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 2.0

Phase 3

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ISSUED:

Amendment 1, version 2.0:	**22 June 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

Phase of development: 3

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

Methodology: This will be a double-blind, 2 arm study in which subjects will be randomized in a 1:1 ratio to receive either 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide for 24 weeks followed by 4 weeks of no active therapy. Dosing regimens will be blinded to both investigators and subjects. In addition, an attempt will be made to enroll subjects in a separate standard of care cohort, which will serve as an observational cohort for the 24-week treatment period and 4-week follow-up. The subjects in the standard of care cohort will follow the same visit schedule as the randomized subjects.

All subjects will be screened for a minimum of 2 weeks prior to start of treatment to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters. After screening, the 24-week treatment period will consist of site visits at baseline, weekly for the first 2 weeks, and then every other week for the next 8 weeks (through Week 12). From Weeks 13 to 24, visits at the sites will be conducted at Weeks 15, 18, 21, and 24. Telephone contacts will be made on all other weeks during the treatment period. A final visit will be scheduled at Week 28, 4 weeks following the end of treatment (EOT). Telephone contact will be made during the interim weeks from EOT to end of study (EOS).

To maintain consistency across all centers, sites and subjects (treated and standard of care) must follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding parenteral nutrition/intravenous (PN/IV) support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability.

Number of Subjects: Approximately 20 teduglutide-naïve subjects (at least 10 subjects per treatment arm) will be enrolled into the active treatment groups at approximately 10 to 20 investigational sites globally.

In addition, attempts will be made to enroll up to 8 teduglutide-naïve subjects in a standard of care cohort (who will not be treated with teduglutide) to serve as an observational cohort.

Duration of Study: There will be, at a minimum, a 2-week screening period followed by 24 weeks of on-treatment study visits. There will be one final scheduled visit at Week 28, 4 weeks after the EOT (Week 24).

The proposed duration of the clinical phase is from July 2015 through December 2016. The start of the clinical phase is defined as first subject screened. The end of the clinical phase is defined as the last visit of the last subject.

Diagnosis and main criteria for inclusion: Male and female children and adolescents, through 17 years of age, who meet the following inclusion and exclusion criteria will be enrolled in the 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 for at least 3 months (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]) prior to screening, as assessed by the investigator

6. Female subjects of child-bearing potential (in the active treatment group only) must use medically acceptable methods of birth control during and for 30 days after the treatment period.

Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens (ie, subjects with oral aversion)
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, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)
5. Severe, known dysmotility syndrome, such as pseudo-obstruction and persistent, severe, active gastroschisis-related motility disorders that are the primary contributing factors to feeding intolerance and inability to reduce parenteral support, prior to screening
6. Evidence of clinically significant obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
7. Major gastrointestinal 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 active treatment group only)
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegavan) within 1 month or an experimental antibody treatment within 3 months prior to screening, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide
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-IV (DPP-IV) 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] or natalizumab) within the 6 months prior to the screening visit

16. Subjects with inflammatory bowel disease (IBD) who required 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 unscheduled hospital admission which may affect parenteral support requirements within 1 month prior to the screening visit (up to 48-hour observations [ie, such as those to rule out sepsis/infection] or central line replacement/repair, in an otherwise stable subject, are allowed)

19. Body weight < 10 kg at screening and randomization visits

20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results during the screening period:

    a. Total bilirubin ≥ 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 ≥ 2 x ULN

21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by any of the below laboratory test results during the screening period:

    a. Serum creatinine ≥ 2 x ULN
    b. Creatinine clearance < 50 mL/min*

       *Only applies to subjects with a known history of chronic renal disease who must then have a screening creatinine clearance (CrCl) < 50 mL/min or, if CrCl cannot be measured, an eGFR level below 40 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 the table below.

Examples of Excluded Diseases and Illnesses

Body system	Known conditions excluded
Related to SBS	• Ongoing radiation enteritis • Untreated celiac disease • Refractory or tropical sprue • Pseudo-obstruction
Gastrointestinal	• Tufting or autoimmune enteropathy or microvillous inclusion disease • Untreated pre-malignant or malignant change in upper GI, biopsy or polypectomy • Known, untreated, 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, Eversmeyerous polypius)
Immune	• Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency).
Psychiatric	• Alcohol or drug addiction within the previous year • Major uncontrolled psychiatric illness
General	• Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

Test Product, Dose, and Mode of Administration:

After randomization, daily doses of either 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide will be administered to the subjects in the active treatment cohorts. The dose calculation will be

based on body weight measured at the Baseline Visit (Visit 2). No adjustments to dose will be made during the study period, unless discussed with the NPS medical monitor.

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

Reference Therapy, Dose and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety and tolerability:

Safety and tolerability will be assessed by evaluation of:

- Adverse events, including GI symptoms. A GI Symptom History Worksheet will be completed daily during the screening period, prior to baseline. GI symptoms will be recorded as none, mild, moderate, or severe. The principal investigator will assess the aggregate diary entries to determine a baseline of GI symptoms for each subject.
- Physical examinations
- Vital signs, including oral temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), height/length, and length trends on growth charts
- Electrocardiograms
- Laboratory safety data, including electrolyte balance and glucose
- Antibodies to teduglutide (active treatment groups only). Samples for antibody analysis will be drawn at baseline and at the EOT (Week 24) and EOS (Week 28) visits prior to the administration of teduglutide and at least 14 hours after the previous dose. One sample will be collected at the final visit 4 weeks after the EOT (EOS, Week 28). Any subjects testing positive for antibodies specific to teduglutide (positive/specific antibodies) at Week 28 will have follow-up visits 3 and/or 6 months after the last dose of study drug to assess antibody status.
- Changes in oral/enteral feeding
- Nutritional intake and urinary/fecal output (where collection is possible)
- GI-specific testing including imaging (eg, colonoscopy, sigmoidoscopy) abdominal ultrasound, fecal occult blood testing upper GI series with small bowel follow-through

Pharmacodynamics:

The primary pharmacodynamic (PD) parameter is parenteral support reduction of 20% to 100% at 24 weeks (or EOT) compared to baseline.

Analysis of additional PD endpoints will include:

- 100% reduction in PN/IV volume support (any subjects who are able to completely wean off PN/IV support) compared to baseline at EOS
- A decrease in parenteral support (calories and volume)
- An increase in enteral nutritional tolerance (calories and volume)
- Change from baseline in PN/IV support, citrulline, and enteral support at Week 24 (or EOT)
- Change from baseline in PN/IV support, citrulline, and enteral support at Week 28 (or EOS)
- Change from baseline in PN/IV support, citrulline, and enteral support at Week 24 (or EOT) compared to Week 28 (or EOS)
- Change in urine output (collected or calculated volume)
- Change in weight, height (length), and head circumference (where appropriate)
- Change in PN/IV support 3 and 6 months (as applicable) after EOT compared to baseline for those subjects who developed antibodies specific to teduglutide
- Change in hours per day or days per week of PN/IV support.
- Intensity of response (PN/IV reduction and advance in enteral support) at each visit.
- Proportion of responders (ie, subjects who achieve at least a 20% reduction in parenteral support) at Weeks 4, 8, 12, 16, 20, and 24 weeks.

To maintain consistency across all centers, sites and subjects (treated and standard of care) must follow the nutritional support adjustment guidelines (developed with SBS expert input) for decisions regarding PN/IV support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability.

Safety and tolerability will be evaluated by a data safety monitoring board (DSMB) every 3 months during the active study period. The DSMB review will include all cumulative safety data (ie, adverse events, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period including any reasons for dose adjustment and discontinuations.

Statistical methods:

Due to the limited size of the study population descriptive statistics will be used with a goal of summarizing the sample. As such, 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.

Efficacy/Pharmacodynamics:

Efficacy/pharmacodynamics data including reduction in parenteral support, increase in enteral nutritional tolerance, change in PN/IV support, citrulline, enteral support, urine output, weight, height, hours per day or days per week of PN/IV support, and time to PN/IV reduction and advance in enteral support will be summarized by visit and time point.

Safety:

Safety data including clinical laboratory tests, physical examinations, concomitant medications, electrocardiogram monitoring, and vital signs assessments will be summarized by visit and time point. Adverse events will also be collected and summarized, including Grade 3 and 4 adverse events of special interest, based on Common Terminology Criteria for Adverse Events (CTCAE) criteria. 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.

SIGNATURE PAGE

Protocol TED-C14-006

Reviewed and Approved:

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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

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 5 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 IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EN	Enteral nutrition
EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
FOCBP	Females of child-bearing potential
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-2	Glucagon-like peptide 2
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NOAEL	No Observed Adverse Effect Level
NPS	NPS Pharmaceuticals, Inc.
PD	Pharmacodynamic
PK	Pharmacokinetic
PN	Parenteral nutrition
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SC	Subcutaneous
SMT	Safety Management Team
SUSAR	Suspected, unexpected, serious, adverse reaction
ULN	Upper limit of normal
WMA	World Medical Association

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. The European Commission granted a centralised 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.

