

**A 24-week Double-blind, Safety, Efficacy, and Pharmacodynamic
Study Investigating Two Doses of Teduglutide in Pediatric Subjects
Through 17 Years of Age with Short Bowel Syndrome who are
Dependent on Parenteral Support**

Clinical Study Protocol TED-C14-006

Version 5.0

Phase 3

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(*NPS Pharmaceuticals was acquired by Shire, Inc on 21 February 2015)

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SYNOPSIS

Protocol TED-C14-006

Title of Study: A 24-week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age with Short Bowel Syndrome who are Dependent on Parenteral Support

Protocol No: TED-C14-006

Development phase: 3

Objective: The objective of this clinical study is to evaluate the safety, tolerability, pharmacokinetics, and efficacy/pharmacodynamics of teduglutide in pediatric subjects through 17 years of age with short bowel syndrome (SBS) and who are dependent on parenteral support.

Methodology: This study will include 2 treatment arms: a teduglutide treatment arm and a standard of care treatment arm. Subjects in both arms will participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects will choose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide treatment arm will receive daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. These subjects will be randomized 1:1 in a double-blinded manner into two parallel teduglutide dose groups: 0.025 mg/kg/day and 0.05 mg/kg/day. Randomization across dose groups will be stratified by age: <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years.

Each subject will be screened minimally for 2 weeks before the baseline visit (day 0) to allow for adequate time verifying enrollment eligibility. Subjects in both arms will follow the same visit schedule. After the screening period, subjects will visit the site at baseline (day 0), weekly for the first 2 weeks (ie, weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, subjects will visit the sites once every 3 weeks (ie, weeks 15, 18, 21, and 24). For all other study weeks, subjects will be contacted by telephone. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. At the end of the treatment period (week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (week 28/EOS) during which time no study drug (ie, teduglutide) will be administered. A final visit will occur at week 28, 4 weeks after EOT. Telephone contact will be made during the weeks from EOT to EOS to monitor safety and any changes in nutritional support.

All subjects who complete the study, including those in the SOC treatment arm, may participate in a long-term extension study in which eligible subjects could receive teduglutide.

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 PN/IV support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Any departure from the guidelines will not constitute a protocol deviation.

If a blood sample is positive for antibodies to teduglutide at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) that will convene approximately every 3 months during the treatment period. The treatment period for the study is defined as the date of the first subject's baseline visit to the date of the last subject's visit at week 24/EOT. The DMC committee members will include all cumulative safety data from study assessments through the end of each review period.

Number of Subjects: Approximately 26 subjects who are teduglutide-naïve (a minimum of 10 subjects per teduglutide dose arm) will be enrolled into the teduglutide treatment arm and at least 8 subjects who are teduglutide-naïve will be enrolled into the SOC treatment arm. Enrollment will proceed at approximately 28 investigational sites globally.

Attempts will be made to enroll into each teduglutide dose group at least 1 subject younger than 1 year and at least 2 subjects aged 12 to <17 years.

Duration of Study: For each subject, the study duration will be a minimum of 30 weeks:

- 2-week minimum screening period
- 24-week treatment period
- 4-week follow-up period

A subject will be considered enrolled in the study at the baseline visit (day 0) when the choice of treatment arm (ie, teduglutide or SOC) has been made.

Criteria for inclusion/exclusion: Male and female children and adolescents through 17 years of age, who satisfy all of the following inclusion criteria and none of the following exclusion criteria will be eligible to be enrolled in this study.

Inclusion Criteria

1. Informed consent by a parent or guardian or emancipated minor prior to any study-related procedures
2. When applicable, an informed assent by the subject (as deemed appropriate by the Ethics Committee/Institutional Review Board) prior to any study-related procedures
3. Current history of SBS as a result of major intestinal resection, (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
4. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs prior to screening
5. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
6. Sexually active female subjects of child-bearing potential (in the teduglutide treatment arm only) must use medically acceptable methods of birth control during and 4 weeks after the treatment period

Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening

3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to the screening visit (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤ 10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, and patent ductus arteriosus (PDA) ligation
9. History of cancer or clinically significant lymphoproliferative disease, not including resected cutaneous basal or squamous cell carcinoma, or in situ non-aggressive and surgically resected cancer
10. Pregnant or lactating female subjects (in the teduglutide treatment arm only)
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic glucagon-like peptide-2 (GLP-2)
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight < 10 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
 - a. Total bilirubin (TBL) ≥ 2 x upper limit of normal (ULN)
 - b. Aspartate aminotransferase (AST) ≥ 7 x ULN
 - c. Alanine aminotransferase (ALT) ≥ 7 x ULN

For subjects with Gilbert's disease:

- d. Indirect (unconjugated) bilirubin $\geq 2x$ ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m²
 22. Parent(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
 23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
 24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are provided in [Table 4-1](#).

Test Product, Dose, and Mode of Administration

Subjects who elect to receive teduglutide treatment will be randomized 1:1 in a double-blinded manner into two dose groups: 0.025 mg/kg/day and 0.05 mg/kg/day. The dose calculation will be based on subject body weight measured at the baseline visit (visit 2) and adjusted, as needed, based on measurements made at week 12 (visit 14). Subjects in both dose groups of the teduglutide treatment arm will receive 0.005 mL/kg of reconstituted study drug at a blinded concentration. No other adjustments to the dose will be made during the treatment period, unless discussed with the Shire medical monitor.

Teduglutide will be administered by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

Reference Therapy, Dose, and Mode of Administration: Not applicable

Criteria for Evaluation

Pharmacokinetics: Subjects in the teduglutide treatment arm only

For the PK evaluation, blood will be collected at the clinic on day 0 when the subject receives the first dose of teduglutide. Blood sampling will occur at the following timepoints: predose and 1, 2, and 4 hours postdose. In smaller children for whom blood sampling may impose unacceptable phlebotomy volume, the number of PK samples may be reduced.

If a subject is unable to provide blood samples at baseline (day 0) on the first day of treatment, then blood may be collected for PK analysis during any other future clinic visit while the subject is still receiving treatment with teduglutide.

Safety and tolerability

Safety and tolerability will be assessed by evaluating the following:

- Assessment of adverse events including those pertaining to GI symptoms
- Physical examinations
- Vital signs, including temperature, heart rate, blood pressure
- Body weight, height (or length), head circumference (up to 36 months of age), body mass index (BMI); z-scores will be calculated for height (or length), weight, head circumference, and BMI

- Electrocardiograms
- Laboratory safety data (ie, clinical chemistry, hematology, urinalysis)
- Urine output
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide (teduglutide treatment arm only)
- GI-specific testing (teduglutide treatment arm only) including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow through

Efficacy/pharmacodynamics

The primary efficacy/PD endpoint is a reduction in PN/IV volume of at least 20% at week 24 (or EOT) compared to baseline.

Additional PD endpoints include:

- 100% reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 (or EOT) compared to baseline
- Changes (absolute and percent change) from baseline in PN/IV support (volume and calories), citrulline, and enteral nutritional support (volume and calories), separately, at each clinic visit
- Changes (absolute and percent change) from week 24 (or EOT) in PN/IV support (volume and calories), citrulline, and enteral nutritional support (volume and calories), separately, to week 28 (or EOS)
- Change in hours per day and days per week of PN/IV support
- $\geq 20\%$ reduction in PN/IV volume at each clinic visit

Statistical methods

Because of the small size of the study population only descriptive statistics will be used to summarize data. Accordingly, no claims of significance will be made for any of the data.

Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Demographics and baseline

Summary statistics will be presented for demographic and baseline variables. Analysis of variance computations will be applied as appropriate.

Pharmacokinetics

The PK parameters will be estimated based on measured teduglutide plasma concentrations using a population PK modeling approach.

Safety

Safety data will include clinical laboratory test results; physical examinations; measurements of weight, height or length, and head circumference (if applicable); vital signs; concomitant medications; and electrocardiogram monitoring. Adverse events will be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Efficacy/Pharmacodynamics

Efficacy/pharmacodynamics data will include changes in PN/IV support, enteral nutritional support, citrulline, and hours per day or days per week of PN/IV support and will be summarized by visit and time point.

SIGNATURES FOR PROTOCOL TED-C14-006

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PRINCIPAL INVESTIGATOR AGREEMENT FOR PROTOCOL TED-C14-006

I agree:

To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To maintain drug records, electronic copies of case report forms, laboratory records, data sheets, correspondence records, and signed subject consent/assent documents for at least 10 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

Principal Investigator (Print Name)

Principal Investigator (Signature)

Date (DD MMM YYYY)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|----------------------|--|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| AUC _{0-inf} | AUC from zero to infinity |
| AUC _{last} | AUC from zero to the last measurable concentration |
| AUC | AUC at steady state |
| CL/F | apparent clearance |
| C _{max} | maximum plasma concentration |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EN | enteral nutrition |
| EOS | end of study |
| EOT | end of treatment |
| ET | early termination |
| FDA | Food and Drug Administration |
| FOCBP | female (subjects) of child-bearing potential |
| GI | gastrointestinal |
| GLP-2 | glucagon-like peptide 2 |
| IB | Investigator's brochure |
| IBD | inflammatory bowel disease |
| ICF | Informed Consent Form |
| ICH | International Council on Harmonisation |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IV | Intravenous fluids |
| IWRS | Interactive Web Response System |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | New Drug Application |
| PD | pharmacodynamic |
| PK | pharmacokinetic |
| PN | parenteral nutrition |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBS | Short bowel syndrome |

| Abbreviation | Definition |
|---------------------|--|
| SC | subcutaneous |
| SOC | standard of care |
| SUSAR | suspected, unexpected, serious, adverse reaction |
| $t_{1/2}$ | terminal-phase half-life |
| TEAEs | treatment-emergent adverse events |
| T_{max} | time to C_{max} |
| UGI/SBFT | upper GI series with small bowel follow through |
| ULN | upper limit of normal |
| $V_{\lambda z}/F$ | apparent volume of distribution |

1 INTRODUCTION

1.1 Background

Compound

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide-2 (GLP-2) that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase-IV and therefore maintains a longer elimination half-life ($t_{1/2}$) of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Thymann et al. 2014; Tappenden et al. 2013). The European Commission granted a centralized marketing authorization valid throughout the European Union for teduglutide (Revestive™) on 30 August 2012 and a New Drug Application (NDA) for teduglutide (Gattex®) was approved by the US Food and Drug Administration (FDA) on 21 December 2012 for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.

Subsequent supplemental submissions in the US and EU in 2013 and 2014 provided long-term data from the completed long-term safety and efficacy study in support of subsequent changes to the label which provide for long-term use of Gattex in adults.

Preclinical Studies

A comprehensive preclinical evaluation of the toxicological profile of teduglutide has been conducted (acute and repeat dose toxicology, safety pharmacology, genetic and reproductive toxicology, juvenile animal studies, carcinogenicity, and special studies). Subcutaneous injections of teduglutide have been shown to be well tolerated at acute doses as high as 200 mg/kg/day (mouse) or repeated doses of up to 50 mg/kg/day for 6 months in mice and 25 mg/kg/day for 12 months in cynomolgus monkeys. At dose levels of teduglutide up to 50 mg/kg/day, there were no adverse effects on in utero fetal development in rats and rabbits or on reproductive parameters (viability, growth, mating) or fertility in the offspring of treated rats. Toxicity studies in juvenile animals have been completed using mini-pigs. A No Observed Adverse Effect Level (NOAEL) of teduglutide in juvenile mini-pigs treated subcutaneously twice daily for 14 days was found to be 25 mg/kg/day. In a 90-day toxicology study in juvenile mini-pigs, the changes observed in the gastrointestinal tract were consistent with those observed in studies conducted using adult animals (rodents and primates). No treatment-related malignant tumors were noted in a 2-year carcinogenicity study in rats; treatment-related changes included benign tumors of the bile duct epithelium and adenomas of the jejunal mucosa in males treated at 35 mg/kg/day. The results from a second 2-year carcinogenicity study in Crl:CD1(ICR) mice were provided to the FDA in a NDA Supplement which received agency approval on 26 June 2014. Subcutaneous doses of 1, 3.5, and 12.5 mg/kg/day (about 20, 70, and 250 times the recommended daily human dose of 0.05 mg/kg, respectively) were studied and adenocarcinoma in the jejunum was observed in males given a dose of 12.5 mg/kg/day.

Clinical Studies

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

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

Study CL0600-020 was a randomized, double-blind, placebo-controlled study in which subjects were randomized to teduglutide 0.05 mg/kg/day or placebo on a 1:1 ratio. The first stage of the study included a screening and optimization period and a stabilization period that demonstrated stable administration of PN/IV volume for a minimum of 4 weeks up to a maximum of 8 weeks. The second stage was a dosing period of 24 weeks. Subjects on 0.05 mg/kg/day teduglutide achieved a higher responder rate (defined as a 20% to 100% reduction from baseline in PN/IV volume at weeks 20 and 24) than the placebo-treated subjects (27/43 subjects [62.8%] versus 13/43 subjects [30.2%], respectively). This difference was clinically and statistically significant in both the intention-to-treat (ITT) ($p = 0.002$) and per protocol ($p < 0.001$) populations. Generally, the incidence of treatment-emergent AEs (TEAEs) was distributed similarly across all treatment groups. The TEAEs with a higher incidence in the teduglutide group were mainly of GI origin. A long-term, open-label extension study (CL0600-021) assessed safety and efficacy for up to 24 additional months (ie, up to 30 months of exposure for subjects who received teduglutide in Study CL0600-020). Overall, 30 of 43 subjects who received teduglutide in Study CL0600-020 and entered Study CL0600-021 completed a total of 30 months of treatment with teduglutide. Of these, 28 subjects (93%) achieved a 20% or greater reduction of parenteral support resulting in a PN/IV volume reduction of 7.55 L/week, corresponding to a mean reduction of 65.6% relative to baseline prior to exposure to teduglutide at the beginning of Study CL0600-021. PN/IV frequency was reduced by at least 1 day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 3.11 L/week from baseline at the start of Study CL0600-021 (a 28% reduction). Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. Of the 12 subjects entering

Study CL0600-021 directly, 6 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 4.0 L/week (a 39.4% reduction from baseline at the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of parenteral support.

