CLINICAL STUDY PROTOCOL

NCT Number: NCT02980666

Study Title: A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months Through 15 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support

Study Number: SHP633-302

Protocol Version and Date:

Original Protocol:	18 Dec 2015
Amendment 1:	27 Apr 2016
Amendment 2:	06 Jun 2017
Amendment 3:	24 Jan 2018
Amendment 4:	12 Jun 2018

Clinical Trial Protocol: SHP633-302

TITLE:	A 24-Week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects through 15 Years of Age with Short Bowel Syndrome who are Dependent on Parenteral Support
NUMBER:	SHP633-302
PHASE:	3
DRUG:	Teduglutide
IND:	058213
OTHER NO.:	NA
INDICATION:	Short bowel syndrome
SPONSOR:	Shire, Inc. 300 Shire Way Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Original Protocol: 18 Dec 2015

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD, PhD [redacted] [redacted], Clinical Medicine	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-302.

Title: A 24-Week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects through 15 Years of Age with Short Bowel Syndrome who are Dependent on Parenteral Support

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

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

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

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

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

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

_____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event, the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by fax or e-mail using the details below.

For protocol- or safety-related issues during normal business hours (Monday-Friday, 9:00 AM to 5:00 PM, EST), the investigator should contact the Shire Medical Monitor:

[redacted], MD, PhD
[redacted], Clinical Medicine
Phone: [redacted]
Email: [redacted]
Fax: [redacted]

For protocol- or safety-related issues outside of normal business hours, the investigator should contact:

[redacted], MD
Phone: [redacted]
Email: [redacted] or [redacted]
SAE Fax Number: [redacted] or [redacted] (Japan domestic line only)

In-country Clinical Caretaker:

[redacted], [redacted]:
Quintiles Transnational Japan K.K
Phone: [redacted]
Email: [redacted]
Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

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

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

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LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-t}	AUC from zero to the last measurable concentration
AUC_{0-inf}	AUC of zero to infinity
AUC_{ss}	AUC at steady state
C_{max}	maximum plasma concentration
$C_{max,ss}$	C_{max} at steady state
$C_{min, ss}$	minimum plasma concentration at steady state
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EC	ethics committee
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-2	glucagon-like peptide 2
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PK	pharmacokinetic
PN	parenteral nutrition
PN/IV	parenteral nutrition/intravenous fluid
SAE	serious adverse event

SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2\lambda z}$	terminal-phase half-life
t_{max}	time to C_{max}
ULN	upper limit of normal

STUDY SYNOPSIS

Protocol number: SHP633-302 **Drug:** Teduglutide

Study Title:

A 24-Week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects through 15 Years of Age, with Short Bowel Syndrome who are Dependent on Parenteral Support

Number of subjects:

Planned enrollment is approximately 5 subjects.

Sites and Regions: Approximately 5 investigational sites in Japan are planned.

Study Duration:

There will be, at a minimum, a 2-week screening period followed by 24 weeks of treatment. The final site visit will be scheduled at Week 28, 4 weeks after the end of treatment (EOT) visit (Week 24).

Investigational Product, Dose, and Mode of Administration:

During the treatment period, daily doses of 0.05 mg/kg/day of teduglutide will be administered subcutaneously (SC) to the subjects. The dose calculation will be based on body weight measured at the baseline visit (Visit 2) and adjusted, as needed, based on body weight measured at Week 12 (Visit 14). No other adjustments to dose will be made during the study period, unless discussed with the sponsor's medical monitor.

Objective(s):

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in pediatric subjects (through 15 years of age) with short bowel syndrome (SBS) who are dependent on parenteral support.

Study Design:

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. All subjects will be screened for a minimum of 2 weeks prior to start of treatment (SOT) 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 (Weeks 1 and 2), and then every other week through Week 12 (Weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at Weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. A final visit will be scheduled at Week 28, 4 weeks following EOT. Weekly telephone contact will be made during the interim weeks from EOT to end of study (EOS) to monitor safety and any changes in nutritional support.

To maintain consistency across all centers, the nutritional support adjustment guidelines (developed with SBS expert input and to be provided in the protocol) must be followed for decisions regarding parenteral nutrition/intravenous fluid (PN/IV) support reduction and

advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability.

Study Inclusion and Exclusion Criteria:

Male and female children and adolescents through 15 years of age who satisfy the following inclusion and exclusion criteria will be enrolled in the study.

Inclusion Criteria

1. Informed consent by a parent or legally-authorized representative or emancipated minor prior to any study-related procedures
2. When applicable, an informed assent (as deemed appropriate by the Institutional Review Board) by the subject 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
5. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
6. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks after the treatment period.

Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility disorders; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
7. Major gastrointestinal surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤ 10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) 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-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who 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 major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at the screening and baseline 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 results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2
22. Parent(s)/legally-authorized representative(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 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	• Active IBD which requires chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months • IBD that requires chronic systemic immunosuppressant therapy for symptom control • Tufting or autoimmune enteropathy or microvillus inclusion disease • Untreated pre-malignant or malignant change in the GI tract identified by upper GI series, biopsy or polypectomy • Known polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome) • Intestinal or other major surgery scheduled within the time frame of the study • Chronic active pancreatitis • Cholecystitis
Immune	• 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)

Pharmacokinetic Variables:

Blood samples for drug concentrations will be collected pre-dose, at 1 and 6 hours post-dose at start of treatment and at pre-dose, 2 and 4 hours post-dose at Week 4. If blood samples are not/cannot be collected at Week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product.

The following PK parameters will be derived using population PK analysis approach:

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

Pharmacodynamic/Efficacy Assessments:

The primary PD parameter is PN/IV volume reduction of at least 20% at 24 weeks (or EOT) compared to baseline.

Analysis of additional PD endpoints will include:

- 100% reduction in PN/IV support (any subjects who are able to completely wean off PN/IV support) compared to baseline at EOT
- Change from baseline (absolute and percent change) in PN/IV support (volume and calories), plasma citrulline, and enteral nutritional support (volume and calories) over time
- Change from Week 24 (or EOT) (absolute and percent change) in PN/IV support (volume and calories), plasma citrulline, and enteral nutritional support (volume and calories) at Week 28 (or EOS)
- Change in body weight, height (or length), and head circumference (up to 36 months of age). Derived variables will include height Z-score, weight Z-score, body mass index (BMI), and BMI Z-score
- Fecal output (by volume or number of bowel movements per day)
- Change in hours per day and days per week of PN/IV support
- Proportion of responders (ie, subjects who achieve at least a 20% reduction in PN/IV volume) over time

Safety Assessments:

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 temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), height or length, and trends on growth charts
- Electrocardiograms
- Laboratory safety data, including clinical chemistries, hematology, and urinalysis
- Changes in urine output (collected or calculated volume)
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide. Samples for antibody analysis will be drawn at baseline and at the EOT (Week 24 or early termination visit) prior to the administration of teduglutide and at least 14 hours after the previous dose. One additional sample will be collected at the final visit 4 weeks after EOT (EOS, Week 28). If subjects are determined to have positive/specific antibodies at Week 28 or EOS, they will be asked to return for a follow-up site visit 3 months post EOT for another antibody sample. If the subjects continue to have positive/specific antibodies at 3 months post EOT, they will be asked to return for a follow-up site visit 6 months post-treatment in order to determine their antibody status.
- GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through

Safety and tolerability will be evaluated by a Data Monitoring Committee during the study period.