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 agency 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 present in males given a dose of 12.5 mg/kg/day.

Clinical Studies

Two completed 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. The 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 dose, teduglutide treatment in the initial phase 3 study, which included significant reductions in PN/IV. There was 75% of the subjects who previously responded to teduglutide treatment in Study CL0600-004 who 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. The majority of 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 either 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% and 13/43 subjects, 30.2%, respectively). This difference was clinically and statistically significant in both the Intent-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 (an additional 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

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 which qualifies 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. 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 (volvulus), intestinal atresia, and gastroschisis (Duro et al, 2008). SBS in older children may stem from the same etiologies as in adults (ie, Crohn's disease, trauma, cancer). 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 et al, 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.

The same treatment options are currently available for children and the same associated risks prevail. Treatment of both pediatric and adult patients is focused on achieving adequate intestinal absorption to allow for minimization or discontinuation of PN/IV support. This is achieved far more successfully in infants who develop SBS during the neonatal period and frequently come off their PN/IV requirements within 6 to 12 months of their initial surgical insult such that they achieve enteral autonomy by age 1 year. Recent data suggest that up to 85% of patients achieve spontaneous adaptation by age 1 year.

In the US, data from the Organ Procurement and Transplant Network reflect improvement in the medical and non-transplant surgical management of intestinal failure after 2010. The peak number of pediatric intestinal transplants in North America occurred between 2004 to 2009 (up to 111 in 2007) with falling levels from about 2010 onward (52 to 62 transplants annually). In 2012, 56 transplants took place and in 2013, 36 transplants took place.

This study proposes to investigate the safe and appropriate use of teduglutide in the pediatric population for up to 24 weeks for the purpose of providing longer-term data in regard to safety and 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. 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 (QD) in adult SBS subjects requiring PN. The recommended clinical dosage for the adult SBS patient population is 0.05 mg/kg QD. Population pharmacokinetic (PK) modeling and simulations were conducted to determine the dose to be used in pediatric subjects. Subcutaneous dosing of teduglutide in pediatric patients with SBS was based on data collected in 5 adult Phase 1 studies and 3 adult Phases 2/3 studies, as well as an adult population PK meta-analysis. The PK results from the adult SBS clinical program also were used to model and simulate PK parameters in pediatric SBS patients to provide guidance on pediatric dosing for teduglutide. An ongoing 12 week pediatric study (TED-C13-003) includes doses of 0.0125, 0.025, and 0.05 mg/kg/day. Interim data evaluated by the DSMB has concluded that all three doses are safe and tolerable with trends of PN/IV volume reduction

and advance in feeds observed. Modeling and simulation data from previously completed studies suggested that pediatric patients are likely to require the same dose as used in adults and that the 0.05 mg/kg/day adult dose will be sufficient to provide similar blood levels in all subjects over 1 year of age. To further explore additional safety and efficacy, a 24 week study is currently proposed.

Treatment Duration/Design

Safety, tolerability and pharmacodynamic measures over a 24-week period will be the main outcomes of the current study. The main PD effect of teduglutide to be measured in children will include a decrease in the volume of PN/IV requirement. Measurement of a decrease in PN/IV volume requirements 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 24 weeks of treatment was used as the primary endpoint in the adult clinical development program during pivotal Phase 3 studies and will be the same endpoint used in the current pediatric study.

The current study will employ a double-blind, 2 arm design with treatment of either 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide for up to 24 weeks. The 24-week treatment period will provide further information on longer term safety and additional efficacy including complete weaning of treatment beyond the 12-week period previously evaluated in the first pediatric study.

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

Subject Population

The current significant unmet medical need is for patients over age 1 year who remain dependent on parenteral support. These patients reach a plateau in their ability to advance oral/enteral feeds or decrease PN/IV support and are not expected to achieve spontaneous adaptation. The subjects in the study will be children whose intestines have not reached full enteral adaptation after 12 months of PN/IV treatment and whose PN/IV requirement had been stable without any clinically meaningful or substantial reduction in parenteral support for the 3 months prior to study enrollment.

Therefore, this study will be performed in PN/IV-dependent children with SBS through 17 years of age who have demonstrated that they have reached a plateau with regard to their ability to fully continue intestinal adaptation in terms of their ability to advance feeds and subsequently reduce their needs for parenteral support. Stability for these subjects will be defined as at least 3 months in which patients still are requiring at least 30% of their volume and/or calories from PN/IV with no clinically meaningful change in advances in their enteral feeds (specialized nutrition such as formula via mouth or tube).

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

Gastrointestinal Screening Measures

Pediatric SBS patients who are dependent on PN/IV have significant comorbidities such as biliary disease in addition to risk for obstruction due to history of surgery. Teduglutide has been found to have a targeted intenstinotrophic effect on the GI tract and areas of special interest in regards to safety have been identified throughout the development program. Taken into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests which are usually part of the routine care of these subjects will be performed on subjects in the active treatment groups to ensure safety. These include: abdominal ultrasound, upper GI series with contrast, fecal occult blood testing, and, if deemed clinically relevant, 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, which will include measures for weight, growth, and hydration status. The pharmacodynamic endpoint for this study is a ≥ 20% reduction in PN/IV support guided by clinical status. A suggested guidance for nutrition support adjustment is provided in Appendix 1 and should be followed by all sites to ensure uniform care across study sites and participants.

2 OBJECTIVES

2.1 Primary Objective

The objective of this clinical study is to evaluate the safety, tolerability, efficacy, and pharmacodynamic effects of teduglutide in pediatric subjects (through 17 years) with SBS who are dependent on parenteral support.

See Section 8.2 and Section 8.3 for further details of the variables being measured.

3 STUDY DESIGN

3.1 Overall Design and Control Methods

This will be a double-blind, 2 arm study in which subjects will be randomized in a 1:1 ratio to receive either 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide for 24 weeks followed by 4 weeks of no active therapy. Dosing regimens will be blinded to both investigators and subjects. In addition, an attempt will be made to enroll subjects in a separate standard of care cohort, which will serve as an observational cohort for the 24-week treatment period and 4-week follow-up. The subjects in the standard of care cohort will follow the same visit schedule as the randomized subjects.

All subjects will be screened for a minimum of 2 weeks prior to start of treatment to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters. After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks, and then every other week through Week 12. From Weeks 13 to 24, visits at the sites will be conducted at Weeks 15, 18, 21, and 24. Telephone contacts will be made on all other weeks during the treatment period in order to monitor safety. A final visit will be scheduled at Week 28, 4 weeks following the end of treatment (EOT). Telephone contact will be made during the interim weeks from EOT to end of study (EOS). If necessary, unscheduled visits can be arranged in place of the telephone contacts. Schedules of study parameters are displayed in Table 6-1 and Table 6-2.

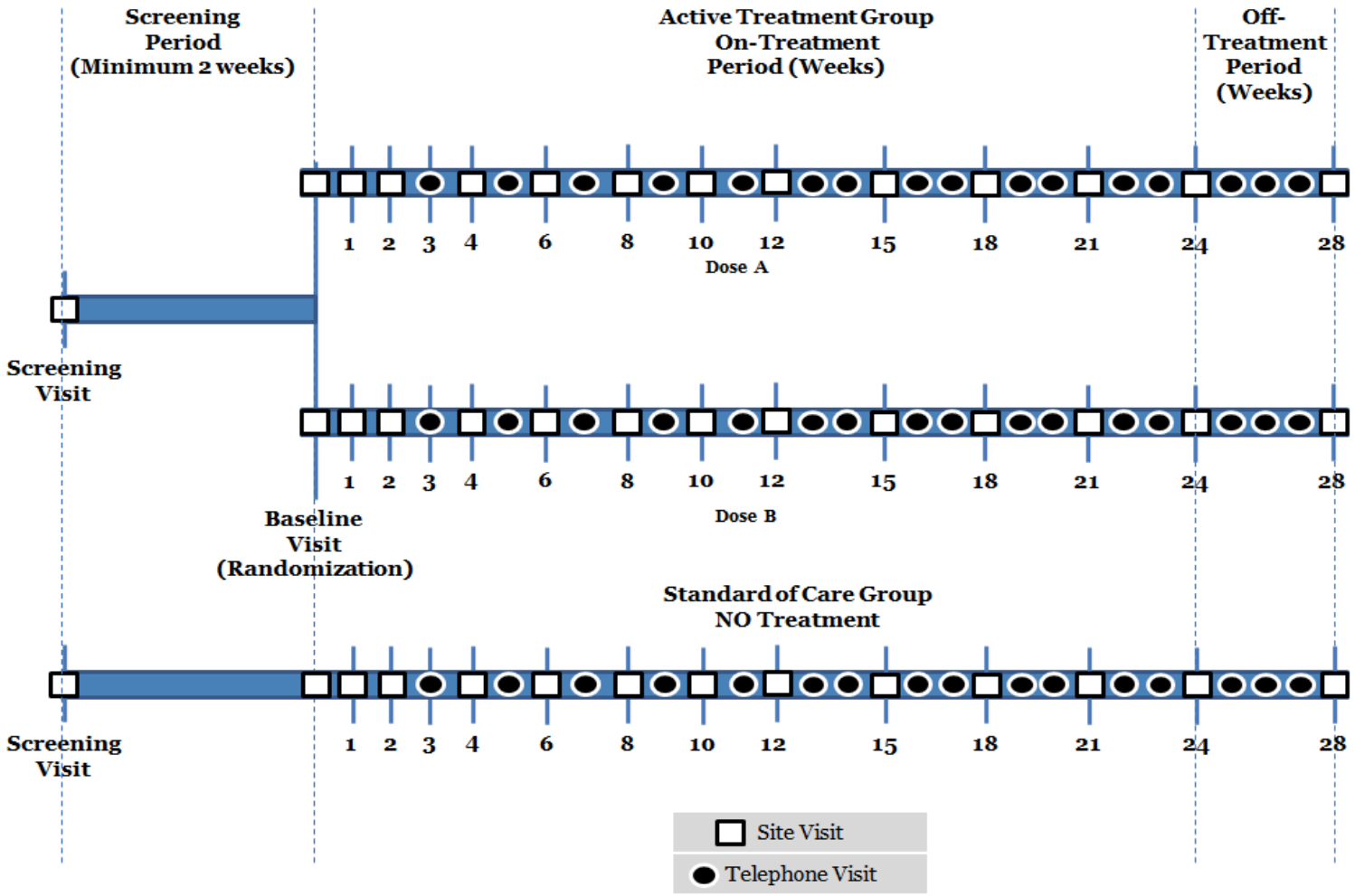
To maintain consistency across all centers, sites and subjects (treated and standard of care) must follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in Appendix 1) for decisions regarding PN/IV support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability.