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

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

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

1.2 Rationale for the Clinical Study

Short bowel syndrome is a rare disorder. At the time of the initial development program with teduglutide, the Oley Foundation in 1992 reported an estimated prevalence of about 10,000 to 15,000 parenteral nutrition (PN)-dependent adult SBS patients in the U.S. Most recently, market research performed in 2012 indicates that the true addressable adult patient population is between 3000 to 5000 patients qualifying SBS as an ultra-orphan condition. In addition to adult SBS patients, it is estimated that, at most, there are a few hundred children 1 year and older with SBS (Wales et al. 2004). As a result of congenital abnormalities or severe intestinal disease in children and adolescents, major surgical resections of the intestine can become necessary, resulting in SBS. Common causes of SBS in children include necrotizing enterocolitis (NEC) in infants, midgut volvulus, intestinal atresia, and gastroschisis (Duro et al. 2008; Squires et al. 2012). New onset SBS in older children may stem from the same etiologies as in adults (ie, Crohn's disease, trauma, cancer) but is far less common. As the characteristics are similar to the adult disease, pediatric SBS is defined as a disease where there is diminished absorptive capacity for fluids and/or nutrients, sometimes requiring a dependence on PN/IV support to maintain energy and clinical status.

There is heterogeneity within SBS. Where some patients with intestinal insufficiency are able to adapt metabolically and compensate for their malabsorption of fluids, electrolytes, trace elements, vitamins or nutrients by increasing oral/enteral intake (Messing et al. 1999; Jeppesen and Mortensen 2000), other patients with intestinal failure depend on PN/IV for nutritional support (Fleming et al. 1980; O'Keefe et al. 2006; Buchman et al. 2003). Although PN/IV can provide this nutritional support for patients with compromised fluid and nutritional status, it is also associated with serious complications, such as infections and liver damage. The risk for these effects increases over time with longer duration of PN/IV support.

Treatment of both pediatric and adult patients is focused on achieving adequate intestinal absorption to allow for minimization or discontinuation of PN/IV support. Because children are at higher risk for intestinal failure-associated liver disease, reducing PN support is far more urgent in this population. About 30% of infants who develop SBS during the neonatal period become independent of PN/IV requirements by 12 months of age, and an additional 10% wean off PN/IV support by 24 months of age. After this time, intestinal adaptation and growth occurs much more slowly, and many children remain terminally dependent on PN/IV support. Due to the risks of intestinal failure-associated liver disease, catheter-related blood stream infections, central line-associated venous thrombosis and dwindling central venous access, achieving autonomy from parenteral support remains an urgent goal for all affected children (Khan et al. 2015; Squires et al. 2012).

This study proposes to investigate the safe and appropriate use of teduglutide in the pediatric population for up to 24 weeks of administration for the purpose of providing longer-term data in regard to safety and the potential to explore further efficacy including PN reduction and ability to completely wean off parenteral support. This protocol was developed with input from expert advisors from intestinal rehabilitation centers who offered advice on the most appropriate use of teduglutide in pediatric patients. The aim of teduglutide treatment is to increase absorptive capacity in order to yield decreases in parenteral support requirements. The experts anticipated that there would be several direct benefits from decreased parenteral support, including less exposure to PN/IV constituents, less central line manipulation with lower risk of infection, and more time to focus on oral rehabilitation strategies.

1.3 Rationale for Study Design

Dose

The efficacy and safety of teduglutide has been investigated at doses ranging from 0.03 to 0.15 mg/kg once daily in adult SBS subjects requiring PN. The recommended daily clinical dosage for the adult SBS patient population is 0.05 mg/kg. The completed 12 week pediatric study (TED-C13-003) included doses of 0.0125, 0.025, and 0.05 mg/kg/day. It 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 (PK) 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 phase 2 and 3 studies as well as the pediatric phase 3 study, TED-C13-003. The analysis suggested that pediatric patients aged 1 to 17 years were likely to require the same dose as that used in adults, namely 0.05 mg/kg/day. To further explore additional safety and efficacy of 0.025 and 0.05 mg/kg/day doses, a 24-week study is currently proposed.

Treatment Duration/Design

Safety, tolerability, pharmacokinetics, and efficacy/PD measures will be the main outcomes of the current study. The main efficacy/PD effect of teduglutide to be measured in children is a decrease in the volume of PN/IV support. Measurement of a decrease in PN/IV volume was the primary endpoint in the adult SBS clinical studies and can be used in children with SBS who are dependent on PN/IV support.

A 20% reduction or greater (including complete weaning) from baseline in volume of PN/IV at the end of treatment was used as the primary endpoint in the adult clinical development program during pivotal phase 3 studies and the previous pediatric study and will be the same endpoint used in the current pediatric study. A 20% decrease in PN/IV volume over 24 weeks is considered clinically meaningful to these PN/IV-dependent children who have plateaued in their ability to wean PN/IV requirements and advance their oral/enteral feeds. A decrease of this magnitude may allow a child several hours a day for more age-appropriate activities or an opportunity to introduce an extra oral/enteral feed to encourage oral rehabilitation.

This study will include 2 treatment arms: a teduglutide treatment arm and a standard of care treatment arm. Subjects in both arms will participate in a 24-week treatment period and a 4-week follow-up period. The teduglutide treatment arm will have a double-blind, parallel group design in which subjects are randomized 1:1 to teduglutide at either 0.025 mg/kg/day or 0.05 mg/kg/day subcutaneous injection for 24 weeks. The 24-week teduglutide treatment period will provide additional pharmacokinetic, safety, tolerability, and efficacy data beyond that which was collected in the previous 12-week pediatric study (TED-C13-003).

Thus, this study is designed to provide further information on the safety, PK, and efficacy/PD profile of teduglutide in pediatric subjects treated for up to 24 weeks.

Subject Population

The current significant unmet medical need is for children who remain dependent on parenteral support. Patients who reach a plateau in their ability to advance oral/enteral feeds or decrease PN/IV support are not expected to achieve spontaneous adaptation. The subjects in the study will be children who have not reached full enteral autonomy and whose PN/IV requirements had been stable without any clinically meaningful or substantial reduction in parenteral support for the 3 months prior to, and during, screening.

This study will be conducted in accordance with FDA Guidance E11, *Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000).

Gastrointestinal Screening Measures

Pediatric patients with SBS who are dependent on PN/IV have significant comorbidities such as biliary disease in addition to risk for small bowel obstruction due to history of intestinal surgery. Teduglutide has been found to have a targeted intestinotrophic effect on the GI tract and areas of special interest in regards to safety have been identified throughout the development program. Taking into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests that are usually part of the routine care of these subjects will be performed on subjects in the treatment arms only to ensure safety. These include: abdominal ultrasound, upper GI series with small bowel follow through (UGI/SBFT), fecal occult blood testing, and colonoscopy/sigmoidoscopy.

General Guidance for Nutritional Support Adjustment

Consideration for advancement of oral/enteral feed and reductions to PN/IV volume will be based on clinical status and will include measures of weight, hydration status, and stool output. Because the primary efficacy/PD endpoint for this study is a reduction in PN/IV volume of at least 20% at week 24 (or EOT) compared to baseline, guidelines for nutritional support adjustment, including a weaning algorithm, are provided in [Appendix 1](#). These guidelines were

developed with input from SBS experts. All attempts should be made to follow these guidelines to ensure uniform care across study sites and participants; however, a departure from the guidelines will not constitute a protocol deviation.

2 OBJECTIVES

2.1 Primary Objective

The objective of this clinical study is to evaluate the safety, pharmacokinetics, and efficacy/PD of teduglutide in pediatric subjects through 17 years of age with short bowel syndrome (SBS) and who are dependent on parenteral support.

Details of study assessments are provided in Sections [8.2](#) and [8.4](#).

3 STUDY DESIGN

3.1 Overall Design and Control Methods

This study will include 2 treatment arms: a teduglutide treatment arm and a standard of care treatment arm. Subjects in both arms will participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects will choose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide treatment arm will receive daily subcutaneous injections of teduglutide (study drug) in addition to standard medical therapy. These subjects will be randomized 1:1 in a double-blinded manner into two parallel teduglutide dose groups: 0.025 mg/kg/day and 0.05 mg/kg/day. Randomization across dose groups will be stratified by age: <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years.

Each subject will be screened minimally for 2 weeks before the baseline visit (day 0) to allow for adequate time verifying enrollment eligibility. Subjects in both arms will follow the same visit schedule. After the screening period, subjects will visit the site at baseline (day 0), weekly for the first 2 weeks (ie, weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, subjects will visit the sites once every 3 weeks (ie, weeks 15, 18, 21, and 24). For all other study weeks, subjects will be contacted by telephone. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. At the end of the treatment period (week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (week 28/EOS) during which time no study drug (ie, teduglutide) will be administered. A final visit will occur at week 28, 4 weeks after EOT. Telephone contact will be made during the weeks from EOT to EOS to monitor safety and any changes in nutritional support.

All subjects who complete the study, including those in the SOC treatment arm, may participate in a long-term extension study in which eligible subjects could receive teduglutide.

To maintain consistency across all 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 PN/IV support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Any departure from the guidelines will not constitute a protocol deviation.

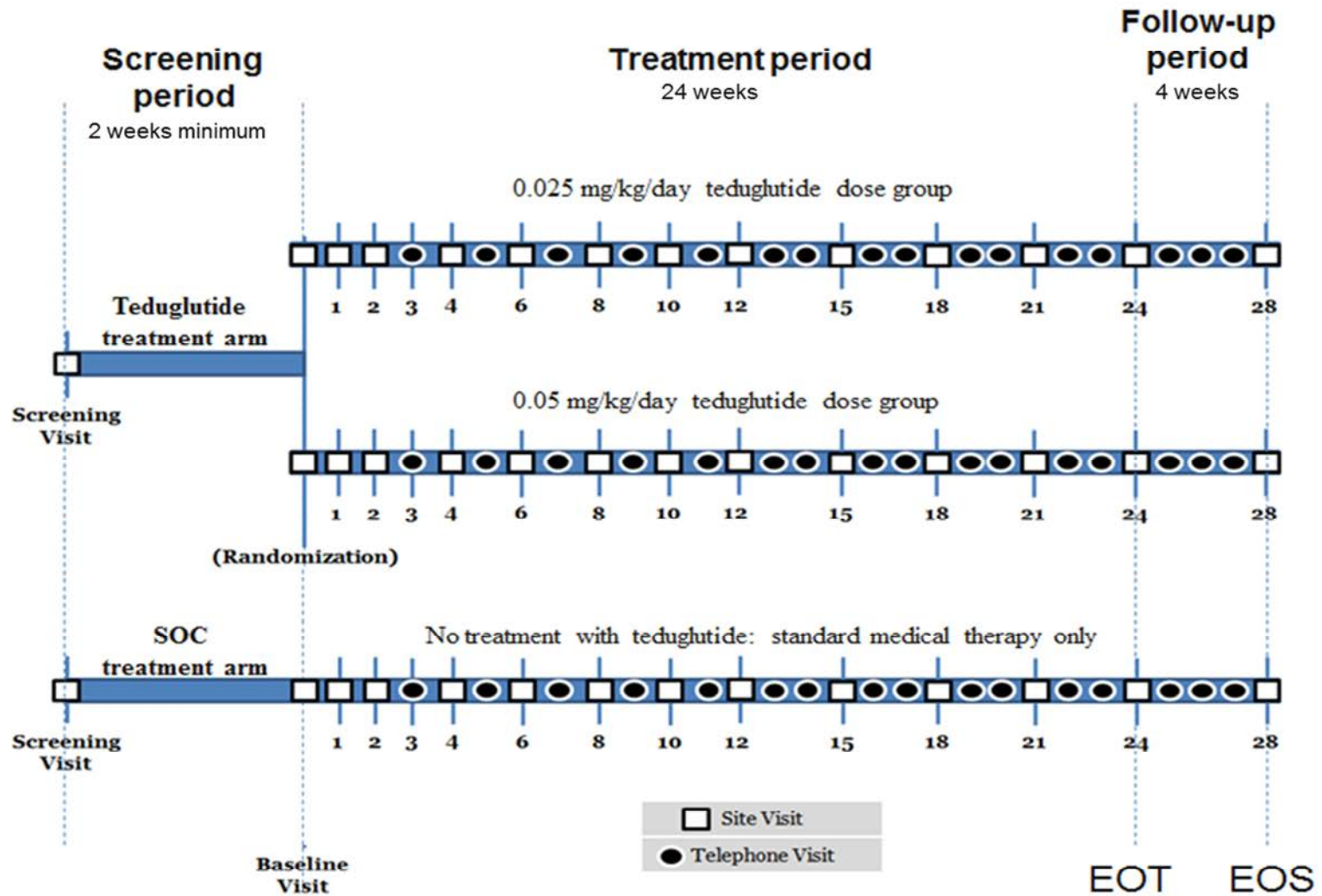
If a blood sample is positive for antibodies to teduglutide at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) that will convene approximately every 3 months during the treatment period. The treatment period for the study is defined as the date of the first subject's baseline visit to the date of the last subject's visit at week 24/EOT. The DMC's data review will include all cumulative safety data from study assessments through the end of each review period.