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.

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

Continuous variables 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.

Efficacy/pharmacodynamics data including reduction in PN/IV support, increase in enteral nutritional support, change in fecal output, change in plasma citrulline, weight Z-score, height Z-score, BMI Z-score, hours per day and 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 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. 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.

Date of Original Protocol: 18 December 2015

Date of Most Recent Protocol Amendment (if applicable): Not applicable

STUDY SCHEDULES

Table 1 Study Schedule of Events – Screening to Week 12

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/assent[a]	X													
Eligibility	X	X												
Demographics	X													
Medical history	X													
SBS history	X													
Dispense drug[b]		X	X	X		X		X		X		X		X
Dispense GI symptoms history worksheet	X													
Review GI symptoms history worksheet		X												
Upper GI with small bowel follow-through[c]	X													
Abdominal ultrasound[c]	X													
Fecal occult blood testing[d]	X													X
Colonoscopy/ sigmoidoscopy[d]	X													
Plasma citrulline[e]		X												X
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X
Review intake and		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Study Schedule of Events – Screening to Week 12

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**
output diaries[f, g]														
Review nutritional support usage[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutritional support adjustment (as needed)[i]			X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[j]	X	X	X	X		X		X		X		X		X
Physical examination and vital signs including weight	X	X	X	X		X		X		X		X		X
Height (length) and head circumference[k]	X	X				X				X				X
Electrocardiogram	X													X
Safety laboratory tests[l]	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Antibodies to teduglutide[m]		X												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic sampling		X[n]				X[o]								
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Study Schedule of Events – Screening to Week 12

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 nutrition; 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] 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. The dose of study medication will be re-evaluated at Week 12, based on weight gain/loss.

[c] If they have not been performed within 6 months of the baseline visit, upper GI with small bowel follow through and abdominal ultrasound can be performed on all subjects at any time after signing of consent/assent but must be completed and results available and reviewed prior to the baseline visit.

[d] Fecal occult blood test will be performed on all subjects after signing of consent/assent. Colonoscopy/sigmoidoscopy will be conducted on all subjects 12 years of age and older and any 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.

[e] Plasma citrulline should be collected 2 to 4 hours postprandially, whenever possible.

[f] Intake diaries will collect data on PN/IV support volume, EN, and other food and fluid intake daily throughout the study.

[g] Output diaries will collect data on urine and stool output for the 48 hours prior to the next scheduled visit or telephone contact.

[h] Nutritional support includes PN/IV, EN, and other food and fluid intake daily throughout the study.

[i] 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 and Appendix 2.

[j] Female subjects of childbearing potential

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

[l] At site visits, safety lab assessments consist of serum chemistry, hematology and urinalysis. Safety lab assessments done between site visits approximately 7 days following any PN/IV adjustment consist of serum chemistry and urinalysis. Safety labs performed during site visits must be processed via central lab. Safety labs performed at alternate times in between site visits may be done locally and processed for submission to the central lab.

[m] Antibody collection is to be done prior to first investigational product administration at study site.

[n] Baseline (Visit 2) samples for PK analysis will be drawn predose and 1 and 6 hours postdose.

[o] Week 4 (Visit 6) samples for PK analysis will be drawn predose and 2 and 4 hours postdose.

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET)[k]	Weeks 25, 26, 27[l]	Week 28 (or EOS)
Visit Number:	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit Type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study Day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175, 182, 189**	**196**
Visit Window (days)	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**
Dispense drug			X			X			X					
Fecal occult blood testing[a]												X		
Colonoscopy/ sigmoidoscopy[a]												(X)		
Plasma citrulline[b]												X		X
Dispense intake and output diaries			X			X			X			X		
Review intake and output diaries and nutritional support usage [c d, e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutritional support adjustment (as needed)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy testing[g]			X			X			X			X		X
Physical examination and vital signs, including weight			X			X			X			X		X
Height (length) and head circumference[h]			X			X			X			X		X
Electrocardiogram												X		X
Safety laboratory tests[i]	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	X

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET)[k]	Weeks 25, 26, 27[l]	Week 28 (or EOS)
Visit Number:	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit Type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study Day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175, 182, 189**	**196**
Visit Window (days)	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**
Antibodies to teduglutide[j]												X		X
Adverse events	X	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	X

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; PN/IV=parenteral nutrition/intravenous fluid

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

[b] Plasma citrulline should be collected 2 to 4 hours postprandially, whenever possible.

[c] Intake diaries will collect data on PN/IV support volume, EN, and other food and fluid intake daily throughout the study.

[d] Output diaries will collect data on urine and stool output for the 48 hours prior to the next scheduled visit or telephone contact.

[e] Nutritional support includes PN/IV, EN feeds, and other food and fluid intake daily throughout the study. .

[f] 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 Considerations for Management of Nutritional Support During the Study and appendix 2 Weaning Algorithms.

[g] Female subjects of childbearing potential

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

[i] At site visits, safety lab assessments consist of serum chemistry, hematology and urinalysis. Safety lab assessments done between site visits approximately 7 days following any PN/IV adjustment consist of serum chemistry and urinalysis. Safety labs performed during site visits must be processed via central lab. Safety labs performed at alternate times in between site visits may be done locally and processed for submission to the central lab.

[j] Antibody blood draw is to be taken prior to the last dose of investigational product, at least 14 hours following the previous dose of investigational product. 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 investigational product. If antibodies are still positive/specific they will be collected again approximately 6 months after the last dose of investigational product.

[k] If a subject terminates from the study prematurely, all EOT procedures should be done at the time of termination and a follow-up visit should be scheduled 4 weeks later.