At the conclusion of the follow-up period (Week 28), if subjects are determined to have positive/specific antibodies, they will be asked to return for a follow-up visit 3 months post EOT for another antibody sample. If the subjects continued to have positive/specific antibodies at 3 months post EOT, they will be asked to return for follow-up visit(s) up to 6 months post-treatment in order to determine their antibody status. At all follow-up visits, an assessment of the subject's current PN/IV support and an adverse event determination will be conducted.

Safety and tolerability results will be evaluated by a DSMB every 3 months during the active study period (date of the first subject's first dose to date of the last subject's last dose). The DSMB review will include all cumulative safety data (ie, adverse events, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period including any reasons for dose adjustment and discontinuations.

A schematic representation of the study design is displayed in Figure 3-1.

Figure 3-1 Study Diagram



Note: The Standard of Care cohort follows the same visit schedule as the active treatment groups.

3.2 Study Duration

There will be, at a minimum, a 2-week screening period followed by 24 weeks of treatment. There will be one final scheduled visit 4 weeks after the end of treatment. Those subjects who test positive for teduglutide-specific antibodies at the 4-week follow up visit (Week 28) will be asked to return for additional follow-up visit(s) as described in Section 6.1 in order to determine their antibody status.

The proposed duration of the clinical phase is from July 2015 through December 2016. The start of the clinical phase is defined as first subject screened. The end of the clinical phase is defined as the last visit of the last subject.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

Approximately 20-30 teduglutide-naïve subjects (minimum 10 subjects per treatment arm) will be enrolled into the active treatment groups.

In addition, attempts will be made to enroll up to 8 teduglutide-naïve subjects in the standard of care cohort.

Subjects will be enrolled at approximately 10 to 20 investigational sites globally.

4.2 Inclusion Criteria

Male and female children and adolescents, through 17 years of age, who meet the following inclusion criteria will be enrolled in the study.

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 prior to any study-related procedures (as deemed appropriate by the Ethics Committee/Institutional Review Board)

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 for at least 3 months (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]) prior to screening, as assessed by the investigator

6. Sexually active female subjects of child-bearing potential (in the active treatment group only) must use medically acceptable methods of birth control during and for 30 days after the treatment period

4.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria at baseline are not eligible for enrollment into the study:

1. Subjects who are not expected to be able to advance oral or tube feeding regimens (ie, subjects with oral aversion)

2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening

3. Known clinically significant untreated intestinal obstruction

4. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)

5. Severe, known dysmotility syndrome, such as pseudo-obstruction and persistent, severe, active gastroschisis-related motility disorders that are the primary contributing factors to feeding intolerance and inability to reduce parenteral support prior to screening

6. Evidence of clinically significant obstruction on upper GI series done within 6 months prior to screening

7. Major gastrointestinal 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 active treatment group only)

11. Participation in a clinical study using an experimental drug (other than glutamine or Omegavan) within 1 month or an experimental antibody treatment within 3 months prior to

screening, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide

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-IV (DPP-IV) 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] or natalizumab) within the 6 months prior to the screening visit

16. Subjects with inflammatory bowel disease (IBD) who required 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 unscheduled hospital admission which may affect parenteral support requirements within 1 month prior to the screening visit(up to 48-hour observations [ie, such as those to rule out sepsis/infection] or central line replacement/repair, in an otherwise stable subject, are allowed)

19. Body weight < 10 kg at the screening and randomization visits

20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results during the screening period:

    a. Total bilirubin ≥ 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 ≥ 2 x ULN

21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by any of the below laboratory test results during the screening period:

a. Serum creatinine ≥ 2 x ULN
b. Creatinine clearance < 50 mL/min*

*Only applies to subjects with a known history of chronic renal disease who must then have a screening creatinine clearance (CrCl) < 50 mL/min or, if CrCl cannot be measured, an eGFR level below 40 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 the table below.

Table 4-1 Excluded Diseases and Illnesses

Body system	Known conditions excluded
Related to SBS	Ongoing radiation enteritis Untreated celiac disease Refractory or tropical sprue Pseudo-obstruction
Gastrointestinal	Active IBD which required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months IBD that required chronic systemic immunosuppressant therapy for symptom control Tufting or autoimmune enteropathy or microvillous inclusion disease Untreated pre-malignant or malignant change in upper GI, biopsy or polypectomy Known, untreated, 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, Eversmeyerous polypius) Intestinal or other major surgery scheduled within the time frame of the study Chronic active pancreatitis Cholecystitis

Table 4-1 Excluded Diseases and Illnesses

Body system	Known conditions excluded
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency)
Psychiatric	Alcohol or drug addiction within the previous year Major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

4.4 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 NPS 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, Institutional Review Board (IRB) or NPS, 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 criterion for exclusion
- 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 possibly related to study drug and not alleviated with treatment of symptoms
- Adverse event (including Grade 3 or 4 events of special interest [Section 6.1.4])
- Hypersensitivity determined by the investigator to be possibly 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 6.1.1. Reasons for discontinuation other than AEs must be reported within 4 weeks of the EOS date in order to be included in the database. Any reason for discontinuation obtained after this time will be included in the subject's medical record only unless the EOS visit date is amended and the database remains open.

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.

4.5 Data Safety Monitoring Board

The DSMB 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 DSMB will be an external, independent board comprised of physicians with relevant training and an independent statistician (not associated with NPS, study sites, or investigators). The DSMB will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DSMB will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators, individuals employed by NPS, independent contractors hired by NPS , or members of regulatory agencies. The DSMB may serve as an advisory board to NPS; however, NPS will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped.

The DSMB members will review the data approximately every 3 months after the beginning of dosing of the first subject and then approximately every 3 months thereafter. The DSMB will be provided the following: 1) all cumulative safety data from the study for safety assessments; 2) data related to pharmacodynamics and the nutritional progress (ie, any changes in the use of PN/IV and/or enteral nutrition) of each subject; and 3) any other data supporting the decision to discontinue teduglutide throughout the study.

5 TREATMENTS AND TREATMENT PLAN

5.1 Treatment Administered

Daily doses of either 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide will be administered once daily in the morning to the subjects in the active treatment cohorts. The dose calculation will be based on body weight measured at the Baseline Visit (Visit 2). No adjustments to dose will be made during the study period. Teduglutide will be administered by SC injection into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or either thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma will 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 10 mg/mL solution upon reconstitution. The 2.5-mg vial is 5 mg/mL. A maximum of 0.38 mL of reconstituted solution can be withdrawn from the vial.

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. Study drug vial will be supplied in kits containing 7 vials and labeled with the protocol number, the investigational drug warning, general dosage instructions, storage conditions, expiry date, kit number, lot number, and company name. Space will be provided for recording study site and subject numbers at the study site. Ancillary supply kits containing syringes with needles for injection and reconstitution, sterile water, and alcohol swabs will also be provided.

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

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. 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 ^{o}C (35.6 to 46.4 ^{o}F) until dispensed to a subject. Once dispensed to a subject, the study drug can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25 ^{o}C, or 35.6 to 77 ^{o}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 usedf and unused vials must be returned to the distribution center according to the sponsor's instruction. No vial/kit may be destroyed on site.