A schematic of the study design is displayed in [Figure 3-1](#).

Timing of study visits and evaluations can be found in the Schedules of Events ([Table 6-2](#) and [Table 6-3](#) for the teduglutide treatment arm and [Table 6-4](#) and [Table 6-5](#) for the SOC treatment arm).

Figure 3-1 Study Diagram



Note: Subjects in both treatment arms (SOC and teduglutide) will follow the same visit schedule.

3.2 Study Duration

A 2-week minimum screening period will be followed by 24 weeks of teduglutide treatment for all subjects. At EOT, all subjects will enter the follow-up period, during which time subjects will have a final site visit at week 28 (EOS), 4 weeks after EOT (ie, week 24).

A subject will be considered enrolled in the study at the baseline visit (day 0) when the choice of treatment arm (ie, teduglutide or SOC) has been made.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

Approximately 26 subjects who are teduglutide-naïve (a minimum of 10 subjects per teduglutide dose group) will be enrolled into the teduglutide treatment arm and at least 8 subjects who are teduglutide-naïve will be enrolled into the SOC treatment arm. Enrollment will proceed at approximately 28 investigational sites globally.

Attempts will be made to enroll into each teduglutide dose group at least 1 subject younger than 1 year and at least 2 subjects aged 12 to <17 years.

4.2 Criteria for Inclusion/Exclusion

Male and female children and adolescents through 17 years of age, who satisfy all of the following inclusion criteria and none of the following exclusion criteria are eligible to be enrolled in this study.

4.2.1 Inclusion Criteria

1. Informed consent by a parent or guardian or emancipated minor prior to any study-related procedures
2. When applicable, an informed assent by the subject (as deemed appropriate by the Ethics Committee/Institutional Review Board) prior to any study-related procedures
3. Current history of SBS as a result of major intestinal resection, (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
4. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs prior to screening
5. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
6. Sexually active female subjects of child-bearing potential (in the teduglutide treatment arm only) must use medically acceptable methods of birth control during and 4 weeks after the treatment period

4.2.2 Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.

6. Evidence of clinically significant obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
 7. Major GI surgical intervention including significant intestinal resection within 3 months prior to the screening visit (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤ 10 cm, or endoscopic procedure is allowed)
 8. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, and patent ductus arteriosus (PDA) ligation
 9. History of cancer or clinically significant lymphoproliferative disease, not including resected cutaneous basal or squamous cell carcinoma, or in situ non-aggressive and surgically resected cancer
 10. Pregnant or lactating female subjects (in the teduglutide treatment arm only)
 11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
 12. Previous use of teduglutide or native/synthetic glucagon-like peptide-2 (GLP-2)
 13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
 14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
 15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
 16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
 17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
 18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
 19. Body weight < 10 kg at screening and baseline visits
 20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
 - e. Total bilirubin (TBL) $\geq 2x$ upper limit of normal (ULN)
 - f. Aspartate aminotransferase (AST) $\geq 7x$ ULN
 - g. Alanine aminotransferase (ALT) $\geq 7x$ ULN
- For subjects with Gilbert's disease:
- h. Indirect (unconjugated) bilirubin $\geq 2x$ ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below $50 \text{ mL/min/1.73 m}^2$
 22. Parent(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
 23. Unstable, clinically significant, active, untreated pancreatic or biliary disease

24. Any condition, disease, illness, or circumstance that in the investigator’s opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in [Table 4-1](#).

Table 4-1 Excluded Diseases and Illnesses

| Body system | Known conditions excluded |
|--------------------|--|
| Related to SBS | <ul style="list-style-type: none"> • Ongoing radiation enteritis • Untreated celiac disease • Refractory or tropical sprue • Pseudo-obstruction |
| Gastrointestinal | <ul style="list-style-type: none"> • Active IBD which requires chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months • Tufting or autoimmune enteropathy or microvillus inclusion disease • Untreated pre-malignant or malignant change in GI tract identified by upper GI series, biopsy or polypectomy • Known polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner’s syndrome, Cronkhite-Canada syndrome) • Intestinal or other major surgery scheduled within the time frame of the study • Chronic active pancreatitis • Cholecystitis |
| Immune | <ul style="list-style-type: none"> • Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency) |
| Psychiatric | <ul style="list-style-type: none"> • Alcohol or drug addiction within the previous year • Major uncontrolled psychiatric illness |
| General | <ul style="list-style-type: none"> • Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system) |

GI=gastrointestinal; IBD=inflammatory bowel disease; SBS=short bowel syndrome

4.3 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified. However, a discussion should be held by the investigator and the Shire’s medical monitor prior to the patient discontinuing/withdrawing. A subject may (but not automatically) be withdrawn from the study under any of the following circumstances:

- Withdrawal of informed consent and/or assent when applicable
- If, in the opinion of the investigator, IRB or the sponsor, it is no longer in the subject's best interest to continue in the study
- Subject no longer meets all inclusion criteria or meets any of the exclusionary criterion
- Lack of compliance with study procedures or study drug administration, as determined by the investigator
- Occurrence of a serious adverse event (SAE) determined by the investigator to be related to study drug and not alleviated with treatment of symptoms
- AEs resulting in dose interruption (Section 6.14)
- Hypersensitivity determined by the investigator to be related to study drug
- Administrative reasons

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the subject's medical records. If the reason is not known, the subject must be followed-up to establish whether the reason was an AE and, if so, the AE must be reported in accordance with the procedures described in Section 6.3.

As far as possible, all examinations scheduled for the EOT evaluations must be performed on all subjects who participate even if they do not complete the study according to the protocol (ie, early terminate [ET]). Any subject who discontinues treatment prematurely will be asked to return 4 weeks later for the EOS visit and will be contacted weekly for wellness checks during the interim period between EOT and EOS.

4.4 Data Monitoring Committee

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

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

The DMC members will review the data approximately every 3 months during the study's treatment period (defined as the date of the first subject's baseline visit to the date of the last subject's visit at week 24/EOT). DMC's data review will include all cumulative safety data from study assessments through the end of each review period.

5 TREATMENTS AND TREATMENT PLAN

5.1 Treatment Administered

Subjects who elect to receive teduglutide treatment will be randomized 1:1 in a double-blinded manner into one of two dose groups: 0.025 mg/kg/day or 0.05 mg/kg/day. The dose calculation will be based on subject body weight measured at the baseline visit (day 0/visit 2) and adjusted, as needed, based on measurements made at week 12 (visit 14). Subjects in both dose groups of the teduglutide treatment arm will receive 0.005 mL/kg of reconstituted study drug at a blinded concentration. No other adjustments to the dose will be made during the treatment period, unless discussed with the Shire medical monitor.

Teduglutide will be administered by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

5.1.1 Identification of Investigational Product

Teduglutide will be provided in a sterile, single-use, glass vial as a lyophilized powder to be reconstituted with 0.5 mL sterile water for injection provided as the diluent in a prefilled syringe. The 5-mg vial is a 10 mg/mL solution upon reconstitution. The 2.5-mg vial is a 5 mg/mL solution upon reconstitution.

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.

All vial strengths have the same formulation except for a reduced concentration of the active ingredient in the lower strength.

5.1.2 Packaging and Labeling

The study drug will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of study drug will be supplied and these will be labeled in accordance with applicable regulatory requirements. Sterile water for injection syringes will also be provided separately and will be labeled in accordance with the applicable regulatory requirements.

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

5.1.3 Storage, Accountability, and Stability

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

Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug will be stored refrigerated at a temperature between 2 to 8°C (35.6 to 46.4°F) until dispensed to a subject. Once dispensed to a subject, the study drug can be stored refrigerated or

up to a controlled room temperature (acceptable range of 2 to 25°C, or 35.6 to 77°F). Parent/guardian will be instructed to keep the subject's study drug and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the study drug may be refrigerated.

Study drug kits will be dispensed at each of the study visits at which the subject is required to be at the clinic. Each study drug kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period to the next planned study visit. Additional study kits will be provided as necessary.

The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. This record will be made available to the sponsor's site monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded and will include an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

All used and unused study drug vials must be returned by the subjects and/or parent/guardian and will be retained at the site. All original containers, whether empty or containing study drug will be returned to the pharmacy. Returned study drugs will NOT be relabeled or reassigned for use by other subjects. Contents of the study drug containers will not be combined. All used and unused vials must be returned to the distribution center according to the sponsor's instruction. No vial/kit may be destroyed on site without approval by the sponsor.

Please see the Pharmacy Manual for additional information.

5.2 Methods of Assigning Subjects to Study Treatment Arms

At screening, subjects will be assigned an 8-digit subject number. The first 4 digits consist of the study site number. The last 4 digits will be assigned sequentially starting with 0001. These numbers will be used to identify the subjects in the teduglutide treatment arm and those in the SOC treatment arm. Subjects may be rescreened only once and with prior sponsor approval. See Section 7.2 for rescreening instructions.

At any time during the 2-week minimum screening period, the subject or subject's parent/guardian/caretaker will decide whether to participate in the teduglutide treatment arm or the SOC treatment arm. At the end of the screening period, the investigator will review and confirm that the subject continues to meet all inclusion criteria and none of the exclusion criteria.

If the subject or subject's parent/guardian/caretaker decides to participate in the study and receive study drug (defined as treatment with teduglutide), then the investigator or designee will request that the subject be randomized to a teduglutide dose group using an interactive web response system (IWRS) centrally administered as described in the IWRS Manual of Procedures. Subjects in teduglutide treatment arm will be double-blinded and randomized at the baseline visit (day 0) 1:1 into parallel dose groups of either 0.025 mg/kg/day or 0.05 mg/kg/day. To ensure balance across dose groups, randomization will be stratified by the following age subgroups: <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years.

Attempts will be made to enroll into each teduglutide dose group at least 1 subject younger than 1 year and at least 2 subjects aged 12 to <17 years.

Study drug kits will be assigned through IWRS to each subject at each site visit through completion of the treatment period. The IWRS will automatically assign the correct number of kits for each visit based on the randomization date. If additional kits are needed (eg, subject is going on holiday), then the IWRS and the sponsor must be notified to assign additional kits. Subjects will be randomized across centers rather than within a center.

5.3 Dose Regimens

Study drug will be supplied in 2 powder strengths:

- 5.0 mg/vial for subjects randomized to 0.05 mg/kg/day teduglutide
- 2.5 mg/vial for subjects randomized to 0.025 mg/kg/day teduglutide

Subjects in the teduglutide dose groups will be administered study drug for 24 weeks by SC injection. See Section 5.3.2 for more detail. The dose calculation will be based on subject weight measured at the baseline visit (day 0/visit 2), and adjusted as needed, based on weight measured at week 12 (visit 14). No other adjustments will be made during the treatment period unless discussed with the Shire medical monitor.

5.3.1 Selection of Doses in Study

A recently completed 12-week pediatric study (TED-C13-003) that included doses of 0.0125, 0.025, and 0.05 mg/kg/day demonstrated a favorable risk/benefit profile at the 2 higher doses as evident by reduction in PN/IV volume and advance in feeds. Furthermore, results from modeling and simulation data of previously completed studies indicate that pediatric patients are likely to require the same dose as adults (ie, 0.05 mg/kg daily).

This study will evaluate teduglutide doses of 0.05 mg/kg and 0.025 mg/kg administered daily for 24 weeks.

5.3.2 Selection and Timing of Dose for Each Subject in the Teduglutide Treatment Arm

Teduglutide will be administered after reconstitution by SC injection 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. The first SC injection should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours after teduglutide administration during their initial dosing visit. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF. Detailed instructions for reconstitution and injection of teduglutide can be found in the Dosing Instructions. Each day, the injection site should be rotated.

The subject should be dosed at approximately the same time each day. If a dose is forgotten, that day's dose should be administered as soon as possible, even if this is later in the day or evening. Consecutive doses should be separated by at least 12 hours.

The investigator is responsible for contacting the sponsor/designee prior to interrupting the subject's daily teduglutide dosing regimen. Reasons for dosage interruptions may include but are not limited to hospitalization, adverse events, a lapse in teduglutide delivery, etc.

5.3.3 Compliance with Dosing Regimens

Subject compliance with teduglutide dosing will be monitored by the sponsor/designee by counting and examining used and unused vials. In addition, compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or guardian if they have administered teduglutide according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

5.3.4 Prior and Concomitant Treatments

All non-study treatments, including medications, herbal treatments, vitamins, invasive and diagnostic procedures, received within 14 days before screening through week 28 (EOS) or final study contact must be recorded on the appropriate section of the eCRF.