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET)[k]	Weeks 25, 26, 27[l]	Week 28 (or EOS)
Visit Number:	15	16	17	18	19	20	21	22	23	24	25	26	27-29	30
Visit Type	Phone	Phone	Site	Phone	Phone	Site	Phone	Phone	Site	Phone	Phone	Site	Phone	Site
Study Day	91	98	105	112	119	126	133	140	147	154	161	168	175, 182, 189	196
Visit Window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4

[l] A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an Unscheduled Visit.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal disease that results in major surgical resections of the small intestine. In children, most cases of short bowel syndrome begin in infancy. Common causes of SBS in children include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis (Duro et al, 2008; Squires et al, 2012). Similar to adults, new-onset SBS in older children usually stems from the Crohn's disease, trauma, and cancer. The diminished absorptive capacity for fluids and nutrients often results in dependence on parenteral nutrition or intravenous fluids (PN/IV) to maintain energy and fluid and electrolyte homeostasis.

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

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

For this reason, research in the pediatric arena is focused on children with PN/IV-dependent SBS. Given intestinal adaption in younger children, the unmet medical need is the greatest in children who are 1 year of age and older. It is highly unlikely that children with less than 10% of the expected length of small intestine reach enteral independence. These subjects reach a plateau in their ability to advance oral/enteral feeds or decrease PN/IV support (ie, are "stuck") and are not expected to achieve spontaneous adaptation. Subjects who have not progressed to full enteral adaptation by 12 months after their intestinal insults are very unlikely to demonstrate spontaneous improvement in their enteral function (Sigalet et al, 2011).

1.2 Product Background and Clinical Information

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption. Chief among these is hormones glucagon-like peptide 2 (GLP-2), which is secreted from L-type

enteroendocrine cells in the distal ileum and colon. Resection of these regions impairs the adaptive response by limiting endogenous production of GLP-2.

There are no approved pharmacological therapies that promote intestinal adaptation in children with SBS. In the US and Europe, a GLP-2 analog called teduglutide is approved for the treatment of SBS in adult patients who are dependent on PN/IV support.

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 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a t1/2 of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Thymann et al, 2014; Tappenden et al, 2013).

Clinical Studies

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

Results from the extension study supported the clinical benefits of the 0.05 mg/kg/day dose, teduglutide treatment in the initial Phase 3 study, which included significant reductions in PN/IV. Seventy-five percent of the subjects who previously responded to teduglutide treatment in Study CL0600-004 maintained this response or experienced further improved benefit from teduglutide treatment. More than 60% of the subjects previously receiving placebo in Study CL0600-004 achieved a clinical response after switching to teduglutide treatment for 6 months. 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 Intention-to-Treat (ITT) (p=0.002) and Per Protocol ($p < 0.001$) populations. Generally, the incidence of treatment-emergent AEs (TEAEs) was distributed similarly across all treatment groups. The TEAEs with a higher incidence in the teduglutide group were mainly of GI origin. A long-term, open-label extension study (CL0600-021) assessed safety and efficacy for up to 24 additional months (ie, up to 30 months of exposure for subjects who received teduglutide in Study CL0600-020). Overall, 30 of 43 subjects who received teduglutide in Study CL0600-020 and entered Study CL0600-021 completed a total of 30 months of treatment with teduglutide. Of these, 28 subjects (93%) achieved a 20% or greater reduction of parenteral support resulting in a PN/IV volume reduction of 7.55 L/week, corresponding to a mean reduction of 65.6% relative to baseline prior to exposure to teduglutide at the beginning of Study CL0600-021. PN/IV use was reduced by at least 1 day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 3.11 L/week from baseline at the start of Study CL0600-021 (a 28% reduction). Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. Of the 12 subjects entering Study CL0600-021 directly, 6 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 4.0 L/week (a 39.4% reduction from baseline at the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of parenteral support.

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

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

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

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Clinical Study

Teduglutide was designated as an orphan drug indicated for SBS in Japan on 20 November 2014. Based on national surveys, it is estimated that the number of subjects with SBS who are dependent on parenteral nutrition/intravenous fluid (PN/IV) is less than 1000 in Japan. Among the 195 SBS subjects in the 2011 survey, 99 (51%) developed SBS at <1 years old (Takagi and Okada, 1993; Shirotani et al, 1996). Early intervention could potentially improve intestinal adaptation and decrease the need for parenteral support in these patients.

The current study proposes to investigate the safe and appropriate use of teduglutide in the Japanese pediatric population for the purpose of providing pharmacokinetic, pharmacodynamic, and safety data. This protocol was developed similarly to the planned EU/US study, TED-C14-006, 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*. The TED-C14-006 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 teduglutide dose of 0.05 mg/kg daily is supported by results from the completed 12 week pediatric study. The aim of teduglutide treatment is to increase absorptive capacity in order to yield decreases in parenteral support. In addition, the experts anticipated that there would be several direct benefits from decreased parenteral support and advances in enteral feeds, 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.

2.2 Objective(s)

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in pediatric subjects (through 15 years of age) with short bowel syndrome (SBS) who are dependent on parenteral support. Refer to Section 9.8 and Section 9.10.1 for further details of the endpoints being measured.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. All subjects will be screened for a minimum of 2 weeks prior to start of treatment (SOT) 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 (Weeks 1 and 2), and then every other week through Week 12 (Weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at Weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. A final visit will be scheduled at Week 28, 4 weeks following EOT. Weekly telephone contact will be made during the interim weeks from EOT to end of study (EOS) to monitor safety and any changes in nutritional support. The Study Schedules are displayed at the beginning of this protocol.

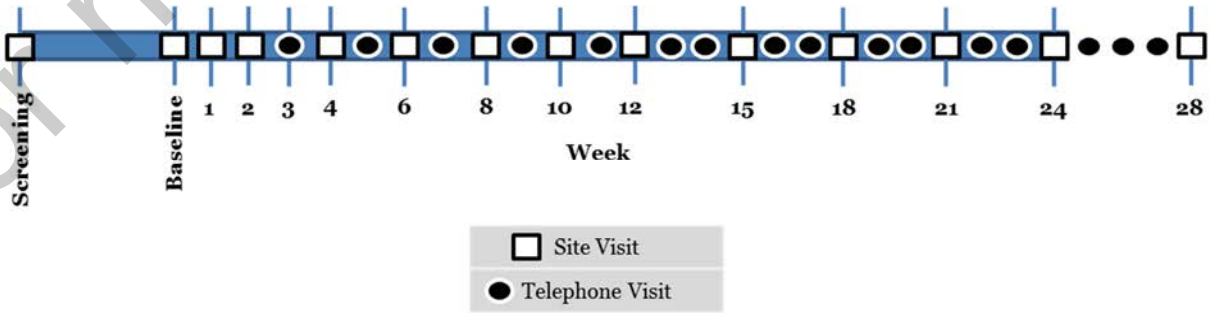
To maintain consistency across all centers, the nutritional support adjustment guidelines (developed with SBS expert input and provided in Appendix 1 and Appendix 2) must be followed for decisions regarding parenteral nutrition/intravenous fluid (PN/IV) support reduction and advances in enteral feeds 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 continue 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.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) periodically during the active study period, based on subject enrollment.