5.2 Methods of Assigning Subjects to Treatment Groups

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 throughout the study period, including any subjects in the standard of care cohort.

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 dosing cohort or the standard of care cohort. At the end of the screening period, the investigator will review and confirm that the subject continues to meet all Inclusion/Exclusion criteria. If the subject or subject's parent/guardian/caretaker decides to participate in the dosing cohort, the investigator or designee will request the subject be randomized at the Baseline Visit using an interactive voice response system (IVRS) at a 1:1 ratio, centrally administered as described in the IVRS Manual of Procedures.

Study drug kits will be assigned through IVRS to each subject at each on-site visit through completion of the dosing period. The IVRS will automatically assign the correct number of kits for each visit based on the date of randomization. If additional kits are needed (eg., subject is going on holiday), the IVRS and NPS will need to be notified so that the additional kits can be assigned. Subjects will be randomized across centers rather than within center.

Those subjects opting for the standard of care cohort will continue in the study but without the study drug.

5.3 Dose Regimens

Teduglutide will be supplied in 2 strengths:

- 5.0 mg/vial for subjects receiving 0.05 mg/kg/day of teduglutide
- 2.5 mg/vial for subjects requiring 0.025 mg/kg/day

Subjects in the active treatment groups are to have the study drug administered daily in the morning by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm, for 24 weeks. For subjects with a stoma, the quadrant of the abdomen containing the stoma

will not be used. The initial dose will be calculated based on body weight measured at the Baseline Visit (Visit 2).

5.3.1 Selection of Doses in Study

A recently completed 12-week pediatric study (TED-C13-003) included doses of 0.0125, 0.025, and 0.05 mg/kg/day. Data evaluated by the DSMB concluded that all 3 doses were safe and tolerable with trends of PN/IV volume reduction and advance in feeds observed. Modeling and simulation data from previously completed studies suggested that pediatric patients are likely to require the same dose as used in adults and that the 0.05 mg/kg/day adult dose will be sufficient to provide similar blood levels in all subjects over 1 year of age.

5.3.2 Selection and Timing of Dose for Each Subject

The study drug will be administered immediately after reconstitution by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm. 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 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 the study drug can be found in the Injection Instructions. Each day, the injection site should be changed. For subjects with a stoma, the abdominal quadrant in which the stoma is situated should be avoided.

The subject should be dosed at approximately the same time each day, preferably in the morning. If a morning 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 approximately 12 hours. The time of the dose should be captured in the appropriate area in the subject diary (ie, Daily [yes/no], Morning [yes/no], and option for other).

The investigator is responsible for contacting the sponsor/designee prior to interrupting the subject's daily study drug dosing regimen. Reasons for dosage interruptions may include but are not limited to hospitalization, adverse events, forgotten doses, lapse in study drug delivery, etc. A single discontinuation period of study drug should not exceed 10 consecutive days. Dosage interruptions of study drug for a maximum of 21 days total during the entire 24 weeks are permissible.

5.3.3 Compliance with Dosing Regimens

Subject compliance with study drug 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 asking the subject or the subject's parent or guardian if they have administered the study drug 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.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered.

5.3.4 Prior and Concomitant Medications

The administration of all medications including concomitant medications must be recorded in the appropriate sections of the eCRF.

In general, no new medications should be started during the screening period or throughout the 24-week treatment period, unless medically necessary and prescribed by the investigator or by another qualified physician involved in the subject's clinical care and who is aware of the subject's study participation.

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), so consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medications should be considered when drugs, including those with a narrow therapeutic range, are given at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

6.1 Evaluations for Safety and Tolerability

Safety variables will be assessed by the following evaluations, according to Schedules of Evaluations and Procedures as outlined in Table 6-1 and Table 6-2, with opportunities for more frequent tests as clinically necessary. Safety variables for the standard of care cohort are displayed in Table 6-3 and Table 6-4.

- Adverse events, including GI symptoms. A GI Symptom History Worksheet will be completed daily during the screening period, prior to baseline. GI symptoms will be recorded as none, mild, moderate, or severe. The principal investigator will assess the aggregate diary entries to determine a baseline of GI symptoms for each subject.
- Physical examinations
- Vital signs, including oral temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), height/length, and length trends on growth charts
- Electrocardiograms
- Laboratory safety data, including electrolyte balance and glucose
- Antibodies to teduglutide (active treatment groups only). Samples for antibody analysis will be drawn at baseline and at the EOT (Week 24) and EOS (Week 28) visits prior to the

administration of teduglutide and at least 14 hours after the previous dose. One sample will be collected at the final visit 4 weeks after the EOT (EOS, Week 28). Any subjects testing positive for antibodies specific to teduglutide (positive/specific antibodies) at Week 28 will have follow-up visits 3 and/or 6 months after the last dose of study drug to assess antibody status.

- Changes in oral/enteral feeding
- Nutritional intake and urinary/fecal output (when available)
- GI-specific testing including imaging (eg, colonoscopy, sigmoidoscopy), abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through

6.1.1 Adverse Events

The investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol, during the study.

6.1.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this 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 and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- 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

Overdose

Defined as an accidental or intentional administration of an excessive dose of a product, an overdose should be reported to the sponsor using the SAE form. This information will be shared with the NPS Safety Management Team (SMT) and the sponsor's medical monitor.

6.1.1.2 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 signing of the informed consent form (ICF) and, if applicable, the informed assent form, through the last study visit or the last study required procedure (including study visit). 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). Also recorded are:

- Start and stop date and time
- Whether the event is continuing
- Frequency (intermittent, continuous)
- Intensity (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.
- Relationship to study drug (not related, related): identify relationship as "related" if a causal relationship between the investigational product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out)
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.1.2 below
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)

- Outcome (resolved, resolved with sequelae, ongoing, fatal). An individual AE receives only one outcome.

Adverse events that are related to study drug and not resolved at the end of treatment will be followed by the site until resolution or until the AE is judged by the investigator to have stabilized.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study

6.1.2 Serious Adverse Events

A serious event must be reported as described in Section 6.1.2.2 and recorded on the sponsor's SAE Form. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug will be captured and must be reported within 24 hours after the investigator is made aware of the event.

6.1.2.1 Serious Adverse Event Definition

An SAE is an AE that results in 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 in an SAE report 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.

6.1.2.2 Procedures for Reporting Serious Adverse Events

Within 24 hours of becoming aware of ANY SAE (regardless of its relationship to investigational product) that occurs during the course of the clinical study from the time the ICF/assent is signed through 30 days after the study drug is completed, the investigator must notify the sponsor. The SAE information, including the time and date that the investigator became aware of the event, must be entered into the SAE reporting system and supplemental data (eg, medical records or lab values, if applicable) faxed to the sponsor. This ensures timely reporting of applicable reports to Health Authorities.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but a serious event criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an adverse event, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

The sponsor/designee will provide a FAX cover sheet for the investigators in the Study Reference Manual.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the sponsor's SAE form.

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 sponsor's SAE 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.

The causality categories are:

Not related

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow a known response pattern to the suspect study product (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject

Related (Possibly Related/Probably Related/Related)

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- Follows a reasonable temporal sequence from administration of the study product
- May follow a known response pattern to the study product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable
- Recurs upon rechallenge after withholding and then reintroducing study product

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol and in the Study Reference Manual.

As required by International Conference 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]). Causality, while assessed, does not negate 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 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. As per regulatory guidance, if it is determined that there is an unanticipated signal, the NPS SMT will analyze the data and prepare a summary supporting the determination and interpretation of the findings. The sponsor/designee will send this summary to the investigators with instructions to provide it to their IEC/IRB.

The investigator should also comply with the IEC/IRB procedures for reporting any other safety information (ie, autopsy reports).

NPS Pharmaceuticals (sponsor) 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.

6.1.3 Unblinding

If a subject becomes pregnant or seriously ill during the study, the blind should be broken only if knowledge of the study medication administered will affect treatment options available to the subject. Before breaking the blind, the investigator should contact the NPS Medical Monitor for discussion on whether unblinding of the subject is warranted. If warranted, the principal investigator or the sponsor or designee will place an unblinding call to the IVRS to receive treatment assignment information. In the case of an extreme emergency and if the Medical Monitor is immediately unreachable, the investigator should break the blind through the IVRS. Please see Manual of Procedures for further details.

In the event prior authorization from the NPS Medical Monitor is not possible, the NPS Medical Monitor must be notified by telephone immediately, but no later than 24 hours following the unblinding of any subject for any reason. A record should be kept of when the blind was broken, who broke it, and why.

6.1.4 Dose Interruption of Individual Subjects

Teduglutide administration for an individual subject may need to be stopped if the subject has an adverse event of special interest (see risks in table below) that is Grade 3 or higher as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). This may occur if an event is attributable to study drug or a subject experiences an unexplained CTCAE Grade 3 or higher that is not reasonably related to the underlying disease process. The determination of length of the discontinuation, temporary or permanent, depends on the clinical situation. A treatment-emergent SAE of special interest that leads to study drug

interruption/discontinuation will be assigned a Grade 3 or 4, if applicable, by the investigator during the SAE reporting and follow-up process.