Prior treatment includes all treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures) received within the 14 days before screening.

Concomitant treatments will be assessed at each site visit and will include all non-study treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures) received between the first teduglutide dose (teduglutide treatment arm) or day 0 (SOC treatment arm) through week 28 (EOS), or the end of the follow-up period. Details of medication changes and/or dosages will be recorded on the eCRF.

The mechanism of action of teduglutide may increase absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, Coumadin, psychotropics, metronidazole, digoxin). Accordingly, due consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medications should be considered when drugs, especially those with a narrow therapeutic range, are prescribed at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

6.1 Pharmacokinetics

Blood samples for PK analysis should be collected at baseline (day 0). If a subject is unable to provide blood samples for PK at the baseline visit (day 0), then PK samples may be collected during any other future site visit while the subject is still receiving treatment with teduglutide.

Pharmacokinetic variables are listed in Section 8.3. Instructions for sample collection and handling are included in the Laboratory Manual.

Blood will be drawn predose and 1, 2, and 4 hours postdose. In smaller children for whom blood sampling may impose unacceptable phlebotomy volume, the number of PK samples may be reduced. For example, the sampling timepoints postdose may be reduced from 3 to 2. The decision to reduce blood sampling postdose timepoints will be made by the investigator and the Shire medical monitor.

The time points indicated for PK blood draws should be adhered to as closely as possible. However, it is recognized that some deviations from these time points may occur. The investigator or designee should keep deviations to a minimum and be guided by the following collection windows:

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose (if the PK blood draw does not occur at day 0)
- 1-hour postdose draw: ± 10 minutes
- 2-hour postdose draw: ± 10 minutes
- 4-hour postdose draw: ± 30 minutes

The actual date and time of teduglutide administration and blood draw must be documented on the PK blood sampling eCRF.

If a subject is unable to provide blood samples for PK at the baseline visit (day 0), then PK samples may be collected during any other future site visit while the subject is still receiving treatment with teduglutide.

6.2 GI-specific Symptoms History

GI symptoms during the screening period will be recorded by the subject/parent/guardian in a GI-Specific Symptoms History diary on a daily basis. At the baseline visit, the investigator or sub-investigator will review the GI-symptoms diary and summarize the findings.

6.3 Diaries

Intake diaries will be used to collect and evaluate each subject's nutritional support.

The subject/parent/guardian will complete the appropriate fields of the PN/IV and enteral nutrition (formula) sections of the Intake diary.

Intake diary: The following information should be provided in the intake diaries, which will be completed *every day of the study from screening through week 28/EOS*:

- PN/IV volume and infusion duration
- EN (formula) volume

Site personnel will determine the actual PN/IV and EN daily calories based on diary entries.

Output diary: Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every clinic visit and within 1 week of implementing a change in the PN/IV prescription.

- Urine data
 - *Toilet-trained subjects WHO DO NOT WEAR DIAPERS*
Measure and record all urine output in mL or cc. The subject or parent will perform dipstick specific gravity tests on the first urine produced after the daily infusions of PN/IV support.
 - *Nontoilet-trained subjects WHO WEAR DIAPERS*
Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc

At the discretion of the investigator, the parent may be asked to collect the first void after the daily PN/IV infusion to measure specific gravity.

Stool data (includes diapers with mixed urine and stool)

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

All ostomy output volume should be recorded. Ostomy output will not be scored using the Bristol scale.

All diaries will be reviewed by the investigator or their designee at each clinic and telephone contact to assess clinical status and opportunity for PN/IV reduction and advance in feeds.

6.4 Nutritional Support

Nutritional support includes PN/IV and EN. Advances in enteral nutrition and/or reductions to PN/IV support will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Guidelines for nutrition support adjustment, including a weaning algorithm, are provided in [Appendix 1](#).

Intake diaries will be used to collect each subject's nutritional support.

6.5 Gastrointestinal-specific Testing

Only subjects in the teduglutide treatment arm will undergo GI-specific testing. GI-specific testing includes upper GI with small bowel follow through, abdominal ultrasound, FOBT, and

colonoscopy/sigmoidoscopy. These procedures will be performed during or before screening (visit 1).

Follow-up testing will be performed as necessary according to the guidelines provided. See [Table 6-2](#) and [Table 6-3](#) for details and scheduling.

6.5.1 Upper Gastrointestinal Series with Contrast

An upper GI with small bowel follow through will be performed following the ingestion of barium contrast material. Results from procedures performed within 6 months prior to visit 1 are acceptable also.

6.5.2 Abdominal Ultrasound

An abdominal ultrasound will be performed. Results from procedures performed within the 6 months before screening (visit 1) are also acceptable.

6.5.3 Fecal Occult Blood Testing

Fecal occult blood testing will be performed at screening, week 12, and week 24 (EOT). Subjects with positive FOBT results at screening or at week 24 for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy. Subjects with positive FOBT results at week 12 for which a cause is not identified by a physical exam will be discussed with the Shire medical monitor. If clinically indicated, an esophagogastroduodenoscopy (EGD) may also be performed.

Subjects with negative endoscopy findings at screening may enroll in the study.

Subjects with positive endoscopy findings at screening who receive treatment may enroll in the study if following consultation with Shire's medical monitor, the subject is considered appropriate to be enrolled in the study.

Subjects with positive endoscopy findings at screening who do not receive treatment will be excluded from the study if following consultation with Shire's medical monitor, the subject is considered inappropriate to be enrolled in the study.

6.5.4 Colonoscopy/Sigmoidoscopy

Subjects who are 12 years and older will undergo a colonoscopy/sigmoidoscopy at screening. Children younger than 12 years will undergo the procedure if they test positive for fecal occult blood at screening and if the source is not identified by physical exam (see [Section 6.5.3](#)).

If the FOBT is negative at screening and the procedure was performed within 1 year before the screening visit (visit 1), then those prior results are acceptable for the screening assessment.

6.6 Laboratory Evaluations

The following laboratory evaluations will be performed according to the Schedules of Events ([Table 6-2](#) and [Table 6-3](#) for the teduglutide treatment arm and [Table 6-4](#) and [Table 6-5](#) for the SOC treatment arm). A result outside of the normal range may be repeated for confirmation.

Laboratory collections that are required at intervals that do not coincide with clinic visits (ie, for lab assessments done following PN/IV adjustments) may be obtained by a Home Health Agency at subjects' homes.

6.6.1 Laboratory Tests

Hematology

| | |
|------------|--|
| Hemoglobin | Red blood cell (RBC) count |
| Hematocrit | RBC morphology, if necessary |
| Platelets | White blood cell (WBC) count with differential |

Coagulation

PT/INR will be measured in subjects in the teduglutide treatment arm at screening and subsequently if DILI is suspected (Section 6.14.2)

Clinical Chemistry

| | |
|---------------------------------------|--|
| Albumin | C-reactive protein |
| ALP | eGFR (Schwartz formula) |
| ALT | Glucose |
| Amylase | Gamma glutamyl transferase |
| AST | HCG for FOCBP in the teduglutide treatment arm (serum at screening only; Section 6.17) |
| Bicarbonate | Lipase |
| Bilirubin (total and direct) | Magnesium |
| Blood urea nitrogen | Phosphorous |
| Calcium (total) | Potassium |
| Chloride | Sodium |
| Cholesterol | Triglycerides |
| Citrulline (plasma) (Section 6.6.1.1) | Uric acid |
| Creatinine | |

Urinalysis

| | |
|---|----------------------|
| Blood | Microscopic analysis |
| Glucose | pH and osmolality |
| HCG for FOCBP in the teduglutide treatment arm (Section 6.17) | Protein |
| Leukocytes | Sodium |
| | Specific gravity |

For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

6.6.1.1 Plasma Citrulline

Plasma citrulline levels will be measured as a biomarker of enterocyte mass. Blood will be collected from all subjects 2 to 4 hours postprandial, whenever possible, timepoints specified in the Schedule of Events (Table 6-2 and Table 6-3 for the teduglutide treatment arm and Table 6-4 and Table 6-5 for the SOC treatment arm). Samples may be drawn from a central line or from peripheral access and processed according to instructions in the Laboratory Manual.

6.6.1.2 Antibodies to Teduglutide

Blood will be sampled from subjects in the teduglutide treatment arm to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the baseline visit (day 0) and ≥ 14 hours after the previous dose at the EOT visit (week 24 or ET); samples may be drawn

from a central line or from peripheral access. One additional sample will be collected at the final visit, 4 weeks after the EOT (ie, week 28/EOS).

If a blood sample is positive for anti-teduglutide antibodies at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

6.7 Physical Examinations

Complete and comprehensive physical examinations will be performed by a medically qualified professional during the study to assess the subject's physical status. Timing of physical examinations is presented in the Schedules of Events ([Table 6-2](#) and [Table 6-3](#) for the teduglutide treatment arm and [Table 6-4](#) and [Table 6-5](#) for the SOC treatment arm).

6.8 Body and Weight Measurements

Body measurements will be recorded on the appropriate section of the eCRF. Subjects should be weighed in kilograms on the same scale at each site visit. Height and body length and head circumference (subjects ≤ 36 months old) will be measured at selected visits.

BMI and z-scores for height/length, weight, and head circumference will be calculated by the sponsor.

Timing of body measurements and weight is provided in the Schedules of Events ([Table 6-2](#) and [Table 6-3](#) for the teduglutide treatment arm and [Table 6-4](#) and [Table 6-5](#) for the SOC treatment arm).

6.9 Vital Signs

Examinations will be made at the timepoints specified in the Schedules of Events ([Table 6-2](#) and [Table 6-3](#) for the teduglutide treatment arm and [Table 6-4](#) and [Table 6-5](#) for the SOC treatment arm).

Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature ($^{\circ}\text{C}/^{\circ}\text{F}$).

6.10 Electrocardiograms

Examinations will be made at the timepoints specified in the Schedules of Events ([Table 6-2](#) and [Table 6-3](#) for the teduglutide treatment arm and [Table 6-4](#) and [Table 6-5](#) for the SOC treatment arm). The ECG tracing will be read by a local experienced physician. Results (normal, abnormal not clinically significant, and abnormal clinically significant with description of the finding) will be recorded on the eCRF.

6.11 Adverse Events

Timing of all safety/tolerability evaluations is presented in the Schedule of Events ([Table 6-2](#) and [Table 6-3](#) for the treatment arms and [Table 6-4](#) and [Table 6-5](#) for the SOC treatment arm).

During the study, the investigator is responsible for the detection and documentation of any and all AEs or SAEs as defined and instructed in this protocol.

6.11.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with study drug treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality, vital sign abnormality, and clinically significant electrocardiogram (ECG) abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study evaluations have begun (after signing of the ICF)
- Pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

6.11.2 Procedures for Reporting Adverse Events

Adverse events may be spontaneously reported by the subject or subject's parent/guardian, obtained through nonleading questioning, or noted during examination of a subject. All AEs and SAEs will be recorded from the time of the signing of the informed consent form (ICF) and, if applicable, the informed assent form, through the last study visit (visit 28 or EOS). SAEs will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug or until resolution or until the SAE is judged by the investigator to have stabilized.

As they occur, new AEs will be recorded sequentially on the AE page of the eCRF. The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). The following features are recorded also:

- Onset and stop date and time
- Frequency (intermittent, continuous)
- Severity (mild, moderate, severe)
 - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
 - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
 - Severe: requires vigorous therapeutic intervention and interrupts usual activities; hospitalization may or may not be required.

- Note that the severity of adverse events that constitute dose interruption criteria will also be evaluated using the NCI CTCAE grading criteria (Section 6.14)

6.11.3 Relationship to study drug (not related, related)

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. |

- Whether the AE is serious (ie, an SAE). An event identified as an SAE should be reported on the form entitled “Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol” (Section 6.12)
- Actions taken with regards to study drug: none; study drug dose changed, interrupted, or permanently discontinued/withdrawn
- Other action taken
- Outcome: fatal; not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; recovering/resolving; unknown

Adverse events 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, blood pressure, ECG evaluations, 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 visit (day 0)
- The finding fulfills SAE criteria, and/or
- The finding results in subject discontinuation

6.11.4 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. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

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

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

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

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

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

- Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.
- Medication errors should be collected and reported for all products under investigation.
- The administration and/or use of the unassigned treatment is/are always reportable as a medication error.
- 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.

6.12 Serious Adverse Events

An SAE must be reported as described in Section 6.12.2 and recorded on the sponsor’s form entitled “Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol”. An SAE requires expeditious handling to comply with regulatory requirements. Any SAE that occurs from the time of the signing of the ICF through last study visit (visit 28 or EOS) will be captured and must be reported within 24 hours after the investigator or the investigator’s site personnel is made aware of the event.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless they result in an SAE.

6.12.1 Serious Adverse Event Definition

An SAE is an AE that has any of the following outcomes:

- Death
- Is life-threatening: a life-threatening AE is any AE that places the subject – in the investigator’s opinion – at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- 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 or may require medical or surgical intervention to prevent one of the other 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 hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- Planned before entry into the clinical study
- Are for elective treatment of a condition unrelated to the studied indication or its treatment
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- Are part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

Any laboratory test result that meets the criteria for an SAE must also be recorded on the sponsor’s form entitled “Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol” so that the sponsor/designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.12.2 Procedures for Reporting Serious Adverse Events

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Pharmacovigilance and Risk Management Department and the Shire 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 unless the event results in an SAE.