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

Figure 1 Study Diagram



3.2 Study Duration

There will be, at a minimum, a 2-week screening period followed by 24 weeks of treatment. Attempts should be made to limit the screening period to 4 weeks. The final site visit will be scheduled at Week 28, 4 weeks after the EOT visit (Week 24).

The start of the clinical phase is defined as first subject consented. The end of the clinical phase is defined as the last visit of the last subject.

3.3 Sites and Regions

This study will be conducted at approximately 5 investigational sites in Japan.

4 STUDY POPULATION

Approximately 5 male and female children and adolescents, through 15 years of age will be enrolled.

4.1 Inclusion Criteria

1. Informed consent by a parent or legally-authorized representative or emancipated minor prior to any study-related procedures
2. When applicable, an informed assent (as deemed appropriate by the Institutional Review Board) by the subject 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
5. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
6. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks after the treatment period.

4.2 Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility disorders; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper GI series done within 6 months prior to screening
7. Major gastrointestinal surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, or endoscopic procedure is allowed)

8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) 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 GLP-2
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who 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 major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at the screening and baseline 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 results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2
22. Parent(s)/legally-authorized representative(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 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	• Active IBD which requires chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months • IBD that requires chronic systemic immunosuppressant therapy for symptom control • Tufting or autoimmune enteropathy or microvillus inclusion disease • Untreated pre-malignant or malignant change in the GI tract identified by upper GI series, biopsy or polypectomy • Known polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome) • Intestinal or other major surgery scheduled within the time frame of the study • Chronic active pancreatitis • Cholecystitis
Immune	• 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)

4.3 Reproductive Potential

Sexually active females of childbearing potential must be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable

contraceptives throughout the study period and for 4 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 4 weeks following the last dose of investigational product.

Female children and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of childbearing potential with a negative urine and/or serum β-HCG pregnancy test at the Screening Visit (Visit 1) and prior to enrollment. Females of childbearing potential must agree to abstain from sexual activity (ie, true abstinence[1]) that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the Screening Visit (Visit 1), plus condoms. Note: If subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.4 Discontinuation of Subjects

4.4.1 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified without prejudice to further treatment. However, a discussion should be held by the investigator and the Shire Medical Monitor prior to the patient discontinuing/withdrawing.

4.4.2 Reasons for Discontinuation

Reasons for discontinuation may include but are not limited to:

- Adverse event
- Death
- Failure to meet enrollment criteria

[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).

- Lost to follow-up
- Non-compliance with investigational product
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problems
- Withdrawal by parent/legally-authorized representative
- Withdrawal by subject

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 adverse event (AE) and, if so, the AE must be reported in accordance with the procedures described in Section 8.1. 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.

To the extent possible, all examinations scheduled for the EOT evaluation must be performed on all subjects who participate, even if they do not complete the study according to the protocol. Any subject who discontinues treatment prematurely will be asked to return 4 weeks later for the EOS visit and will be contacted weekly for wellness checks during the interim period between EOT and EOS.

4.4.3 Subjects "Lost to follow-up" Prior to Last Scheduled Visit

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

5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including non-prescription herbal treatments, vitamins, etc.) received within 14 days prior to the Screening Visit (Visit 1) and through the end of study (ie, including the protocol-defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Treatment

Prior treatment includes all treatment received within 14 days of the first dose of investigational product, but discontinued before the first dose of investigational product.

5.2 Concomitant Treatment

Concomitant medications are those that continue after the start of investigational product or are newly introduced after the start of treatment through the end of study. In all instances the start date of prior and concomitant therapies must be recorded to the extent possible.

5.3 Prohibited Treatment

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, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

The following prior therapies are excluded within the timeframes noted (refer to Section 4.2).

Prior Therapy	**Time Restriction Prior to Screening**
Native/synthetic glucagon-like peptide-2	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Experimental antibody treatment	3 months
Biological therapy (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

Teduglutide for subcutaneous (SC) injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL with sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the Investigator's Brochure.

6.1.1 Blinding of the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

Daily doses of 0.05 mg/kg/day of teduglutide will be administered to the subjects for 24 weeks. The dose calculation will be based on body weight measured at the baseline visit (Visit 2) and adjusted, as needed, based on body weight measured at Week 12 (Visit 14). No other adjustments to dose will be made during the study period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or either thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma will not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day, preferably in the morning. If a dose is delayed, that day's dose should be administered as soon as possible, but consecutive doses should be separated by at least 12 hours.

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 investigational product can be found in the Instructions for Use. Each day, the injection site should be changed.

6.2.1 Allocation of Subjects to Treatment

This is an open-label study; all subjects will receive teduglutide 0.05 mg/kg/day as described in Section 6.2. Subject numbers are assigned to all subjects as consent/assent to take part in the study is provided. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. These numbers will be used to identify the subjects throughout the study period. Once a number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling and Packaging

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Investigational product will be supplied in kits containing 7 vials and labeled with appropriate study information. Space will be provided on the label 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 investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2 to 8°C (35.6 to 46.4°F) until dispensed to a subject. Once dispensed to a subject, the investigational product can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25°C, or 35.6 to 77°F). Parent/legally-authorized representative will be instructed to keep the subject's investigational product and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the investigational product may be refrigerated.

6.4 Drug Accountability

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

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

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

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

enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

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

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

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

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

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

6.5 Treatment Compliance

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

The investigator is responsible for contacting the sponsor or designee prior to interrupting the subject's daily investigational product dosing regimen for reasons such as hospitalization and adverse events, a lapse in investigational product delivery, etc.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered. Subjects falling outside of these parameters will not be included in the per-protocol efficacy analyses (refer to Section 9.6).

7 STUDY PROCEDURES

7.1 Study Schedule

Subject evaluations will be performed during the indicated days and weeks of the study as provided in the Study Schedules.

All data collected are to be recorded on the appropriate electronic case report form (eCRF).

Details for study procedures including sample collection are described in the Operations Manual for this study.

7.1.1 Screening

All subjects will be screened for a minimum of 2 weeks. Attempts should be made to limit the screening period to 4 weeks. All subjects' parents/guardians must sign an informed consent and, if applicable, subjects must sign an informed assent form prior to initiation of any study-related procedure.

Subjects will be designated as a screen failure if they fail to meet all inclusion criteria and/or meet any of the exclusion criteria. Screen failures will not be administered investigation product.

At the discretion of the investigator, subjects who fail screening may be re-screened one time with prior sponsor approval. In the event of re-screening, a new subject number will be assigned.

7.1.2 Treatment Period

Subjects who pass all screening evaluations will be enrolled in the study and will receive the first dose of investigational product at the baseline visit (Visit 2). Subjects will enter a 24-week treatment period consisting of either visits or scheduled weekly telephone contacts as outlined in Section 3.1.