Investigators and the DSMB should be guided by the descriptions of Grade 3 and 4 events below, as they relate to identified risks associated with the administration of teduglutide.

Identified Risk	**Grade 3 Description**	**Grade 4 Description**
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal Obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Alkaline Phosphatase increased	> 5.0 to 20.0 x Upper limit of normal	> 20.0 x Upper limit of normal
Blood bilirubin increased	> 3.0 to 10.0 x Upper limit of normal	> 10.0 x Upper limit of normal
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated

Identified Risk	Grade 3 Description	Grade 4 Description
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 5.0 x Upper limit of normal	> 5.0 x Upper limit of normal
Lipase increased[a]	> 2.0 to 5.0 x Upper limit of normal	> 5.0 x Upper limit of normal
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)
[a]In the setting of clinically acute and symptomatic pancreatitis Source: Common Terminology Criteria for Adverse Events, version 4.03, 14 June 2010		

6.1.5 Early Termination of the Clinical Study

The DSMB may recommend to stop the study if:

- ≥ 2 subjects being administered study drug develop the same CTCAE Grade 3 or
- 1 subject develops a CTCAE Grade 4 adverse event which is attributable to study drug or is not reasonably related to the underlying disease process

6.1.6 Laboratory Evaluations

The following laboratory parameters will be examined according to the Schedules of Evaluations and Procedures as outlined in Table 6-1 and Table 6-2 (Table 6-3 and Table 6-4 for the standard of care cohort). While not all abnormal laboratory results would be considered clinically significant as determined by the investigator (ie, those that are associated with the disease state and were present at baseline), those that are determined to be a clinically significant change (ie, worsening) from baseline or known medical history will be considered adverse events. All such abnormal laboratory values that are considered AEs must be recorded on the appropriate eCRF. A result outside of the normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (Section 6.1.2) must also be recorded in an SAE report 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.

6.1.6.1 Safety Laboratory Tests and Procedures

Hematology

- Hemoglobin
- Hematocrit
- Platelets
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Serum Chemistry

- Albumin
- Alkaline phosphatase
- ALT
- Amylase
- AST
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- Citrulline (plasma)
- Creatinine
- Creatinine clearance
- C-reactive protein
- Creatinine clearance (or Glomerular Filtration Rate [GFR])
- Glucose
- Gamma glutamyl transferase
- Lipase
- Magnesium
- Phosphate
- Potassium
- Sodium
- Triglycerides
- Uric acid

Urinalysis

- Blood
- Glucose
- Leucocytes
- Microscopic analysis
- Specific gravity
- pH and osmolality
- Protein
- Sodium
- Pregnancy tests (females of child-bearing potential) – for active treatment group only

Procedures

Upper GI with contrast

Abdominal ultrasound

Colonoscopy/sigmoidoscopy (subjects 12 years and older or if fecal occult blood testing result is positive regardless of age without a documented or known etiology to explain the fecal positive results, ie, fissures, etc.).

Fecal occult blood testing

6.1.6.2 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Schedules of Evaluations and Procedures (Table 6-1 and Table 6-2). If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the Laboratory Manual and will be collected from subjects from both active treatment and standard of care groups who participate in this study.

6.1.6.3 Antibodies to Teduglutide

Blood samples will be drawn only from the active treatment groups for the analysis of positive/specific antibodies to teduglutide according to the Schedules of Evaluations and Procedures (Table 6-1 and Table 6-2).

6.1.7 Physical Examinations

Complete and comprehensive physical examinations will be performed by a medically qualified person during the study to assess the subject's physical status, according to the Schedules of Evaluations and Procedures (Table 6-1 and Table 6-2) (Table 6-3 and Table 6-4 for the standard of care cohort).

Any significant finding at baseline should be included in the subject's medical history eCRF, including known lab abnormalities such as decreased hemoglobin as part of anemia, history of elevated liver enzymes, etc. Any clinically significant changes from baseline (in the opinion of the investigator) noted during the physical examinations, whether or not these procedures are required by the protocol, should be recorded on the appropriate AE page of the eCRF. This will assist the sponsor/designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.1.8 Vital Signs and Body Weight

Vital signs will be measured according to the Schedules of Evaluations and Procedures (Table 6-1 and Table 6-2) (Table 6-3 and Table 6-4 for the standard of care cohort). Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (^{o}C/^{o}F). Body weight (kg), height (length [cm]), and head circumference (in cm for subjects ≤ 36 months of age) will also be recorded on the eCRF. Subjects should be weighed on the same scale at each study visit.

A weight Z-score will be calculated using the site-provided height and weight data collected at each site visit.

Any clinically significant changes (ie, worsening) in the opinion of the investigator noted in vital signs assessments (ie, those that are associated with the disease state and were present at baseline), should be recorded on the appropriate AE page of the eCRF. This will assist the

sponsor/designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.,

6.1.9 Electrocardiograms

Twelve-lead electrocardiograms will be performed according to the Schedules of Evaluations and Procedures (Table 6-1 and Table 6-2; Table 6-3 and Table 6-4 for the standard of care cohort). 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 eCRFs.

Any clinically significant changes (in the opinion of the investigator) noted during the ECG evaluations should be recorded on the appropriate AE page of the eCRF. This will assist the sponsor/designee in collecting additional information about that abnormality, including information regarding relationship to study drug or other causes, any action taken, and outcome.

6.1.10 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects in the active treatment group during the screening period, as needed. Follow-up testing will be performed as necessary according to the guidelines noted below. See Table 6-1 and Table 6-2 for details and scheduling.

6.1.10.1 Upper Gastrointestinal Series with Contrast

An upper GI with small bowel follow through (UGI/SBFT) will be performed following the ingestion of barium contrast material. Results from procedures performed within 6 months prior to Visit 1 will also be acceptable.

6.1.10.2 Abdominal Ultrasound

An abdominal ultrasound will be performed. Results from procedures performed within 6 months prior to Visit 1 will also be acceptable.

6.1.10.3 Fecal Occult Blood Testing

Fecal occult blood testing will be performed at screening and at the end of treatment. Subjects with positive results for fecal occult blood will undergo a confirmatory colonoscopy/sigmoidoscopy. If no known underlying documented etiology can be attributed to this finding, the results should be discussed with the NPS Medical Monitor.

- Subjects with negative scope results may enroll in the study
- Subjects with positive scope results who receive treatment may enroll in the study
- Subjects with positive scope results who do not receive treatment will be excluded from the study

- In those subjects with positive results for fecal occult blood at the end of the study, the investigator will have to determine the cause for the finding and may perform an additional colonoscopy/sigmoidoscopy, if clinically warranted.

6.1.10.4 Colonoscopy/Sigmoidoscopy

Subjects age 12 years and older will undergo a colonoscopy/sigmoidoscopy at screening. Children under the age of 12 years will also undergo the procedure if they had a positive result on the fecal occult blood testing (see above). Results from procedures performed within 1 year prior to Visit 1 will also be acceptable.

6.1.11 Concomitant Medication Assessment

The subject's usage of concomitant medication will be assessed at each clinic visit and the details of any medications and changes in medication or dosage of medications will be recorded on the eCRF.

6.1.12 Nutritional Support Usage

Consideration for advancement of oral/enteral feed and reductions to PN/IV volume will be based on clinical status which will include measures for weight, growth, and hydration status. The pharmacodynamic endpoints for this study include decreases in PN/IV volume reduction including a ≥ 20% or greater reduction up to 100% reduction (or complete weaning) in PN/IV support guided by clinical status. 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 and advance their oral/enteral feeds. A decrease of this magnitude may translate to several hours a day for more age-appropriate activities or an opportunity to introduce an extra oral/enteral feed to encourage oral rehabilitation. A guidance for nutrition support adjustment to be followed for this protocol is provided in Appendix 1.