The investigator must complete, sign, and date the form entitled “Shire Clinical Study Serious Adverse Event and Non-serious AEs 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) and fax or e-mail the form to the Shire Global

Pharmacovigilance and Risk Management Department. A copy of the sponsor's form (and any applicable follow-up reports) must also be sent to the Shire medical monitor using the details specified in the key sponsor contact information provided at the beginning of the protocol.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator and/or the investigator's site personnel at any interval after the study has completed must be reported to Shire's Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline
or
- Becomes stable to a clinically acceptable level that is safe for the subject

The investigator is required to assess the causal relationship of each reported SAE to the study drug (see below). A causality assessment should always be included on the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" form. The investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

Relationship of an AE to investigational product is to be determined by the physician/investigator based on the definitions of "related" and "not related" provided in Section 6.11.2.

Contact information for SAE reporting and emergency contact details can be found in the key sponsor contact information provided at the beginning of the protocol and in the Investigator Site File.

As required by International Council of Harmonisation (ICH) guidelines and global health authorities, the sponsor/designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Lack of causality does not negate SAE reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator's brochure (IB) or if the event is of greater frequency, specificity, or severity than is mentioned in the IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study; however, the investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

Upon receiving such notices, the investigator must review and retain the notice.

The investigator should also comply with the IEC/IRB procedures for reporting any other safety information.

The sponsor/designee will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe. All fatal and life-threatening SUSAR reports will be submitted by the sponsor or designee within 7 days of receipt (day 0) of the initial report. All other SUSAR reports will be submitted by day 15 following the event.

6.13 Adverse Events of Special Interest

An adverse event of special interest (AESI) 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 AESIs that require expedited reporting for this study include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the gastrointestinal 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 AESIs, the sponsor will be informed within 24 hours as per the SAE notification instructions described in Section 6.12.2 even if the event does not fulfill the serious criterion.

6.14 Dose Interruption of Individual Subjects in the Teduglutide Treatment Arm

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, incidents of certain AEs, SAEs considered to be related to the study drug, a lapse in investigational product delivery, etc.

Study drug (teduglutide) must be 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 anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE listed in Table 6-1 that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to study drug administration
- Confirmed drug-induced liver injury (DILI) related to teduglutide (See Section 6.14.2).

6.14.1 Dose Interruption Criteria Based on Known Risks of Teduglutide

The study drug may be discontinued if the subject has an adverse event listed in Table 6-1 that is of severity \geq Grade 3 per the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE). All such AEs should be discussed with Shire's medical monitor as soon as possible. Teduglutide administration must be discontinued if the AE is considered related to study drug. The length of discontinuation, whether it is temporary or permanent, depends on the clinical situation.

Investigators and the DMC members should be guided by the descriptions of Grade 3 and 4 events presented in [Table 6-1](#).

Table 6-1 Adverse Events that May Lead to Dose Interruption

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

Table 6-1 Adverse Events that May Lead to Dose Interruption

| Adverse Event | Grade 3 Description | Grade 4 Description |
|--|---------------------|---------------------|
| ULN=upper limit of normal a In the setting of clinically acute and symptomatic pancreatitis Source: Common Terminology Criteria for Adverse Events, version 4.03, 14 June 2010 | | |

6.14.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

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

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

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. INR should be measured with this set of verification labs 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, HepA IgM, HepB sAg, HepC Ab, CMV IgM, EBV antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (antinuclear, anti-smooth muscle, anti-actin, or anti-liver/kidney mucosal 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 Shire medical monitor.

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

6.15 Early Termination of the Clinical Study

The DMC members may recommend stopping the study if:

- ≥2 subjects being administered study drug develop the same event listed in [Table 6-1](#) of severity CTCAE Grade 3

or

- 1 subject develops an event listed in [Table 6-1](#) of severity CTCAE Grade 4 that is attributable to teduglutide or is not reasonably related to the underlying disease process

6.16 Prior and Concomitant Treatments

All non-study treatments, including invasive and diagnostic procedures, herbal treatment, and vitamins received within 14 days before screening through week 28 or final study contact must be recorded on the appropriate section of the eCRF. The following information should be included, as appropriate:

- Medication name, route, dose, indication, dates used
- Procedure type, reason, dates

Changes in any medication and/or dosage will be recorded on the eCRF. See also Sections [5.3.4](#) and [8.1](#).

6.17 Female Subjects of Child-bearing Potential

Any female subject in the teduglutide treatment arm who has reached menarche must have a negative serum pregnancy test to enroll or continue in the study. Pregnancy tests will be performed at screening (serum HCG) and at all subsequent clinic visits (urine HCG). Female subjects in the standard of care treatment arm will not be required to undergo pregnancy testing. Sexually active females of child-bearing potential (FOCBP) must use medically acceptable methods of birth control during and for 4 weeks after the treatment period (eg, true abstinence¹, oral contraceptive pills, barrier methods with spermicide) in a manner such that the risk of failure is minimized. The investigator will discuss these methods as well as their side effects with the subject. If a pregnant subject also reports an SAE, then the SAE form will be completed and submitted within 24 hours.

At the time of signing the ICF/assent, FOCBP must be advised of the importance of avoiding pregnancy during trial participation, and the potential risk factors for pregnancy.

In the event a subject becomes pregnant during the study, teduglutide administration must be discontinued immediately, unless clearly needed, and a Pregnancy Report Form should be completed to capture potential drug exposure during pregnancy. The pregnancy should be reported within 24 hours of becoming aware of the condition. The subject should be followed until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous abortion (miscarriage), voluntary abortion, or therapeutic abortion).

¹ True abstinence: Abstention of sexual activity that is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

6.18 Unblinding

The treatment assignment must not be broken during the study except in emergency situations where the identification of the dose of the investigational product is required for further treatment of the subject. If warranted, the principal investigator or designee will place an unblinding call to the IWRS to receive treatment assignment information. The investigator should contact the Shire medical monitor as soon as possible after the investigator has been unblinded. Greater detail is provided in the Investigator Site File.

In the event that the treatment assignment is broken, the date, the name of the person who broke the code and the reason for breaking the code are recorded in the IWRS and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes.

Schedules of Events

Table 6-2 Schedule of Events in the Teduglutide Treatment Arm – Screening to Week 12

| Study week | Screening Baseline | | Treatment period | | | | | | | | | | | |
|--|--------------------|-----|------------------|------|------|------|------|------|------|------|------|------|------|------|
| | SRN | BL | W1 | W2 | W3 | W4 | W5 | W6 | W7 | W8 | W9 | W10 | W11 | W12 |
| Visit Number/Type: S=site/T=telephone | 1/S | 2/S | 3/S | 4/S | 5/T | 6/S | 7/T | 8/S | 9/T | 10/S | 11/T | 12/S | 13/T | 14/S |
| Study day±window | ≥-14 | 0 | 7±2 | 14±2 | 21±3 | 28±3 | 35±3 | 42±3 | 49±3 | 56±3 | 63±3 | 70±3 | 77±3 | 84±3 |
| PE/Vitals/Weight | X | X | X | X | | X | | X | | X | | X | | X |
| Height (or length) and head circumference ^m | X | X | | | | X | | | | X | | | | X |
| Adverse event collection | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

(X)=as needed; BL=baseline; eCRF=electronic case report form; EN=enteral nutrition; GI=gastrointestinal; PE=physical examination; PN/IV=parenteral nutrition/intravenous fluid; S=site; SRN=screening; T=telephone; W=week

Note: Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate subject visits to the site.

- a Informed consent/assent must be obtained before performing any study-related procedure.
- b If the subject has undergone an upper GI with small bowel follow through and/or an abdominal ultrasound within the 6 months before visit 1 (screening), then those test results will be acceptable for the screening assessments. If the subject has not had these procedures within the 6 months before visit 1 (screening), then the procedure(s) will be performed any time after providing informed consent with the results available and reviewed before the baseline visit (day 0).
- c All subjects enrolled in a treatment arm will have an FOBT after providing consent/assent. Subjects with positive FOBT at screening for whom a readily detectable cause cannot be not identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy. Colonoscopy/sigmoidoscopy will be conducted at screening on all subjects 12 years of age and older; however if the screening FOBT is negative and the subject has undergone the procedure within 1 year before visit 1 (screening), then that result will be acceptable for the screening assessment (See Section 6.5.4). Subjects with positive FOBT results at week 12 for which a cause is not identified by a physical exam will be discussed with the Shire medical monitor (See Section 6.5.3).
- d Treatment arm assignment and randomization and will be completed before dispensing teduglutide.
- e The first subcutaneous injection of teduglutide 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) must be specified and recorded in the eCRF. Teduglutide dose may be adjusted based on weight at week 12.
- f See Section 6.1 for PK blood draw timepoints. If a subject is unable to provide blood samples for PK at the baseline visit (day 0), then PK samples may be collected during any other future site visit while the subject is still receiving treatment with teduglutide.
- g Safety lab assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits may be collected by a Home Health Agency and submitted to a central lab or performed locally and will consist of clinical chemistry and urinalysis only. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately within 5-7 days of any adjustment to the PN/IV prescription. For all subjects in the teduglutide treatment arm, PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.
- h All female subjects of child-bearing potential will be tested for pregnancy: serum testing at screening; urine thereafter.
- i Blood samples for measuring citrulline levels should be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 6.6.1.1).
- j For antibody testing, blood will be obtained from subjects in the teduglutide treatment arm at the site before receiving the first dose of teduglutide. Blood samples may be drawn from a central line or from peripheral access (See Section 6.6.1.2).
- k The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 6.6). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every clinic visit and within 1 week of each change in PN/IV prescription. (See Section 6.6 for more detail). Nutritional support includes PN/IV and EN (formula) (See Section 6.4).
- l Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data and according to the guidelines provided in Appendix 1.

Schedules of Events

Table 6-2 Schedule of Events in the Teduglutide Treatment Arm – Screening to Week 12

| Study week | Screening Baseline | | Treatment period | | | | | | | | | | | |
|---------------------------------------|--------------------|-----|------------------|------|------|------|------|------|------|------|------|------|------|------|
| | SRN | BL | W1 | W2 | W3 | W4 | W5 | W6 | W7 | W8 | W9 | W10 | W11 | W12 |
| Visit Number/Type: S=site/T=telephone | 1/S | 2/S | 3/S | 4/S | 5/T | 6/S | 7/T | 8/S | 9/T | 10/S | 11/T | 12/S | 13/T | 14/S |
| Study day±window | ≥-14 | 0 | 7±2 | 14±2 | 21±3 | 28±3 | 35±3 | 42±3 | 49±3 | 56±3 | 63±3 | 70±3 | 77±3 | 84±3 |

m Head circumference will be measured in subjects 36 months of age and younger (Section 6.8).

Table 6-3 Schedule of Events in the Teduglutide Treatment Arm – Weeks 13 to 28 (EOT)

| Week number | Treatment period | | | | | | | | | | | Follow-up period | | |
|---|------------------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------------------------------|-------------------------|------------|
| | W13 | W14 | W15 | W16 | W17 | W18 | W19 | W20 | W21 | W22 | W23 | W24 EOT ET ^a | W25 W26 W27 | W28 EOS |
| Visit number/type S=site; T=telephone | 15/T | 16/T | 17/S | 18/T | 19/T | 20/S | 21/T | 22/T | 23/S | 24/T | 25/T | 26/S | 27/T 28/T 29/T | 30/S |
| Study day ±window (day) | 91 ±3 | 98 ±3 | 105 ±3 | 112 ±3 | 119 ±3 | 126 ±3 | 133 ±3 | 140 ±3 | 147 ±3 | 154 ±3 | 161 ±3 | 168 ±3 | 175±3 182±3 189±3 | 196 ±4 |
| Adverse event collection | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense drug | | | X | | | X | | | X | | | | | |
| Provide intake and output diaries | | | X | | | X | | | X | | | X | | |
| Review diaries and nutritional support ^b | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adjust nutritional support ^c | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| Safety laboratory testing ^d | (X) | (X) | X | (X) | (X) | X | (X) | (X) | X | (X) | (X) | X | (X) | X |
| Pregnancy test ^e | | | X | | | X | | | X | | | X | | X |
| Citrulline test ^f | | | | | | | | | | | | X | | X |
| PE/vitals/weight/height (or length)/head circumference ^g | | | X | | | X | | | X | | | X | | X |
| Fecal occult blood test ^h | | | | | | | | | | | | X | | |
| Colonoscopy/Sigmoidoscopy | | | | | | | | | | | | (X) | | |
| Electrocardiogram | | | | | | | | | | | | X | | X |
| Antibodies to teduglutide ⁱ | | | | | | | | | | | | X | | X |

(X)=as needed; EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; PE=physical examination; PN/IV=parenteral nutrition/intravenous fluid; S=site visit; T=telephone contact; W=week

- Any subject who discontinues from the study before week 24 (EOT) (ie, early terminates) will undergo EOT procedures at the time of discontinuation and will complete a follow-up visit 4 weeks later.
- The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 6.6). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every clinic visit and within 1 week of each change in PN/IV prescription. (See Section 6.6 for more detail). Nutritional support includes PN/IV and EN (formula) (See Section 6.4).
- Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data and according to the guidelines provided in Appendix 1.