7.1.3 Follow-up Period

The follow-up period for this protocol is 4 weeks. At the end of this period (Week 28, EOS) there will be a follow-up visit to query for serious adverse events (SAEs), adverse events (AEs), and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8.1). As described in Section 3.1, weekly telephone visits will be conducted on the interim weeks between EOT and EOS.

7.2 Study Evaluations and Procedures

7.2.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent (and, when applicable, informed assent) must be obtained from the subject's parent(s) or legally authorized representative(s) and from the subject (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject, the subject's parent(s), or the subject's legally authorized representative by the investigator or designee in accordance with the guidelines described in Section 10.3.1. Documentation and filing of informed consent documents should be completed according to Section 10.2.

7.2.2 Study Entrance Criteria

At screening, each subject will be reviewed for eligibility against the study entrance criteria by the investigator or designee. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.2.3 Confirmation of Study Eligibility

Subject eligibility according to the study inclusion and exclusion criteria will be confirmed at baseline by the investigator or designee on the basis of review of the study entrance criteria.

7.2.4 Demographics and Other Baseline Characteristics

Demographic and/or other baseline variables obtained at the screening and/or baseline visits 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 (including surgical history) and SBS history (including remnant anatomy) will be collected at the screening visit.
- SBS history, including remnant anatomy
- Vital signs including temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), and height or length, and trends on growth chants
- Physical examination
- Prior medications (medications used within 14 days prior to screening and discontinued prior to the first dose of investigational product), including drug name, dose, route, reason for use, and therapy dates. Medications used during the treatment period (after the first dose of investigational product) will be recorded as concomitant medications.
- Electrocardiogram (12-lead) variables include general findings (normal/abnormal/abnormal, clinically significant). The cause of any clinically significant electrocardiogram (ECG) will be specified.
- Laboratory test results: Serum chemistries, hematology, and urinalysis
- Plasma citrulline levels
- Presence of antibodies to teduglutide and titer level, if present

- Gastrointestinal imaging (upper GI with small bowel follow through [UGI/SBFT], abdominal ultrasound, colonoscopy/sigmoidoscopy, fecal occult blood)
- Pregnancy testing for females of childbearing potential
- Nutritional support (eg, PN/IV and EN volume and calorie usage)
- Data entered in the nutritional diaries

7.2.5 Pharmacokinetic Assessments

Blood samples for drug concentrations will be collected at baseline (prior to first teduglutide dose) and at Week 4. Pharmacokinetic assessments are listed in Section 9.10.1. A schedule of PK sample collection is provided in below in Table 3. Instructions for sample collection and handling are included in the laboratory manual.

Table 3 Blood Sample Collection Schedule for Pharmacokinetic Testing

Study Week	**Baseline**			**Week 4**		
Visit Number	2			6		
Hour	0[a]	1	6	0[a]	2	4

[a] Prior to investigational product administration

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

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose (at the Week 4 draw).
- 1-hour postdose draw: ±5 minutes
- 2-hour postdose draw: ±5 minutes
- 4-hour postdose draw: ±5 minutes
- 6-hour postdose draw: ±5 minutes

The date and time of administration of the investigational product must be documented on the PK Blood Sampling eCRF.

7.2.6 Pharmacodynamic/Efficacy Assessments

Assessment of PD/efficacy parameters will be based on PN/IV volume, enteral nutritional support, fecal output, plasma citrulline, and changes in body weight, height (or length) and head circumference (up to 36 months of age). Pharmacodynamic endpoints are listed in Section 9.8.

7.2.7 Safety Assessments

7.2.7.1 Physical Examination

Physical examinations will be performed by the principal investigator or designee. 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.

7.2.7.2 Vital Signs

Vital signs will be measured according to the Study Schedules. Measurements will include temperature, heart rate, blood pressure, and body weight. Subjects should be weighed on the same scale at each study visit. Height (or length [cm]) and head circumference (in cm for subjects ≤36 months of age) will be measured at selected visits.

7.2.7.3 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing according to the Study Schedules. Subjects should be in a seated or supine position during blood collection.

Laboratory collections that are required at intervals that do not coincide with site visits (ie, for safety lab assessments done following PN/IV adjustments) may be obtained locally or at the investigational site.

Clinical laboratory tests will include the following (refer to Table 4):

Table 4 List of Laboratory Tests

Hematology: - Hematocrit - Hemoglobin - Platelet count - Red blood cell count - White blood cell count with differential - RBC morphology, if needed Urinalysis: Blood Glucose Leucocytes Microscopic analysis Specific gravity pH and osmolality Protein Sodium Urine Pregnancy tests (females of childbearing potential)	Serum Chemistry: - Albumin - Alkaline phosphatase - Alanine aminotransferase - Amylase - Aspartate aminotransferase Bicarbonate Bilirubin (total and indirect) Blood urea nitrogen Calcium (total) Chloride Cholesterol Citrulline (plasma) C-reactive protein - Creatinine Estimated Glomerular Filtration Rate (Schwartz formula) - Gamma-glutamyl transferase - Glucose - Lipase - Magnesium - Phosphorus - Potassium - Sodium - Triglycerides - Uric acid

7.2.7.4 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Study Schedules. Plasma citrulline should be collected 2 to 4 hours postprandially, whenever possible. Blood samples for citrulline may be drawn from a central line or peripheral access. The samples will be processed according to instructions in the Laboratory Manual.

7.2.7.5 Antibody Assessments

Samples for antibody analysis will be drawn at baseline and at the EOT (Week 24 or early termination) visits prior to the administration of teduglutide and at least 14 hours after the previous dose. One additional sample will be collected at the final visit 4 weeks after the EOT (EOS, Week 28). If subjects are determined to have positive/specific antibodies at Week 28 or EOS, they will be asked to return for a follow-up site 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 a follow-up visit 6 months post-treatment in order to determine their antibody status.

Blood samples for antibodies may be drawn from a central line or peripheral access.

7.2.7.6 Pregnancy Testing

Any female subject in the study of childbearing potential must have a negative urine pregnancy test to enroll or continue in the study. Pregnancy tests will be performed at screening and at all site visits.

7.2.7.7 Volume of Blood

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

The amount of blood to be drawn may vary according to instructions provided by the manufacturer or laboratory for an individual assessment. When more than one blood assessment is to be done at the same time point, the assessments should be combined if they require the same type of tube.

7.2.7.8 Electrocardiogram

Twelve-lead ECGs will be performed in accordance with the clinical site's standard practice(s) as indicated in the Study Schedules. Electrocardiogram recordings will be read locally by an experienced physician. Results (normal, abnormal not clinically significant, and abnormal clinically significant with a description of the abnormality) will be recorded on the eCRF.