Evaluation of each subject's nutritional support will be made during screening and at all visits at the study site. The following information will be collected and can be used to evaluate each subject's nutritional support:

- Daily PN/IV support volume and calories
- Daily enteral nutrition (EN) volume and calories (oral or tube feeds, including formula and specialized electrolyte solution)
- Other nutritional intake (regular diet and drink)
- 72-hour urine output prior to each phone and site visit
- 72-hour stool output collected by volume, stool count, or stool consistency (when available)

6.1.13 Diaries

Subjects or subjects' parent or guardian will be required to complete the following:

- Intake Diaries, completed daily, which will include:
    - PN/IV volume and calories (days per week, hours per day)
    - EN (formula and specialized electrolyte solutions) volume and calories (days per week, hours per day)
    - Other Nutrition (regular diet and drink) intake
- Urine/Stool Output Diary, completed for 3 days (72 hours) just prior to the upcoming scheduled visit or telephone contact, consisting of :
    - Collection of urine data:
        - For those who are toilet trained and NOT in diapers: urine volume
        - For those who are NOT toilet trained and in diapers: measure of urine volume/weight from urine-only diapers. Volume will be calculated based on the formula: 1g (scale weight) = 1 ml or 1 cc.
        - The subject/parent of subject will also be required to perform dipstick specific gravity tests on the first urine produced after the completion of the previous day's/or overnight PN/IV support at the end of each day during the 72-hour collection periods.
    - Collection of stool output data (including stool only and mixed urine/stool diapers):
        - For those who are toilet trained and NOT in diapers: a stool count will be attempted.
        - For those who are NOT toilet trained and in diapers: stool volume (including diapers that are stool only or mixed stool/urine). Stool volume will be calculated based on the formula: 1 g (scale weight = 1 ml or 1 cc
        - Ostomy output will only be used if no stool is passed via the rectum (applicable to those subjects without a colon). Ostomy output will be measured in cc or ml.
        - In addition all subjects (toilet trained or not) will report on the average consistency (form) of the stool passed each day during the 72-hour period. The subjects/parent of subject will use the Bristol Stool Form Scale (Lewis and Heaton, 1997) to make the assessment.

During the screening period, these diaries focusing on Intake and Output will be completed every day.

All diaries will be reviewed by the investigator or their designee at each visit or telephone contact to assess clinical status and opportunity for PN/IV changes and advance in feeds. At each visit, the diaries will be reviewed for completeness and accuracy of the data.

6.1.14 Female Subjects of Child-bearing Potential

Any female subject in an active treatment group who has reached menarche must have a negative urine pregnancy test to enroll or continue in the study. Pregnancy tests will be performed at screening and at all study visits. Female subjects in the standard of care group subjects 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 30 days after the treatment period (eg, true abstinence[1], 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.

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. Male subjects must be advised that their partners must use medically acceptable methods of birth control during and for 30 days after the treatment.

In the event a subject becomes pregnant during the study, study drug will be discontinued and a Pregnancy Form will be completed to capture potential drug exposure during pregnancy. The pregnancy will be reported within 24 hours of becoming aware of the condition. The subject will be followed until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous abortion (miscarriage), voluntary abortion, or therapeutic abortion). If a pregnant subject also experiences an SAE, the SAE form will be completed and submitted within 24 hours as discussed above.

In the event a female partner of a subject becomes pregnant within 30 days after the subject completes the trial and she or the fetus experiences an SAE, the SAE is deemed "suspected" to study drug by the principal investigator and a supplemental SAE form will be completed to capture the event.

[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).

Table 6-1 Schedule of Evaluations and Procedures – Screening to Week 12 – Active Treatment Groups

Procedures	Screen-ing	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit Type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**
Study Day	**≥-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
Visit Window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Informed Consent[a]	X													
Eligibility	X	X												
Demographics	X													
Medical history	X													
SBS history	X													
Review nutritional support usage[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutritional support adjustment (as needed)[c]			X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X		X		X		X		X		X
Upper GI with small bowel follow through[d]	X													
Abdominal ultrasound[d]	X													
Fecal occult blood testing[d,e]	X													X
Colonoscopy/ Sigmoidoscopy[d,e]	X													
Vital signs including body weight and head circumference[f]	X	X	X	X		X		X		X		X		X
Electrocardiogram	X													X
Safety laboratory tests	X	X	(X)[g]	(X)[g]	(X)[g]	X	(X)[g]	(X)[g]	(X)[g]	X	(X)[g]	(X)[g]	(X)[g]	X

Table 6-1 Schedule of Evaluations and Procedures – Screening to Week 12 – Active Treatment Groups

Procedures	**Screen-ing**	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit Type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**
Study Day	**≥-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
Visit Window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Pregnancy testing[h]	X	X	X	X		X		X		X		X		X
Citrulline[i]		X												X
Antibodies to teduglutide[j]		X												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense GI Symptoms History Worksheet	X													
Dispense Intake Diaries	X	X	X	X		X		X		X		X		X
Dispense Urine/Stool Output Diary	X	X	X	X		X		X		X		X		X
Review GI Symptoms History Worksheet		X												
Review Intake Diaries[k]		X	X	X	X	X	X	X	X	X	X	X	X	X
Review Urine/Stool Output Diary[l]		X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[m]		X												
Drug dispensing[n]		X	X	X		X		X		X		X		X

Table 6-1 Schedule of Evaluations and Procedures – Screening to Week 12 – Active Treatment Groups

Procedures	Screen-ing	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Visit Type	Site	Site	Site	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site
Study Day	≥-14	0	7	14	21	28	35	42	49	56	63	70	77	84
Visit Window (days)			± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2

eCRF = electronic case report form; EN = enteral feeds; GI = gastrointestinal; PN/IV = parenteral nutrition/intravenous fluid; SBS = Short Bowel Syndrome; SC = subcutaneous

[a] Informed Consent and, if applicable, informed assent must be obtained prior to performing any study-related procedure.

[b] Nutritional support includes PN/IV, EN feeds (formula and other specialized electrolyte solutions), and regular diet/drink.

[c] Nutritional support adjustments can be made after review of the subject's intake and output data recorded on the diaries and the subject's safety lab data following the guidance for nutrition support adjustment provided in Appendix 1.

[d] If it is necessary to perform the upper GI with small bowel follow-through, abdominal ultrasound, fecal occult blood testing, and/or colonoscopy/sigmoidoscopy, these tests can be performed at any time after signing of consent but must be completed and results available prior to the baseline visit. The results must be available and reviewed prior to the baseline visit.

[e] Colonoscopy/sigmoidoscopy will be conducted on subjects 12 years of age and older or subjects who have a positive fecal occult blood result without etiology to explain. Results of colonoscopies done within the prior year may also be used.

[f] Head circumference is to be collected as appropriate (ie, up to 36 months of age).

[g] Safety lab assessments to be done approximately 7 days following any PN/IV adjustment.

[h] Female subjects of child-bearing potential only

[i] Citrulline should be collected 2 to 4 hours post prandially, whenever possible.

[j] Antibody collection to be done prior to first study drug administration at study site.

[k] Intake Diaries will collect data on PN/IV support volume, EN feeds (formula and specialized electrolyte solutions), and regular diet/drink taken DAILY.

[l] Urine/Stool Output Diary will collect data on urine and stool output for the 72 hours prior to the next scheduled visit or telephone contact.

[m] Randomization and therapy assignment is to be completed prior to drug dispensing.

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

Table 6-2 Schedule of Evaluations and Procedures –Weeks 13 to 28 – Active Treatment Groups

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (or EOT)[j]	Week 28[j]
Visit Number:	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Visit Type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Site**
Study Day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**196**
Visit Window (days)	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**
Review nutritional support usage[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutritional support adjustment (as needed)[b]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination			X			X			X			X	X
Fecal occult blood testing												X[k]	
Colonoscopy/ Sigmoidoscopy												(X)[k]	
Vital signs including body weight and head circumference[c]			X			X			X			X	X
Electrocardiogram												X	X
Safety laboratory tests	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	X	X
Pregnancy testing[e]			X			X			X			X	X
Citrulline[f]												X	X
Antibodies to teduglutide												X[g]	X[g]
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Intake Diaries			X			X			X			X	

Table 6-2 Schedule of Evaluations and Procedures –Weeks 13 to 28 – Active Treatment Groups

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (or EOT)[j]	Week 28[j]
Visit Number:	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Visit Type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Site**
Study Day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**196**
Visit Window (days)	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**
Dispense Urine/Stool Output Diary			X			X			X			X	
Review Intake Diaries[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Urine/Stool Output Diary[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispensing			X			X			X				

EOT = end of treatment; EN = enteral feeds; PN/IV = parenteral nutrition/intravenous fluid; SBS = Short Bowel Syndrome

[a] Nutritional support includes PN/IV and , EN feeds (formula and other specialized electrolyte solutions), and regular diet/drink.

[b] Nutritional support adjustments can be made after review of the subject's intake and output data recorded on the diaries and the subject's safety lab data following the guidance for nutrition support adjustment provided in Appendix 1.

[c] Head circumference is to be collected as appropriate (ie, up to 36 months of age).

[d] Safety lab assessments to be done approximately 7 days following any PN/IV adjustment.

[e] Female subjects of child-bearing potential only

[f] Citrulline should be collected 2 to 4 hours post prandially, whenever possible.

[g] EOT antibody blood draw is to be taken prior to the last dose of study drug, at least 14 hours following the previous dose of study drug. Subjects who test positive/specific for antibodies to teduglutide at the Week 28 visit will have follow-up blood draws for positive/specific antibodies to teduglutide at approximately 3 months following the last dose of study drug. If antibodies are still positive/specific they will be collected again approximately 6 months after the last dose of study drug. Adverse events and PN/IV support will also be assessed at these visits.