Table 6-3 Schedule of Events in the Teduglutide Treatment Arm – Weeks 13 to 28 (EOT)

| | Treatment period | | | | | | | | | | | Follow-up period | | |
|--|------------------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------------------------------|-------------------------|------------|
| Week number | W13 | W14 | W15 | W16 | W17 | W18 | W19 | W20 | W21 | W22 | W23 | W24 EOT ET ^a | W25 W26 W27 | W28 EOS |
| Visit number/type S=site; T=telephone | 15/T | 16/T | 17/S | 18/T | 19/T | 20/S | 21/T | 22/T | 23/S | 24/T | 25/T | 26/S | 27/T 28/T 29/T | 30/S |
| Study day ±window (day) | 91 ±3 | 98 ±3 | 105 ±3 | 112 ±3 | 119 ±3 | 126 ±3 | 133 ±3 | 140 ±3 | 147 ±3 | 154 ±3 | 161 ±3 | 168 ±3 | 175±3 182±3 189±3 | 196 ±4 |

- d Safety lab assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits may be collected by a Home Health Agency and submitted to a central lab or performed locally and will consist of clinical chemistry and urinalysis only. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed within approximately 5-7 days of any adjustment to the PN/IV prescription. For all subjects in the teduglutide treatment arm, PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.
- e All female subjects of child-bearing potential will be tested for pregnancy: serum testing at screening; urine thereafter.
- f Blood samples for measuring citrulline levels should be collected 2 to 4 hours postprandial, whenever possible and may be drawn from a central line or from peripheral access (Section 6.6.1.1).
- g Head circumference will be measured in subjects 36 months of age and younger (Section 6.8).
- h Subjects with positive FOBT at week 24 (EOT)/ET for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a confirmatory colonoscopy/sigmoidoscopy. See Section 6.5.3.
- i Blood draw to test for antibodies to teduglutide before the last dose of teduglutide, ≥14 hours after the previous dose of teduglutide. If a blood sample is positive for antibodies at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

Table 6-4 Schedule of Events in the Standard of Care Treatment Arm – Screening to Week 12

| Study week | Screening Baseline | | Treatment period | | | | | | | | | | | |
|--|--------------------|-----|------------------|------|------|------|------|------|------|------|------|------|------|------|
| | SRN | BL | W1 | W2 | W3 | W4 | W5 | W6 | W7 | W8 | W9 | W10 | W11 | W12 |
| Visit Number/Type: S=site/T=telephone | 1/S | 2/S | 3/S | 4/S | 5/T | 6/S | 7/T | 8/S | 9/T | 10/S | 11/T | 12/S | 13/T | 14/S |
| Study day±window | ≥14 | 0 | 7±2 | 14±2 | 21±3 | 28±3 | 35±3 | 42±3 | 49±3 | 56±3 | 63±3 | 70±3 | 77±3 | 84±3 |
| Informed consent/assent ^a | X | | | | | | | | | | | | | |
| Eligibility | X | X | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| Medical/Surgical history | X | | | | | | | | | | | | | |
| Electrocardiogram | X | | | | | | | | | | | | | X |
| Short bowel syndrome history | X | | | | | | | | | | | | | |
| Provide GI-specific symptoms history diary | X | | | | | | | | | | | | | |
| Review GI-specific symptoms history diary | | X | | | | | | | | | | | | |
| Safety laboratory testing ^b | X | X | X | X | (X) | X | (X) | X | (X) | X | (X) | X | (X) | X |
| Citrulline test ^c | | X | | | | | | | | | | | | X |
| Provide intake and output diaries | X | X | X | X | | X | | X | | X | | X | | X |
| Review diaries and nutritional support ^d | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adjust nutritional support ^e | | | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| PE/Vitals/Weight | X | X | X | X | | X | | X | | X | | X | | X |
| Height (or length) and head circumference ^h | X | X | | | | X | | | | X | | | | X |
| Adverse event collection | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

(X)=as needed; AE=adverse event; BL=baseline; eCRF=electronic case report form; EN=enteral nutrition; GI=gastrointestinal; PE=physical examination; PN/IV=parenteral nutrition/intravenous fluid; S=site; SRN=screening; T=telephone; W=week

Note: Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate subject visits to the site.

a Informed consent/assent must be obtained before performing any study-related procedure.

b Safety lab assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits may be collected by a Home Health Agency and submitted to a central lab or performed locally and will consist of clinical chemistry and urinalysis only. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed within approximately 5-7 days of any adjustment to the PN/IV prescription.

c Blood samples for measuring citrulline levels should be collected 2 to 4 hours postprandial, whenever possible and may be drawn from a central line or from peripheral access (Section 6.6.1.1).

d The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 6.6). Urine and stool output should be recorded in the

Table 6-4 Schedule of Events in the Standard of Care Treatment Arm – Screening to Week 12

| | Screening Baseline | | Treatment period | | | | | | | | | | | |
|---------------------------------------|--------------------|-----|------------------|------|------|------|------|------|------|------|------|------|------|------|
| Study week | SRN | BL | W1 | W2 | W3 | W4 | W5 | W6 | W7 | W8 | W9 | W10 | W11 | W12 |
| Visit Number/Type: S=site/T=telephone | 1/S | 2/S | 3/S | 4/S | 5/T | 6/S | 7/T | 8/S | 9/T | 10/S | 11/T | 12/S | 13/T | 14/S |
| Study day±window | ≥-14 | 0 | 7±2 | 14±2 | 21±3 | 28±3 | 35±3 | 42±3 | 49±3 | 56±3 | 63±3 | 70±3 | 77±3 | 84±3 |

output diary over a 48 hour period of PN/IV and EN stability before every clinic visit and within 1 week of each change in PN/IV prescription. (See Section 6.6 for more detail). Nutritional support includes PN/IV and EN (formula) (See Section 6.4).

- e Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data and according to the guidelines provided in [Appendix 1](#).
- f Head circumference will be measured in subjects 36 months of age and younger (Section 6.8).

Table 6-5 Schedule of Events in the Standard of Care Arm – Weeks 13 to 28 (EOT)

| Week number | Treatment period | | | | | | | | | | | Follow-up period | | |
|---|------------------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------------------------------|-------------------------|------------|
| | W13 | W14 | W15 | W16 | W17 | W18 | W19 | W20 | W21 | W22 | W23 | W24 EOT ET ^a | W25 W26 W27 | W28 EOS |
| Visit number/type S=site; T=telephone | 15/T | 16/T | 17/S | 18/T | 19/T | 20/S | 21/T | 22/T | 23/S | 24/T | 25/T | 26/S | 27/T 28/T 29/T | 30/S |
| Study day ±window (day) | 91 ±3 | 98 ±3 | 105 ±3 | 112 ±3 | 119 ±3 | 126 ±3 | 133 ±3 | 140 ±3 | 147 ±3 | 154 ±3 | 161 ±3 | 168 ±3 | 175±3 182±3 189±3 | 196 ±4 |
| Adverse event collection | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Provide Intake and Output diaries | | | X | | | X | | | X | | | X | | |
| Diary and nutritional support review ^b | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adjust nutritional support ^c | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| Safety laboratory testing ^d | (X) | (X) | X | (X) | (X) | X | (X) | (X) | X | (X) | (X) | X | (X) | X |
| Citrulline test ^e | | | | | | | | | | | | X | | X |
| PE/vitals/weight/height (or length)/head circumference ^f | | | X | | | X | | | X | | | X | | X |
| Electrocardiogram | | | | | | | | | | | | X | | X |

(X)=as needed; EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; PE=physical examination; PN/IV=parenteral nutrition/intravenous fluid; S=site visit; T=telephone contact; W=week

- a Any subject who discontinues from the study before week 24 (EOT) (ie, early terminates) will undergo EOT procedures at the time of discontinuation and will complete a follow-up visit 4 weeks later.
- b The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 6.6). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every clinic visit and within 1 week of each change in PN/IV prescription. (See Section 6.6 for more detail). Nutritional support includes PN/IV and EN (formula) (See Section 6.4).
- c Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data and according to the guidelines provided in Appendix 1.
- d Safety lab assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits may be collected by a Home Health Agency and submitted to a central lab or performed locally and will consist of clinical chemistry and urinalysis only. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed within approximately 5-7 days of any adjustment to the PN/IV prescription.
- e Blood samples for measuring citrulline levels should be collected 2 to 4 hours postprandial, whenever possible and may be drawn from a central line or from peripheral access (Section 6.6.1.1).
- f Head circumference will be measured in subjects 36 months of age and younger (Section 6.8).

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent/assent signed), all subjects will be assigned an 8-digit subject number, including subjects in the SOC treatment arm. The first 4 digits consist of the study site number. The last four digits will be assigned sequentially starting with 0001. This number is the main identifier for subjects.

Data collected during the study will be recorded in the subject's eCRF by the investigational site staff. The staff will keep records of the subject's visit in the files considered as source documents for that site (eg, hospital chart, research chart, etc.). Source data are all information contained in original records of clinical findings, observations, or other trial-related activities necessary for evaluation and reproducibility of data (eg, progress notes, hospital records, computer print-outs, screening logs, and recorded data from automated instruments). In case of computerized source data, the investigator must provide Shire access to the subject files at each monitoring visit. To ensure that data has been entered correctly on the eCRF, they will be 100% source-data verified by a site monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. The investigator or designee will be responsible for the timely recording of subject data into the eCRF.

The investigator and study site must permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections by providing direct access to source data/documents.

The investigator or designee will review all eCRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will sign the eCRF via an electronic signature. The investigator will be responsible for reviewing the data in a timely manner. Non-eCRF data (eg, labs) will be sent to the sponsor/designee via a data transfer from the appropriate vendor. Paper copies of laboratory reports and other non-eCRF data (eg, ECGs) will be signed and dated by the investigator and filed.

Diaries will be used by the subjects' parent or guardian to record study information, including PN/IV support, enteral administration, urine output (as either collected or calculated volume), stool form and volume, and urine specific gravity. The subject diaries will provide the source documentation for the diary data that is to be recorded in the eCRF by the study staff. Original diary data should be entered into the eCRF and takes precedence over data collected over the phone.

All data collected in this study will be entered into a study-specific database and submitted for statistical evaluation. The sites will be provided with eCRF completion guidelines outlining the specific procedures to use when entering the data into the clinical database. Data validation and edit checks will be conducted on the data. Any discrepancies will generate queries that must be resolved at the study site in a timely manner.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file is defined as when the data in the database and the reference values are complete and logical according to the clinical study protocol, general guidelines, and data management plan. Once the sponsor/designee acknowledges that all data are acceptable, the data will be declared a "clean file," and the data will be frozen/locked.

A quality audit will be performed by the Data Management group. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be ready for statistical analysis by the sponsor/designee.

7.2 Rescreening

Subjects may be rescreened only once and with prior sponsor approval. In the event of re-screening, a new subject number will be assigned. Subjects who are rescreened will be re-consented. See also Section 5.2.

7.3 Record Retention

All source documents, records, and reports will be retained by the study site in accordance with ICH guidelines. These documents include all primary data or copies thereof (eg, drug records, copies of eCRFs, laboratory records, data sheets, correspondence, signed subject consent/assent documents, ECGs, photographs, and computer records) which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report.

The clinical investigators will maintain copies of these essential documents for approximately 10 years or as dictated by local regulatory requirements or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor. In accordance with regulatory guidelines, these records will be available for inspection and copying if requested by a properly authorized employee of the FDA/European Health Authorities.

8 STATISTICAL METHODOLOGY AND SAMPLE SIZE

Detailed statistical analysis methods will be conducted as described in the statistical analysis plan (SAP) for this study. Deviations from the SAP (if any) will be described and justified in the clinical study report (CSR).

Because of the small size of the study population only descriptive statistics will be used to summarize data. Accordingly, no claims of significance will be made for any of the data.

Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

8.1 Demographic and Baseline Variables

Demographic and/or other baseline variables obtained at the screening or baseline visit are listed below.

- Demography (including age, sex, and race)
- Medical history
- SBS history, including remnant anatomy
- GI-specific symptoms history
- Vital signs, including temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), and height or length
- Physical examination
- Prior treatment(s)
- Electrocardiogram (12-lead)
- Laboratory test results: hematology, coagulation, clinical chemistry, and urinalysis
- Citrulline levels
- Presence of antibodies to teduglutide and titer level, if present (teduglutide treatment arm only)
- Gastrointestinal imaging (UGI/SBFT, abdominal ultrasound, colonoscopy/sigmoidoscopy, fecal occult blood) (teduglutide treatment arm only)
- Pregnancy testing for females of child-bearing potential (teduglutide treatment arm only)
- Nutritional support prescriptions (eg, PN/IV and EN volume and calories, PN/IV hours per day and days per week)
- Nutritional support diary data

Descriptive statistics (mean, median, standard deviation, minimum and maximum values, and the number and percentage of subjects in specified categories by treatment arm) will be presented, as appropriate, to summarize the demographic and baseline variables.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized by treatment and SOC treatment arms.

Medical history (including surgical/procedural history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with

specific histories will be summarized by system organ class and preferred term for each study arm.