7.2.8 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during or prior to the screening period, as indicated below. Follow-up testing will be performed as necessary according to the guidelines noted below and the Study Schedules.

7.2.8.1 Upper Gastrointestinal Series with Contrast

An 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.

7.2.8.2 Abdominal Ultrasound

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

7.2.8.3 Fecal Occult Blood Testing

Fecal occult blood testing will be performed at screening, Week 12, and at the end of treatment. Subjects with positive results for fecal occult blood for whom a cause is not readily identified (eg, anal fissure) 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 sponsor's Medical Monitor.

- Subjects with negative endoscopy findings may enroll in the study
- Subjects with positive endoscopy findings who receive definitive treatment may enroll in the study
- Subjects with positive endoscopy findings who do not receive definitive 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.

7.2.8.4 Colonoscopy/Sigmoidoscopy

Subjects age 12 years and older will undergo a colonoscopy/sigmoidoscopy at screening. Children under the age of 12 years may 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 for the screening measurement.

7.2.9 Other Study Procedures

7.2.9.1 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, linear growth, hydration status, and safety laboratory results. The pharmacodynamic endpoints for this study include a ≥20% or greater reduction in PN/IV support guided by clinical status. A 20% decrease in PN/IV volume over 24 weeks is considered clinically meaningful to PN/IV-dependent children who have plateaued in their ability to wean PN/IV and advance their 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 feed to encourage oral rehabilitation. Guidance for nutrition support adjustment to be followed for this protocol is provided in Appendix 1 and Appendix 2.

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

- Daily PN/IV support volume, calories, and infusion duration as prescribed and as recorded by the subject/parent or legally-authorized representative

- Daily enteral nutrition (EN) volume and calories (as prescribed and as recorded by the subject/parent or legally-authorized representative)
- Other nutritional intake (regular diet and drink)
- 48-hour urine output and urine specific gravity prior to each phone and site visit
- 48-hour stool output (by volume or daily stool count) and stool consistency, prior to each phone and site visit
- Clinical chemistry and urinalysis
- Weight trajectory (measured at site visits)

7.2.9.2 Diaries

Subjects or subjects' parent or legally-authorized representative 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 (to be converted into calories by site personnel)
- Urine/stool output diary, completed every day during the screening period and for 2 days (48 hours) just prior to every scheduled visit and telephone contact, consisting of:
  - Collection of urine data:
    - For those who are toilet trained and NOT IN DIAPERS: All urine output should be measured and recorded in mL. The subject or parent/legally-authorized representative will perform dipstick specific gravity tests on the first urine produced after the daily infusions of PN/IV support.
    - For those who are not toilet trained and IN DIAPERS: The weight of all urine-only diapers will be recorded. Volume will be calculated based on the formula: 1g (scale weight)=1 mL or 1 cc. At the discretion of the investigator, the parent/legally-authorized representative may be asked to collect the first void after the daily infusion of PN/IV support to measure the specific gravity.
  - Collection of stool output data (including stool only and mixed urine/stool diapers):
    - For those who are toilet trained and NOT IN DIAPERS: Daily stool count will be recorded.
    - For those who are not toilet trained and IN DIAPERS: The weight of all diapers that contain stool (including diapers that contain mixed stool and urine) will be recorded as stool output. Stool volume will be calculated based on the formula: 1 g (scale weight=1 mL or 1 cc).

- All ostomy output will be recorded as stool output and measured in cc or mL.
- In addition all subjects (toilet trained or not) will record the consistency (form) of the stool passed each day during the 48-hour period prior to each visit. The subjects/parent or legally-authorized representative of subject will use the Bristol Stool Form Scale (Lewis and Heaton, 1997) to make the assessment.

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.

8 ADVERSE AND SERIOUS ADVERSE EVENT ASSESSMENTS

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

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

All AEs are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

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

8.1.1 Severity Categorization

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

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

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

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

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

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy

data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent/assent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

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

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

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed

Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol.)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 0.05 mg/kg/day of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

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

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Pharmacovigilance and Risk Management Department and the Shire Medical Monitor or designee within 24 hours of the first awareness of the event. Note: The 24-hour reporting

requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (refer to Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global Pharmacovigilance and Risk Management Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2 and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the Shire Medical Monitor or designee within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

The sponsor and/or designee are responsible for notifying the relevant regulatory authorities/ central institutional review boards (IRBs)/ethics committees (ECs) of related, unexpected SAEs. In addition the sponsor and/or designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the teduglutide program.

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

8.3 Adverse Events of Special Interest

Teduglutide administration for an individual subject may need to be stopped if the subject has an adverse event of special interest (refer to risks in table below) that is severe in intensity (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 investigational product 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.

Investigators and the DMC should be guided by the descriptions of Grade 3 and 4 events, as they relate to identified risks associated with the administration of teduglutide (refer to Table 5).

Table 5 CTCAE Criteria for Teduglutide Adverse Events of Special Interest

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

Table 5 CTCAE Criteria for Teduglutide Adverse Events of Special Interest

Identified Risk	Grade 3 Description	Grade 4 Description
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0 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

The DMC may recommend stopping the study if:

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

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

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

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

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Shire Global Pharmacovigilance and Risk Management database.

9.3 Statistical Analysis Process

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

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 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.

All statistical analyses will be performed using SAS®.

9.4 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis or adaptive design.

9.4.1 Data Monitoring Committee

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

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

Safety and tolerability results will be evaluated by a DMC periodically during the active study period (date of the first subject's first dose to date of the last subject's last dose), based on subject enrollment. The DMC review will include all cumulative safety data (ie, adverse events, laboratory assessments, physical examinations, etc.) from study assessment through each cutoff period.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility of this orphan population in children in Japan, rather than power calculation.

9.6 Study Population

The ITT population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least 1 administration of investigational product 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. The per-protocol population is defined as the subset of subjects in the ITT population without a major protocol deviation. Details will be prospectively defined in the final SAP prior to database lock.

9.7 Demographics and Baseline Characteristics

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

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

Medical history (including surgical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

9.8 Efficacy/Pharmacodynamic Endpoints

The primary PD parameter is PN/IV volume reduction of at least 20% at 24 weeks (or EOT) compared to baseline.

Analysis of additional PD endpoints will include:

- 100% reduction in PN/IV support (any subjects who are able to completely wean off PN/IV support) compared to baseline at EOT
- Change from baseline (absolute and percent change) in PN/IV support (volume and calories), plasma citrulline, and enteral nutritional support (volume and calories) over time
- Change from Week 24 (or EOT) (absolute and percent change) in PN/IV support (volume and calories), plasma citrulline, and enteral nutritional support (volume and calories) at Week 28 (or EOS)
- Change in body weight, height (or length), and head circumference (up to 36 months of age). Derived variables will include height Z-score, weight Z-score, body mass index (BMI), and BMI Z-score
- Fecal output (by volume or number of bowel movements per day)
- Change in hours per day and days per week of PN/IV support
- Proportion of responders (ie, subjects who achieve at least a 20% reduction in PN/IV volume) over time

No formal statistical test will be performed due the limited sample size.