[h] Intake Diaries will collect data on PN/IV support volume, EN (formula and specialized electrolyte solutions), and regular diet/drink taken DAILY.

[i] Urine/Stool Output Diary will collect data on urine and stool output for the 72 hours prior to the next scheduled visit or telephone contact.

[j] During the period between Visits 26 and 27 (Weeks 25, 26, and 27), the study staff will complete follow-up telephone contact(s) with the subject and parent/guardian/caretaker in order to monitor safety. If a visit to the site by the subject is necessary, this can be completed as an Unscheduled Visit.

[k] If fecal/occult blood is positive without explanation, then a colonoscopy/sigmoidoscopy may be warranted.

Table 6-3 Schedule of Evaluations and Procedures – Screening to Week 12 – Standard of Care Cohort

Procedures	**Screen-ing**	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit Type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**
Study Day	**≥-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
Visit Window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Informed Consent[a]	X													
Eligibility	X	X												
Demographics	X													
Medical history	X													
SBS history	X													
Review Nutritional support usage[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutritional support adjustment (as needed)[c]			X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X		X		X		X		X		X
Vital signs including body weight and head circumference[d]	X	X	X	X		X		X		X		X		X
Safety laboratory tests	X	X	(X)[e]	(X)[e]	(X)[e]	X		(X)[e]		X		(X)[e]		X
Citrulline[f]		X												X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense GI Symptoms History Worksheet	X													
Dispense Intake Diaries	X	X	X	X		X		X		X		X		X

Table 6-3 Schedule of Evaluations and Procedures – Screening to Week 12 – Standard of Care Cohort

Procedures	**Screen-ing**	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit Type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**
Study Day	**≥-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
Visit Window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Dispense Urine/Stool Output Diary	X	X	X	X		X		X		X		X		X
Review GI Symptoms History Worksheet		X												
Review Intake Diaries[g]		X	X	X	X	X	X	X	X	X	X	X	X	X
Review Urine/Stool Output Diary[h]		X	X	X		X		X		X		X		X

EN = enteral feeds; GI = gastrointestinal; PN/IV = parenteral nutrition/intravenous fluid; SBS = Short Bowel Syndrome; SC = subcutaneous

[a] Informed Consent and, if applicable, informed assent must be obtained prior to performing any study-related procedure.

[b] Nutritional support includes PN/IV and EN feeds (formula and other specialized electrolyte solutions), and regular diet/drink

[c] Nutritional support adjustments can be made after review of the subject's intake and output data recorded on the diaries and the subject's safety lab data following the guidance for nutrition support adjustment provided in Appendix 1.

[d] Head circumference is to be collected as appropriate (ie, up to 36 months of age).

[e] Safety lab assessments to be done approximately 7 days following any PN/IV adjustment.

[f] Citrulline should be collected 2 to 4 hours post prandially, whenever possible.

[g] Intake Diaries will collect data on PN/IV support volume, EN (formula and specialized electrolyte solutions), and regular diet/drink taken DAILY.

[h] Urine/Stool Output Diary will collect data on urine and stool output for the 72 hours prior to the next scheduled visit or telephone contact.

Table 6-4 Schedule of Evaluations and Procedures – Weeks 13 to 28 – Standard of Care Cohort

Procedures	**Week 13**	**Week 14**	**Week 15**	**Week 16**	**Week 17**	**Week 18**	**Week 19**	**Week 20**	**Week 21**	**Week 22**	**Week 23**	**Week 24 (or EOT)[h]**	**Week 28[h]**
Visit Number:	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Visit Type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Site**
Study Day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**196**
Visit Window (days)	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**
Nutritional support usage[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutritional support adjustment (as needed)[b]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination			X			X			X			X	X
Vital signs including body weight and head circumference[c]			X			X			X			X	X
Safety laboratory tests	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	X	X
Citrulline[e]												X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Intake Diaries			X			X			X			X	
Dispense Urine/Stool Output Diary			X			X			X			X	
Review Intake Diaries[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Urine/Stool Output Diary[h]			X			X			X			X	X

Table 6-4 Schedule of Evaluations and Procedures – Weeks 13 to 28 – Standard of Care Cohort

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (or EOT)[h]	Week 28[h]
Visit Number:	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Visit Type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Site**
Study Day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**196**
Visit Window (days)	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**

EOT = end of treatment; EN = enteral feeds; PN/IV = parenteral nutrition/intravenous fluid; SBS = Short Bowel Syndrome

[a] Nutritional support includes PN/IV and, EN feeds (formula and other specialized electrolyte solutions), and regular diet/drink.

[b] Nutritional support adjustments can be made after review of the subject's intake and output data recorded on the diaries and the subject's safety lab data following the guidance for nutrition support adjustment provided in Appendix 1.

[c] Head circumference is to be collected as appropriate (ie, up to 36 months of age).

[d] Safety lab assessments to be done approximately 7 days following any PN/IV adjustment.

[e] Citrulline should be collected 2 to 4 hours post prandially, whenever possible.

[f] Intake Diaries will collect data on PN/IV support volume, EN (formula and specialized electrolyte solutions), and regular diet/drink taken DAILY.

[g] Urine/Stool Output Diary will collect data on urine and stool output for the 72 hours prior to the next scheduled visit or telephone contact.

[h] During the period between Visits 26 and 27 (Weeks 25, 26, and 27), the study staff will complete follow-up telephone contact(s) with the subject and parent/guardian/caretaker in order to monitor safety. If a visit to the site by the subject is necessary, this can be completed as an Unscheduled Visit.

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent/assent signed), all subjects will be assigned an eight-digit subject number, including subjects in the standard of care cohort. The first four 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 the sponsor 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 for assimilation into the database. 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, regular diet/drink intake, urine output (as either collected or calculated volume), stool form, and urine specific gravity. The time of the dose should be captured in the appropriate area in the subject diary (ie, Daily [yes/no], Morning [yes/no], and option for other). The subject diaries will provide the source documentation for the diary data that is to be recorded in the eCRF by the study staff.

All data collected in this study will be entered into an appropriate pre-formatted database and submitted for statistical evaluation. The sites will be provided with eCRF 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 NPS or designee.

7.2 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/EU 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).

Due to the limited size of the study population descriptive statistics will be used with a goal of summarizing the sample which discourages the use of inferential statistics.

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 and baseline visit are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, sex, and race)
- Medical history
- SBS history, including remnant anatomy
- Vital signs, including oral temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), height/length, and length trends on growth charts
- Physical examination
- Prior medications (medications used within 14 days prior to screening), including drug name, dose, route, reason for use, and therapy dates. Medications used concomitantly will be recorded as concomitant medications.
- Electrocardiogram (12-lead) variables will include general findings of (normal/abnormal/abnormal, clinically significant). The cause of any clinically significant ECG will be specified.
- Laboratory test results: Serum chemistries, hematology, and urinalysis
- Citrulline levels
- Presence of antibodies to teduglutide and titer level, if present (active treatment groups only)
- Gastrointestinal imaging (upper GI with contrast, abdominal ultrasound, colonoscopy/sigmoidoscopy, fecal occult blood) (active treatment groups only)
- Pregnancy testing for children of child-bearing potential (active treatment groups only)
- Nutritional support (eg, PN/IV volume and calorie usage)
- Data entered in the nutritional diaries

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

Prior and concomitant medications will be coded using the current version of 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 group.

Medical history (including surgical history) will be coded using the current version of 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 treatment group.

8.2 Safety and Tolerability Variables

The safety and tolerability variables include:

- Adverse events, including GI symptoms
- Physical examination
- Vital signs, including oral temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), height/length, and length trends on growth charts
- Electrocardiograms
- Laboratory safety data, including electrolyte balance and glucose
- Antibodies to teduglutide
- Oral/enteral feeding tolerance
- Nutritional intake and urinary/fecal output (intake/output) (when available)
- GI-specific testing including imaging (eg, colonoscopy, sigmoidoscopy) abdominal ultrasound, fecal occult blood testing and upper GI series with small bowel follow-through

Adverse events will be coded using the current version of MedDRA. Treatment emergent AEs will be summarized by system organ class and preferred term for each treatment group. The number and percentage of subjects with AEs, SAEs, AEs that lead to discontinuation, study drug-related AEs (determined by the investigator), and AEs that lead to death will be summarized by treatment group. AEs will also be summarized by treatment group with regard to intensity and relationship to study drug. For AEs of special interest, the CTCAE grading system will be used as described in Section 6.1.4.

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

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 group.