8.2 Safety and Tolerability Variables

The safety and tolerability variables include:

- Adverse events, including GI symptoms
- Physical examination findings
- Vital signs, including temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), height or length, and trends on growth charts
- Electrocardiograms
- Laboratory safety data (ie, clinical chemistry, coagulation, hematology, urinalysis), including the following lab tests at all clinic visits and interim safety labs to detect hepatotoxicity signals: AST, ALT, ALP, and bilirubin
- Change in urine output (measured volume)
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide (teduglutide treatment arm only)
- GI-specific testing (teduglutide treatment arm only) including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, UGI/SBFT

Adverse events will be coded using MedDRA. Treatment emergent AEs will be summarized by system organ class and preferred term for each treatment arm (teduglutide and SOC). The number and percentage of subjects with AEs, SAEs, AEs that lead to discontinuation, study drug-related AEs (determined by the investigator), and SAEs that resulted in a fatal outcome will be summarized by treatment arm and teduglutide dose group. AEs will also be summarized by treatment arm and dose group with regard to severity and, for the teduglutide dose groups, relationship to study drug. For AESIs, the CTCAE grading system will be used as described in Section 6.14.

For laboratory tests, vital signs, body weight, ECG, and output diary 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 absolute values and change from baseline at each scheduled visit for each study arm.

The number and percentage of subjects classified as having positive specific antibodies to teduglutide will be used to summarize the presence of antibodies for each treatment arm.

8.3 Pharmacokinetic Variables

The following pharmacokinetic parameters will be estimated using a population PK modeling approach:

- Area under the plasma concentration-time curve (AUC) of zero to infinity ($AUC_{0-\infty}$)
- AUC from zero to the last measurable concentration (AUC_{last})
- AUC at steady state (AUC_{ss})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{\lambda z}/F$)

Descriptive statistics (mean, median, standard deviation, minimum and maximum values, geometric mean, 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.

8.4 Efficacy/Pharmacodynamic Variables

The primary efficacy/PD endpoint is a reduction in PN/IV volume of at least 20% at week 24 (or EOT) compared to baseline.

The following efficacy/PD parameters will be measured:

- 100% reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 (or EOT) compared to baseline
- Change from baseline (absolute and percent change) in PN/IV support (volume and calories), citrulline, and enteral nutritional support (volume and calories) at each clinic visit
- Change from week 24 (or EOT) (absolute and percent change) in PN/IV support (volume and calories), citrulline, and enteral nutritional support (volume and calories) at week 28 (or EOS)
- Change in hours per day and days per week of PN/IV support
- $\geq 20\%$ reduction in PN/IV volume at each clinic visit

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 for each study arm and teduglutide dose group.

8.5 Other Variables

Other variables will be analyzed by study arm and dose group, as appropriate, including:

- Subject disposition
- Duration of teduglutide exposure
- Subjects will be considered compliant if teduglutide was taken according to protocol and assigned dose group for $\geq 80\%$ of doses. Data will be taken from the Study Drug Accountability completed by the site staff. The number and percentage of subjects who were compliant will be presented by treatment arm.
- The number and percentage of subjects who complete the study, are lost to follow up, or discontinued from the study (including reason for study withdrawal) will be summarized by dose group.
- The teduglutide dose duration will be summarized by dose group.

8.6 Analysis Populations, Data Sets, and Time Points

8.6.1 Analysis Populations

The **efficacy population** will consist of all enrolled subjects.

The **safety population** will include all subjects in the efficacy population who meet the following criteria:

- Teduglutide treatment arm: subjects who have received at least 1 dose of teduglutide and have undergone at least 1 safety assessment
- SOC treatment arm: subjects who have undergone at least 1 safety assessment

The **per protocol population** will consist of all subjects in the efficacy population who have completed the study through EOT (week 24) without incidence of a major protocol violation that could affect the efficacy/PD conclusions of the study

The **PK population** will consist of all enrolled subjects who receive at least one subcutaneous injection of teduglutide and have evaluable and interpretable PK data.

Detailed per-protocol evaluable definitions will be documented in the SAP. Major protocol violations will be determined before database lock.

The primary population analyzed for efficacy/PD will be the efficacy population. An additional per-protocol population analysis will also be performed as secondary/sensitivity analysis.

8.7 Statistical/Analytical Issues

8.7.1 Adjustments for Covariates

Not applicable for this study.

8.7.2 Handling of Dropouts or Missing Data

All subjects randomized will be included in the analyses. Missing safety parameters will not be imputed. Details for the imputation algorithm for the missing endpoint values for PN/IV volume will be detailed in the SAP.

8.7.3 Interim Analyses and Data Monitoring

No interim analyses are planned.

An independent DMC will review the data on a routine basis and may have access to data from the study for safety assessment. Details of the roles and responsibilities of the DMC members and the structure and scope of the DMC meetings will be provided in a separate DMC Charter.

8.7.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Accordingly, no adjustment to the alpha will be made.

8.7.5 Use of an Efficacy Subset of Subjects

A per-protocol population will be analyzed for this study.

8.7.6 Examination of Subgroups

Data from subjects in the teduglutide dose groups will be analyzed according to age strata (subjects aged <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years) and by glutamine use, separately.

8.8 Determination of Sample Size

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

8.9 Changes to Planned Statistical Analyses

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final CSR.

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the current applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association Declaration of Helsinki and its amendments concerning medical research in humans.

In accordance with guidelines, the protocol, any advertisements and, informed consent/assent forms will be reviewed and approved by the IEC/IRB. The sponsor will supply relevant material for the investigator to submit to the IRB for the protocol's review and approval. Verification of the IEC/IRB approval of the protocol and the written consent/assent form will be forwarded to the sponsor/designee.

The investigator will inform the IEC/IRB of subsequent protocol amendments and any SUSARs if the sponsor has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator will provide the IEC/IRB with progress reports at appropriate intervals (not to exceed 1 year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

9.2 Subject Information, Informed Consent and Assent

In accordance with applicable guidelines, informed consent/assent shall be documented by the use of a written consent/assent approved by the IEC/IRB and signed by the subject and/or subject's parent or guardian before any screening and protocol-specific procedures are performed. A consent/assent form template will be provided by the sponsor/designee and adapted by the investigator to meet study site, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject and/or the subject's parent or guardian the nature of the study, the action of the test product, and any risks and benefits. The subject and/or subject's parent or guardian will be informed that participation is voluntary and that the subject can be withdrawn from the study at any time without prejudice to their subsequent care.

The subject and/or the subject's parent or guardian will be given a copy of the fully executed consent/assent and the original will be maintained with the subject's records.

9.3 Subject Data Protection

All data provided to the sponsor/designee will be identified only by subject number and initials, thereby ensuring that the subject's identity remains unknown. Where allowed, the subject's date of birth will also be recorded. The subject and/or the subjects' parent or guardian should be informed in writing, that the subject's data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Study site-specific information must be added to the consent/assent as appropriate.

The subjects and/or the subjects' parent or guardian also should be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require

access to those parts of the hospital/clinic records which are relevant to the study, including medical history, for data verification purposes.

The principal investigator is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (ie, hospital/clinic number). A list of subjects who failed screening must also be maintained and be available for inspection.

9.4 Financial Disclosure

The FDA guidance document entitled “Financial Disclosure by Clinical Investigators” (February 2013) provides guidance to industry on its final rule on financial disclosure that became effective 02 February 1999 and was published as Title 21 Code of Federal Regulations Part 54. This rule applies to all investigators participating in clinical studies to be submitted to the FDA in support of an application for market approval. The financial disclosure statement must be updated if any relevant changes occur during the course of the study, again at the site close-out visit, and for 1 year after the completion of the study.

According to the guidance, financial arrangements that must be disclosed are defined as the following:

- Compensation made to the investigator in which the value of compensation could be affected by study outcome
- A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright, or licensing agreement
- Any equity interest in the sponsor of a covered study (ie, any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices)
- An equity interest in a publicly held company that exceeds \$50,000 in value
- Significant payments of other sorts, which are payments that have a cumulative monetary value of \$25,000 or more made by the sponsor of a covered study to the investigator or the investigator’s institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (eg, a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation, or honoraria) during the time the clinical investigator is carrying out the study and for 1 year after completion of the study

Clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. Participating investigators must provide this information and complete necessary documentation as requested by the sponsor.

The intent of this regulation is to ensure the proper identification and disclosure of financial interests of clinical investigators that could affect the reliability of data submitted to the FDA in support of a market application. Companies must meet these financial disclosure requirements, and failure to do so may result in the refusal by the FDA to accept an application for market approval of the study drug.

9.5 Changes to the Protocol

No change in the study procedures shall be effected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments, or as a revised protocol. Changes to the protocol may require notification to or approval by the IEC/IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the Study Reference Manual.

The sponsor/designee is responsible for the distribution of and training on any protocol amendment(s) to the principal investigator(s) and those concerned within the conduct of the study. The principal investigator is responsible for the distribution of all amendments to the IEC/IRB and all staff concerned at his/her study site.

9.6 Investigator Obligations

The principal investigator at each study site must provide the following to the sponsor/designee prior to the start of the study:

- A completed and signed FDA Form 1572. If during the course of the study any changes are made that are not reflected on the original FDA Form 1572, a revised form must be completed and returned to the sponsor for submission to the FDA.
- A current (within 2 years) signed and dated curriculum vitae for the principal investigator and all subinvestigators listed on FDA Form 1572, including a current office address which matches the address on the FDA Form 1572
- Financial disclosure statement for the principal investigator, and subinvestigators (listed on the FDA Form 1572). An updated financial disclosure statement must be provided at the study close-out visit and/or annually to the sponsor and 1 year after completion of the study.
- A copy of the original approval for conducting the study from the IEC/IRB. Renewals must be submitted at yearly intervals if the study is ongoing or as required by the institution.
- A copy of the IEC/IRB-approved ICF/assent
- IRB membership list or Department of Health and Human Services General Assurance Number, which must be maintained current during the trial
- Laboratory certification and normal ranges, unless a central laboratory is being used exclusively

The “Principal Investigator Protocol Agreement Page” of this protocol must be signed and dated by the principal investigator for the study site.

9.7 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor’s discretion and/or for submission to regulatory agencies. In addition, the sponsor reserves the right to

review data from this study relative to the potential release of proprietary information 30 days prior to submission to any publication or for any presentation.

9.8 Selection of a Primary Principal Investigator

The sponsor will select one primary principal investigator as a representative of all investigators for this study. Roles, affiliations, and qualifications for the principal investigators will be included in the CSR appendices. Where the signature of the principal investigator is required by regulatory authorities, this will also be included in the CSR appendices.

9.9 Study Termination

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

10 REFERENCES

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Appendix 1 Guidelines for Nutritional Support Management during the Study (TED-C14-006)

Nutritional support adjustment in volume and calories should be considered at all planned visits. Please consider the following clinical parameters identified as markers for adequate management of pediatric short bowel syndrome. These parameters should be considered for managing nutritional support (PN/IV and EN) in terms of volume and calories during the treatment period.