Continuous variables 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.

9.9 Safety Analyses

The safety and tolerability variables include:

- 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 temperature, heart rate, blood pressure, body weight, head circumference (up to 36 months of age), height or length, and trends on growth charts
- Electrocardiograms
- Laboratory safety data, including clinical chemistry, hematology, and urinalysis
- Change in urine output (collected or calculated volume) and urine specific gravity
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, UGI/SBFT

Adverse events will be coded using MedDRA. Treatment-emergent AEs will be summarized by system organ class and preferred term. The number and percentage of subjects with AEs, SAEs, AEs that lead to discontinuation, investigational product-related AEs (determined by the investigator), and AEs that lead to death will be summarized. AEs will also be summarized with regard to intensity and relationship to investigational product. For AEs of special interest, the CTCAE grading system will be used as described in Section 8.3.

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.

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

9.10 Other Analyses

9.10.1 Pharmacokinetic Analyses

The following pharmacokinetic parameters will be derived using population PK analysis approach:

- Area under the plasma concentration-time curve (AUC) of zero to infinity ($_{0–inf}$)

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

Descriptive statistics (mean, median, standard deviation, minimum and maximum values, geometric mean, the number and percentage of subjects in specified categories) will be calculated to summarize the absolute values and change from baseline at each scheduled visit.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Public Posting of Study Information

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

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

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all

observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded solely onto the eCRF.

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

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

Original source data to be reviewed during this study will include, but are not limited to subject's medical file, subject diaries, and original clinical laboratory reports, and imaging reports. All key data must be recorded in the subject's medical records.

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

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

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the Pharmaceuticals and Medical Devices Agency) or an auditor.

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

10.2.3.3 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable, from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable

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

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

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

10.3.2 Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent/assent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation. Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

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

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

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

10.4 Privacy and Confidentiality

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

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

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

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

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

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

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

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

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

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

APPENDIX 2 WEANING ALGORITHMS

Figure A-1 Weaning Algorithm for Subjects Who Are NOT TOILET-TRAINED and in Diapers