8.3 Pharmacodynamic Variables

The following pharmacodynamic parameters will be measured:

- 20% to 100% parenteral support reduction at Week 24 (EOT)
- 100% reduction in PN/IV volume support (any subjects who are able to completely wean off PN/IV support) compared to baseline at EOS
- A decrease in parenteral support (calories and volume)

- An increase in enteral nutritional tolerance (calories and volume)
- Change from baseline in PN/IV support, citrulline, and enteral support at Week 24 (or EOT)
- Change from baseline in PN/IV support, citrulline, and enteral support at Week 28 (or EOS)
- Change from baseline in PN/IV support, citrulline, and enteral support at Week 24 (or EOT) compared to Week 28 (or EOS)
- Urine output (collected or calculated volume)
- Change in weight, height (length), and head circumference (where appropriate)
- Change in PN/IV support 3 and 6 months (as applicable) after EOT compared to baseline for those subjects who developed antibodies specific to teduglutide
- Change in hours per day or days per week of PN/IV support.
- Intensity of response (PN/IV reduction and advance in enteral support) at each visit
- Proportion of responders (ie, subjects who achieve at least a 20% reduction in parenteral support) at Weeks 4, 8, 12, 16, 20, and 24 weeks

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 treatment group.

8.4 Other Variables

Other variables will be analyzed by treatment group including:

- Subject disposition
- Duration of study drug exposure
- Subjects will be considered compliant if study drug was taken according to protocol and assigned treatment group for ≥ 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 group.
- 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 treatment group
- The study drug dose by duration will be summarized by treatment group.

8.5 Analysis Populations, Data Sets, and Time Points

8.5.1 Analysis Populations

The intent-to-treat (ITT) population is defined as any subjects who were randomized into the study. The safety population is defined as the subset of ITT with subjects who received at least one administration of study drug with any safety follow-up. The primary population analyzed for efficacy will be the ITT population. An additional per-protocol population analysis will also be performed as secondary/sensitivity analysis. Detailed per-protocol evaluable definitions will be documented in the SAP.

8.6 Statistical/Analytical Issues

8.6.1 Adjustments for Covariates

No Baseline stratification parameter is employed in this study.

8.6.2 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.

8.6.3 Interim Analyses and Data Monitoring

No interim analyses are planned.

An independent DSMB 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 DSMB members and the structure and scope of the DSMB meetings will be provided in a separate DSMB Charter.

8.6.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.6.5 Use of an Efficacy Subset of Subjects

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

8.6.6 Examination of Subgroups

Because a small number of subjects are expected at each study site, data from all study sites will be pooled.

8.7 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.

8.8 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 (WMA) 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 NPS SMT 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. 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: CONSIDERATIONS FOR MANAGEMENT OF NUTRITIONAL SUPPORT DURING THE STUDY

Please consider the following clinical parameters identified as markers for adequate management of pediatric short bowel syndrome. These parameters should also be considered for managing nutritional support (PN/IV and/or oral/enteral feeding) in terms of volume and calories during the treatment period.

- Considerations to adjust nutritional support in volume and calories will be made at all planned visits.
- Maintaining growth (including weight and length and head circumference [for children up to 36 months of age]) by the subjects trending along their growth chart and adjusting calories/volumes to maintain the trend.
- Other clinical evaluations
    - Normal serum electrolytes
    - Stable BUN/creatinine levels
    - Increase in the Volume Intake/Output ratio, including mixed output that can be collected
- General consideration to possible clinical deterioration in SBS
    - Ability to maintain weight and growth velocity
    - Diarrhea (> 50 mL/kg/day with ostomy or >80mg/kg/day without ostomy)
    - Colic/vomiting frequency increased
    - Electrolyte changes or imbalance
    - Skin breakdown (“butt rot”)
- 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 72-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 oral 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

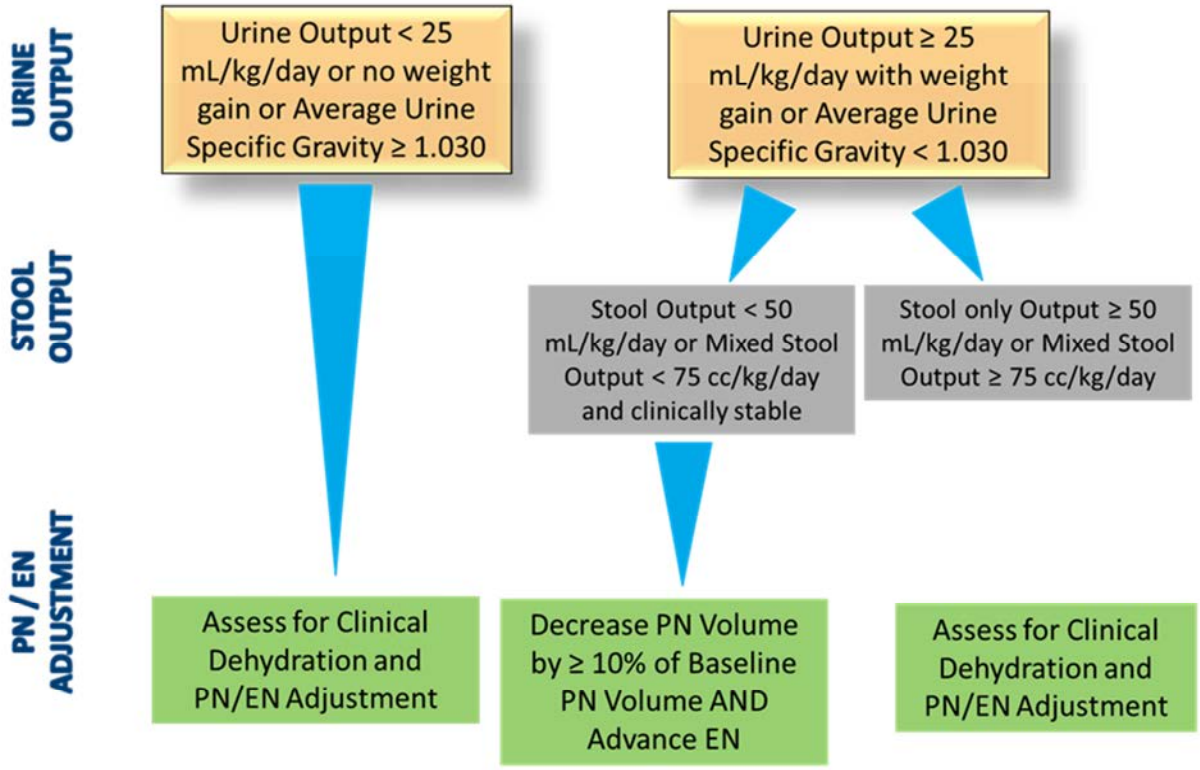

Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

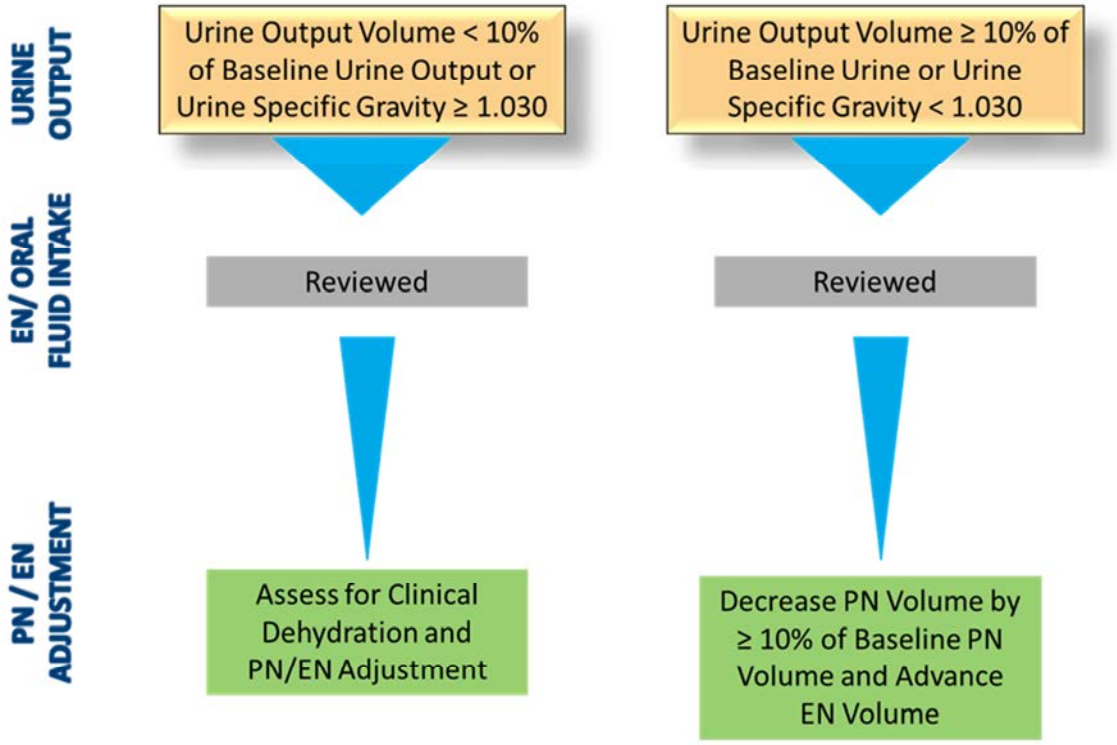

Figure A-3 Clinical Dehydration Assessment and PN/EN Adjustment