Public Posting of Study Information

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

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

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

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. International normalized ratio 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 [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 Shire medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

## 8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

- ≥2 subjects being administered investigational product develop the same event listed in Table 8-1 of severity CTCAE Grade 3

  or

- 1 subject develops an event listed in Table 8-1 of severity CTCAE Grade 4 which is attributable to investigational product or is not reasonably related to the underlying disease process.

# STUDY SYNOPSIS

| | |
|---|---|
| **Protocol number:** SHP633-304 | **Drug:** Teduglutide |
| **Title of the study:** A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome (SBS) Who Completed TED-C14-006 or SHP633-301 | |
| **Number of subjects (total and for each treatment arm):**<br>Approximately 65 subjects who completed the TED-C14-006 or SHP633-301 studies, including subjects in the standard of care treatment arms, are expected to enroll in this extension study. This study will enroll up to as many subjects as complete the TED-C14-006 and SHP633-301 studies. | |
| **Investigator(s):** Multicenter study | |
| **Site(s) and Region(s):**<br>Approximately 28 investigational sites in North America and Europe will participate in this extension study | |
| **Study period (planned):**<br>October 2016 – December 2020 | **Clinical phase:** 3 Extension |
| **Objectives:**<br>**Primary:** To evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS.<br>**Secondary:** To evaluate long-term efficacy of teduglutide treatment in pediatric subjects with SBS. | |
| **Rationale:**<br>This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with short bowel syndrome (SBS) who completed either the TED-C14-006 or SHP633-301 studies (the core studies). 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 and will allow the study of first-time treatment of teduglutide-naïve subjects who participated in the standard of care (SOC) treatment arms in TED-C14-006 or SHP633-301. | |
| **Investigational product, dose, and mode of administration:**<br>This study will allow repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily (QD) injection for eligible pediatric subjects. There is no active comparator or reference product. | |
| **Methodology:**<br>This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 or SHP633-301 studies (core studies).<br><br>Once the informed consent (and if applicable, informed assent) have been reviewed and signed, demographics, and updates to medical history and short bowel syndrome history will be obtained. Subjects not receiving teduglutide treatment (ie, in a no-teduglutide treatment [NTT] period), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. The first NTT visit after the screening visit will occur within 2 to 12 weeks of the screening visit. At any point after screening, including during a NTT period, subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed **immediately** to the pretreatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy.<br><br>After the pretreatment visit, subjects who meet ≥1 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 period (during which no teduglutide is administered) (Figure 3-1). During the 28-week cycle, clinic visits will occur at 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). Safety and PS requirements will be evaluated at every visit, and quality of life assessments will be made approximately every 12 weeks. | |

The scales will be completed by either the parent or legal guardian and subject as indicated in Table 7-3 at the time points outlined in Table 1-1, Table 1-2, and Table 1-3.

### 7.2.13 Qualitative Interviews

The objective of the qualitative interviews is to elicit the key symptoms and impacts of importance associated with SBS as well as the effect of teduglutide in relation to symptoms and impact experienced during the clinical study as described by subjects and caregivers in their own words. In addition, the interviews with caregivers will elicit concepts on aspects of caregiver burden associated with caring for their children with SBS and the impact of teduglutide on the caregiver burden experienced during the study.

The interviews will be offered to English-speaking parents or legal guardians of subjects and subjects aged 12 years or older in selected countries. At the qualified subjects' clinic sites, subjects and caregivers will be provided with a description of the qualitative interview and be offered the opportunity to participate. Subjects and caregivers who agree to participate will be asked to provide written informed consent (for caregiver interviews) and written assent and parental permission (for subject interviews) using forms developed specifically for the interviews.

The format will be a single individual telephone interview using a semistructured interview guide. Each interview will be approximately 45 minutes and will be completed within 14 days after completion of the EOS/ET visit. Subjects and caregivers will be interviewed individually and separately and will be instructed to take the interview at a private setting.

Two interview guides have been developed, one for the caregiver interviews (Appendix 3) and one for the subject interviews (Appendix 4). Interview guides for UK sites will be reviewed by a native speaker of the local dialect. The guides will begin with a brief overview of the interview process and very general questions intended to get the participants talking about their experiences (and the impacts of these experiences) associated with SBS prior to entering the study. These questions will then be followed by a thorough probing of subject and caregiver experience during the study and the importance of the treatment outcomes. Topics included in the interview are listed below:

- Subjects: SBS-related symptoms and impacts
  - Symptoms due to SBS
  - Symptoms due to parenteral support
  - Impact of SBS on daily activities, physical functioning and social functioning
  - Impact of parenteral support on daily activities, physical functioning, and social functioning

## Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

| Period | Pre-treatment | Teduglutide Treatment | Follow-up |
|---|---|---|---|

colonoscopy/sigmoidoscopy. See Section 7.2.9 for details.

[m] A serum pregnancy test is performed on all FOCBP at the teduglutide pre-treatment visit (when the pre-treatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered 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.

[n] Lack of collection of serum samples will not constitute a protocol deviation.

[o] If escape criteria are met, the subject may proceed directly to another pre-treatment visit at the discretion of the investigator.

[p] The first SC injection of teduglutide in treatment-naïve subjects will be administered under the supervision of the investigator/designee after which the subject will be observed for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF. See Section 6.2.3 for dose adjustment.

# 9 DATA MANAGEMENT AND STATISTICAL METHODS

## 9.1 Data Collection

The 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 in the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be collected unless requested.

## 9.2 Clinical Data Management

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

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

## 9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) 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.

## 9.4 Planned Interim Analysis, and Data Monitoring Committee

An interim analysis is planned when 6 months of safety data have been collected for subjects entering from TED-C14-006. Additional interim analyses may be conducted as needed.

A DMC will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (ie, AEs, laboratory assessments, physical examinations, etc.) from study assessments 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.

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least one of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. 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 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 ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, 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.

## Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

| **Period** | **Pre-treatment** | **Teduglutide Treatment** | | | | | | | | | | | | | | | **Follow-up** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **Px[a]** | **Cx D1** | **Cx W1** | **Cx W2** | Phone contact is required approximately 1 week after PS adjustment | **Cx W4** | Phone contact is required approximately 1 week after PS adjustment | **Cx W6** | Phone contact is required approximately 1 week after PS adjustment | **Cx W9** | Phone contact is required approximately 1 week after PS adjustment | **Cx W12** | Phone contact is required approximately 1 week after PS adjustment | **Cx W16** | Phone contact is required approximately 1 week after PS adjustment | **Cx W20** | Phone contact is required approximately 1 week after PS adjustment | **CxW24 (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]** | -21 to 0 | | **±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 testsi | X[i] | X | X | X | | X | | X | | X | | X | | X | | X | | X | (X) | X |
| PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales | | X | | | | | | | | | | X | | | | | | X | | |
| Antibodies to teduglutide[j] | | X | | | | | | | | | | X | | | | | | X | | X |
| Fecal occult blood testing | X | | | | | | | | | | | X | | | | | | X | | |
| Colonoscopy/ sigmoidoscopy[k] | (X) | | | | | | | | | | | (X) | | | | | | (X) | | |