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

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

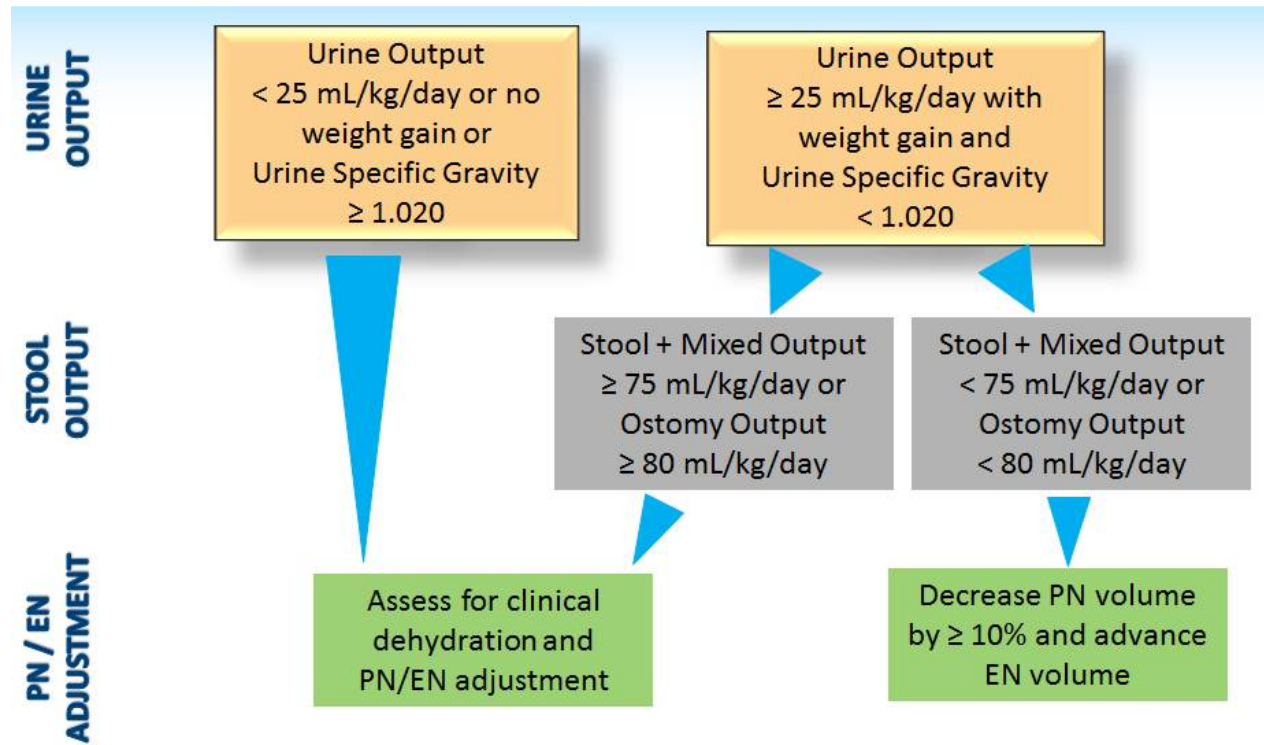


Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

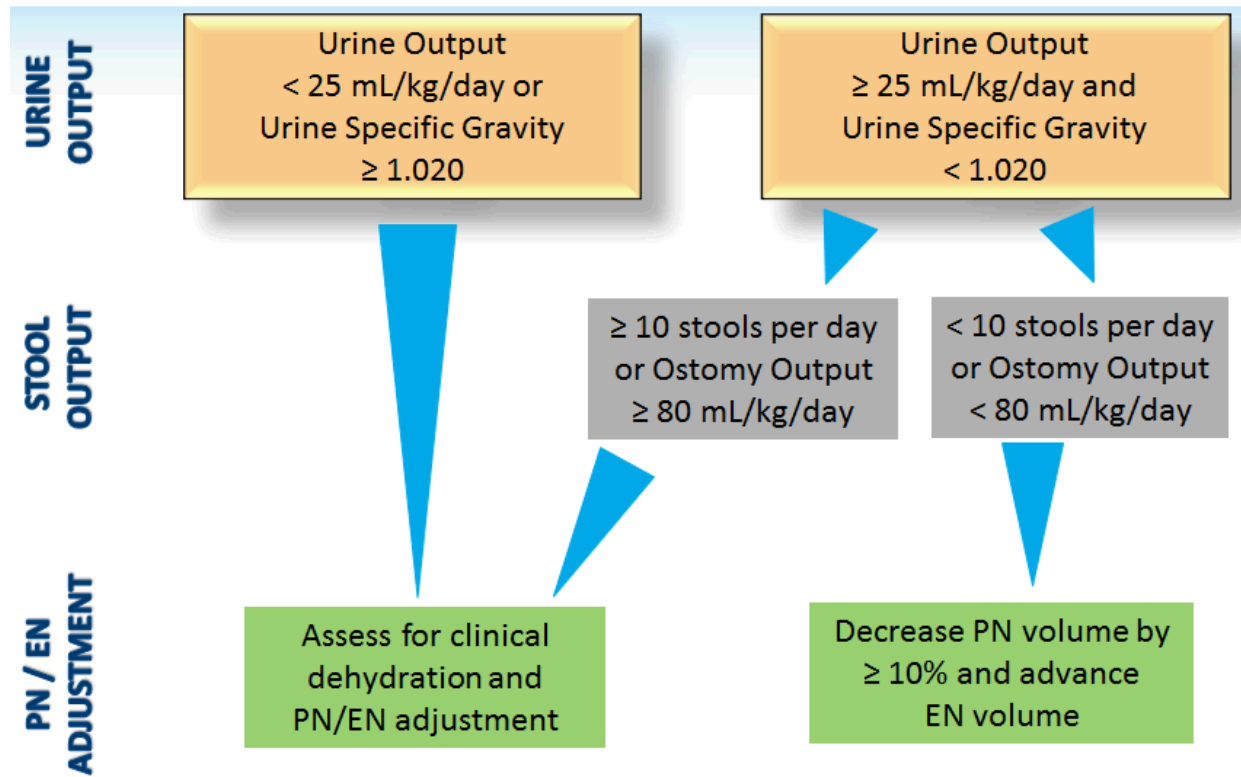
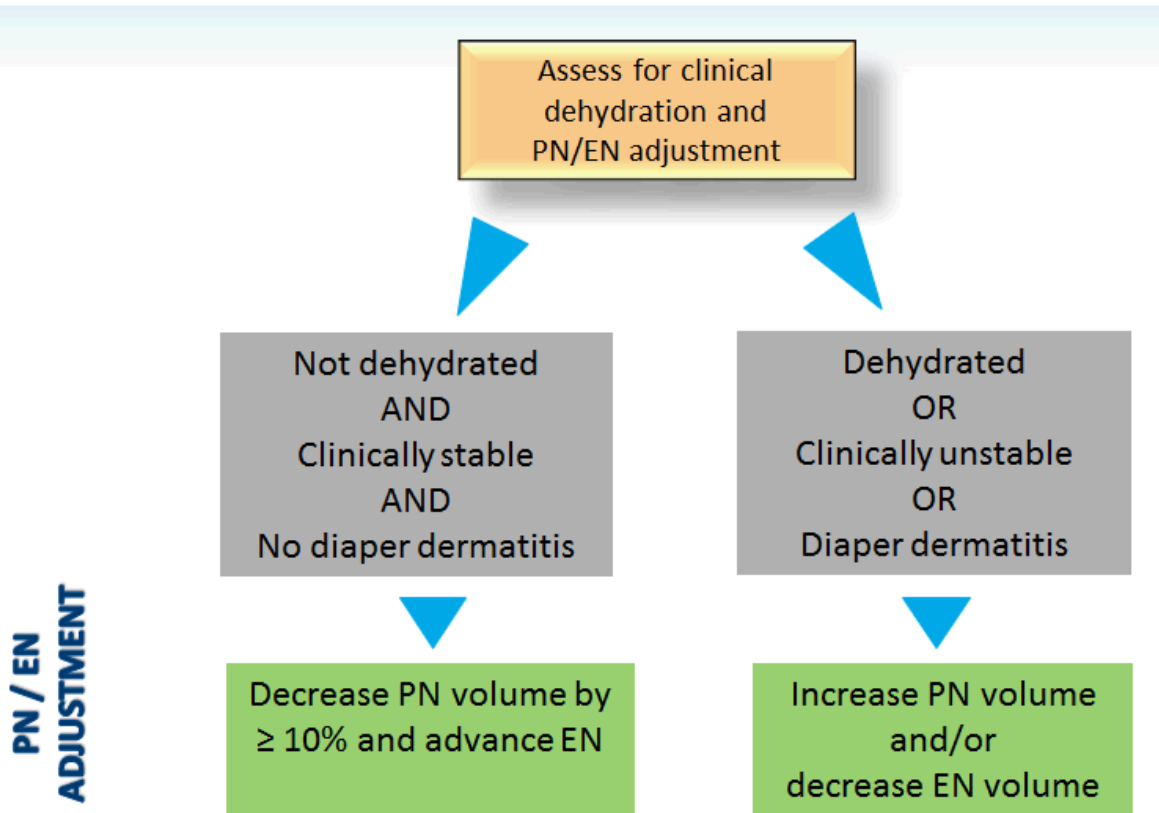


Figure A-3 Clinical Dehydration Assessment and PN/EN Adjustment



Appendix 2 Protocol History

| Document | Date | Global/Country/Site Specific |
|-------------------|------------------|------------------------------|
| Original Protocol | 12 Mar 2015 | Global |
| Amendment 1 | 22 Jun 2015 | Global |
| Amendment 2 | 06 October 2015 | Global |
| Amendment 3 | 25 February 2016 | Global |
| Amendment 4* | 15 March 2016 | Global |

*Amendment 4 was created because a quality control error was identified in amendment 3, in which one of the exclusion criterion was not replicated in the synopsis.

Note: Administrative changes, typographical errors, and text changes made to increase readability are not listed in the table below.

| Protocol Amendments | | |
|--|-------------------------------|--|
| Summary of Change(s) Since Amendment 3 of Approved Protocol | | |
| Differences between amendment number 3 and amendment number 4 | Amendment Date 15 Mar 2016 | Global/Country/Site Specific Global |
| A quality control error was identified in amendment 3, in which an exclusion criterion was not replicated in the synopsis. Sections affected are the Synopsis and Section 4.2.2. | | |

Note: Administrative changes, typographical errors, and text changes made to increase readability are not listed in the table below.

| Protocol Amendments | | |
|---|-------------------------------|---|
| Summary of Change(s) Since Amendment 2 of Approved Protocol | | |
| Differences between amendment number 2 and amendment number 3 | Amendment Date 25 Feb 2016 | Global/Country/Site Specific Global |
| Description of Change | | Section(s) Affected by Change |
| Key study contacts have been updated | | Page 2 |
| Product Quality Complaints information has been updated | | Page 3 |
| Methodology has been clarified; no changes were made to the overall design; clarified terminology for treatment arm and dose group | | Synopsis Protocol Section 3.1 Section 3.2 |
| Statement added that subjects who complete the study may participate in a long-term extension study in which eligible subjects could receive teduglutide. | | Synopsis Protocol Section 3.1 |
| Inclusion and Exclusion have been refined and clarified; there were no additional criteria added | | Synopsis Protocol Sections 4.2.1 and 4.2.2 |
| Exclusion Criteria #11 has been updated to indicate that a subject would be excluded from the study if the subject had participated in a clinical study of experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer. | | Synopsis Protocol Section 4.2.2 |
| Number of subjects in the teduglutide treatment arms was changed from approximately 20 to approximately 26; the number of global | | Synopsis |

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| investigational sites was changed from approximately 20 to approximately 28. | Protocol Section 4.1 |
| Language strengthened describing the number of subjects enrolling into the SOC treatment arm: “attempts will be made to enroll” has been changed to “at least 8 subjects who are teduglutide-naïve will be enrolled”. | Synopsis Protocol Section 4.1 |
| Language has been added to indicate that attempts will be made to enroll into each teduglutide dose group at least 1 subject younger than 1 year and at least 2 subjects aged 12 to <17 years. | Synopsis Protocol Section 4.1 Section 5.2 |
| Clarification that departing from the nutritional support adjustment guidelines provided in Appendix 1 will not constitute a protocol deviation. | Synopsis Protocol Section 3.1 Section 6.4 |
| Specified that randomization across teduglutide dose groups will be stratified by age subgroups. | Synopsis Protocol Section 3.1 Section 5.2 |
| The requirement that teduglutide should be administered in the morning has been removed. | Protocol Section 5.3.2 |
| Reviewing subject diaries has been included in the subject compliance with dosing check. | Protocol Section 5.3.3 Section 7.1 |
| The definition of prior and concomitant medications has been expanded to include treatments. | Protocol Section 5.3.4, Section 6.16; Table 6-2, Table 6-3, Table 6-4, and Table 6-5 |
| The Data Safety Monitoring Board has been replaced with a Data Monitoring Committee. | Synopsis Protocol Section 4.4 |
| A pharmacokinetic component has been added to the study as a criterion for evaluation. | Synopsis Protocol Sections 6.1, 8.3, and 8.6.1; Table 6-2 |
| Adverse event and serious adverse definitions and reporting procedures have been updated to align with Shire processes. Definitions for abuse, misuse, overdose, and medication error have been added. | Protocol Sections 6.3 and 6.12; and subsections therein |
| Adverse events of special interest have been redefined and procedures for reporting them have been added. | Protocol Section 6.13 |
| Dose interruption of individual subjects in the teduglutide treatment arm has been broken out according to known risks of teduglutide administration and to drug-induced liver injury | Protocol Sections 6.14 and added sections within; new Table 6-1 |
| Criteria for DILI have been added. | Protocol Section 6.14.2 |
| PT/INR testing has been added at screening for subjects in the teduglutide treatment arm and if DILI is suspected thereafter. | Protocol Section 6.6.1; Table 6-2 and Table 6-3 |
| Dose discontinuation has been made absolute for an AE known to be a study drug risk that is of severity \geq Grade 3 and considered to be related to study drug; cases of severe hypersensitivity that are determined to be related to study drug; DILI that is related to teduglutide, and pregnancy. SAEs related to study drug are potential but not absolute reasons for dose discontinuation. | Protocol Section 6.14.2 and sections added within; new Table 6-1 |
| Requirement added that female subjects of child-bearing potential in the teduglutide treatment arm have a serum-based pregnancy test at screening. | Protocol Section 6.17 and Table 6-2 |

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| Procedures for unblinding have been made consistent with the EMA GCP guidance that breaking of treatment code resides with the investigator in emergency situations | Protocol Section 6.18 |
| “Other nutrition (regular diet and drink)” has been removed from the Intake diary. | Protocol Section 6.6 Section 7.1 |
| Decrease frequency of capturing Output diary data to the 48 hours of PN/IV and EN stability before every clinic visit and within 1 week of implementing a change in the PN/IV prescription. | Protocol Section 6.6; Table 6-2, Table 6-3, Table 6-4, and Table 6-5 |
| The need for a subject in the teduglutide treatment arm with a positive FOBT at week 12 without a readily identifiable cause to undergo a colonoscopy/sigmoidoscopy is now open to discussion with the Shire medical monitor. | Protocol Sections 6.5.3 and Table 6-2 |
| The requirement has been added that subjects who are rescreened must be reconsented. | Protocol Section 7.2 |
| Definitions of analysis populations have been updated. | Protocol Section 8.6.1 |
| Subgroup analyses have been added based on glutamine use and age strata, separately, for subjects in the teduglutide dose groups. | Protocol Section 8.7.6 |
| Correct amendment 2 summary of change document which misstated that investigators no longer were required to assign CTCAE severity grades to adverse events that may lead to dose interruption. | Not applicable |