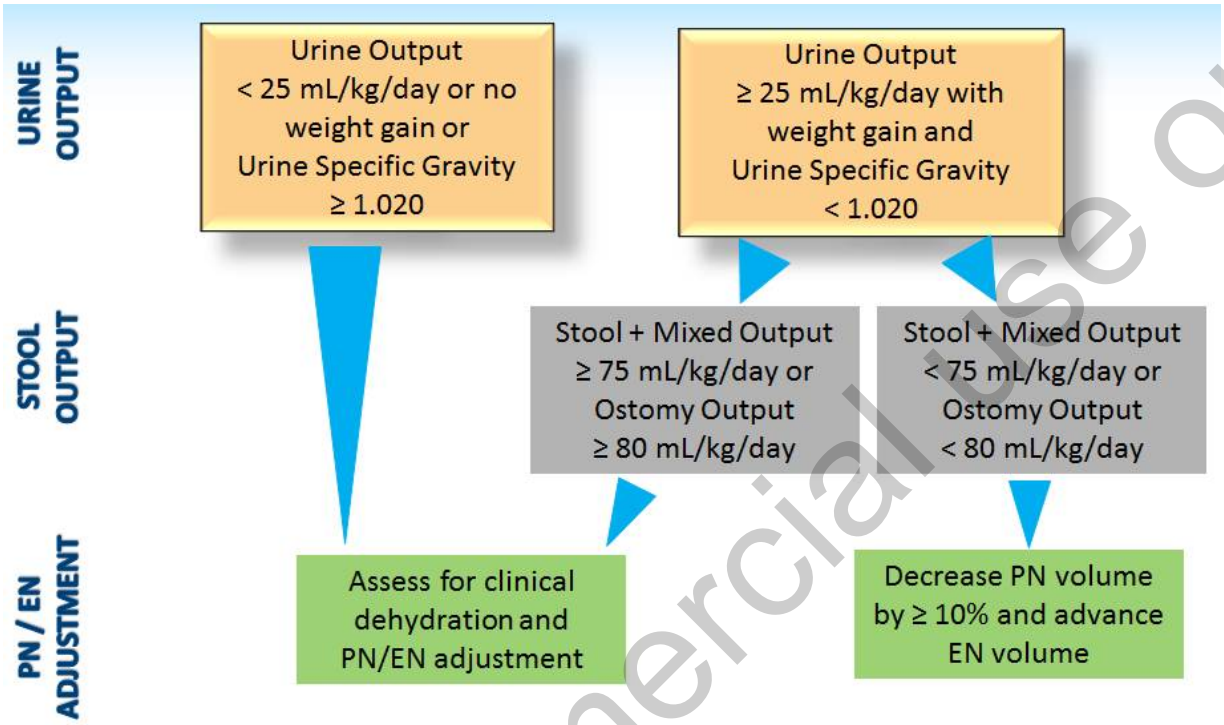


Figure A-2 Subjects Who ARE TOILET-TRAINED and Not in Diapers

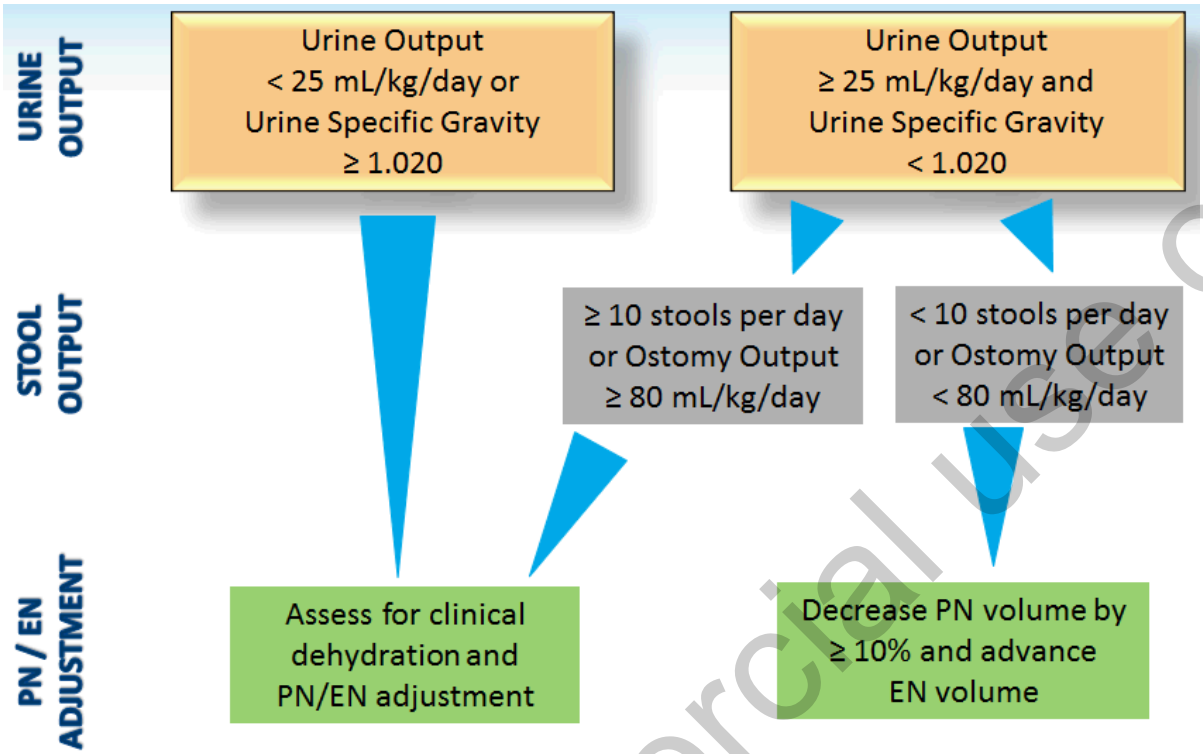
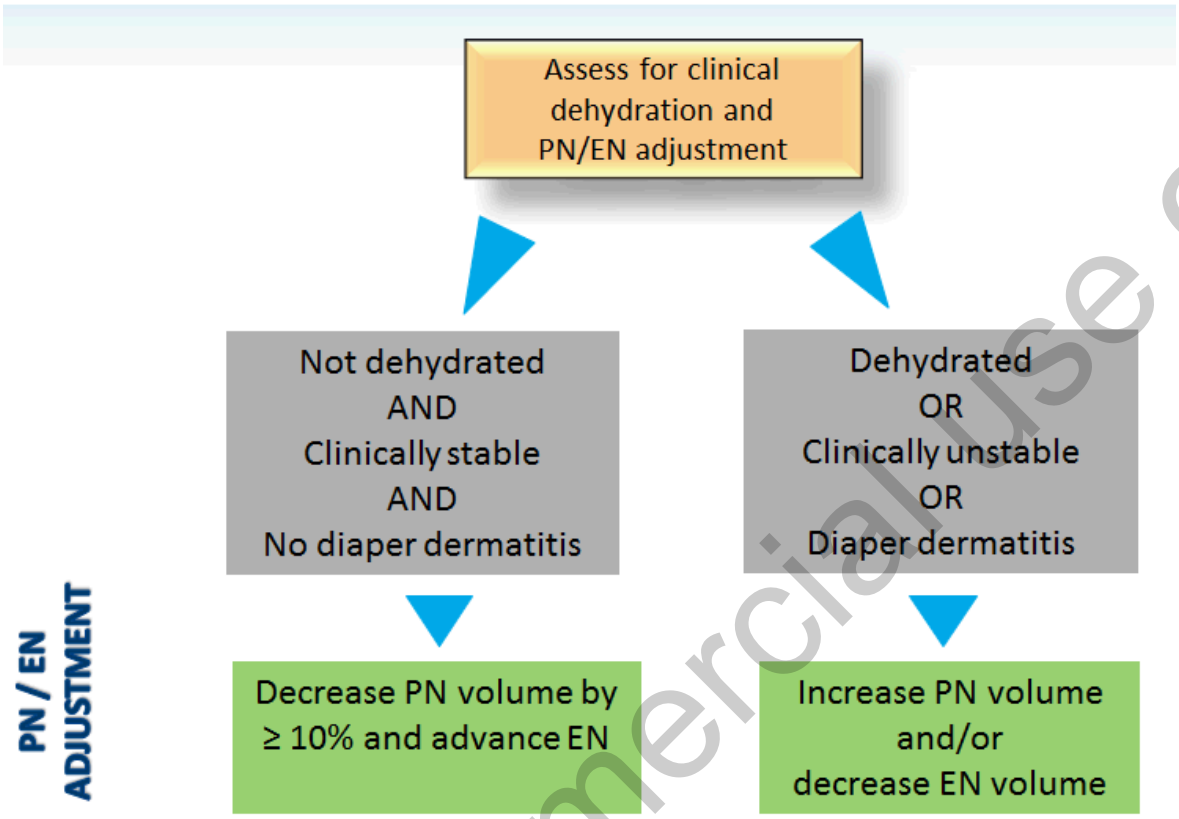


Figure A-3 Clinical Dehydration Assessment and PN/EN Adjustment



Clinical Trial Protocol: SHP633-302

TITLE:	A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support
NUMBER:	SHP633-302
PHASE:	3
DRUG:	Teduglutide
IND:	058213
OTHER NO.:	NA
INDICATION:	Short bowel syndrome
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Amendment 1: 27 Apr 2016 Original Protocol: 18 Dec 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD, PhD [redacted] [redacted], Clinical Medicine	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-302.

Title: A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

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

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

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

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

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

Investigator Name and Address:

(please hand print or type) _____

_____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Age range for subjects has been specified. Subjects will be 1 year through 15 years of age.		Title page Protocol signature page Synopsis Sections 4 and 4.1
Emergency contact information has been updated.		Emergency Contact Information Sections 8.1.6, 8.2.2, 8.2.4
Clarification that departing from the nutritional support adjustment guidelines and weaning algorithms in Appendix 2 and Appendix 3, respectively, will not constitute a protocol deviation.		Synopsis Section 3.1
Statement added that subjects who complete the study may participate in a long-term extension study in which eligible subjects could receive teduglutide.		Synopsis Section 3.1
Inclusion and Exclusion criteria have been refined and clarified; there were no criteria added with the exception of the age of subject population which has been added as an inclusion criterion (was previously in introductory sentence).		Synopsis Sections 4.1 and 4.2
Exclusion Criterion #11 has been updated to indicate that a subject would be excluded from the study if the subject had participated in a clinical study of experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.		Synopsis Section 4.2
Efficacy/PD endpoints have been lumped together and clarified. The small population does not warrant primary versus secondary endpoints. The statistical method has been clarified.		Synopsis Section 9.8
Safety assessments and statistical methods have been clarified.		Synopsis Section 9.9
Study schedule of events tables have been revised to reflect the changes to the protocol and for clarity.		Table 1 Table 2
Any phone contacts may be replaced with unscheduled site visits if necessary.		Table 1 Table 2 Section 3.1
Requirement added that female subjects of child-bearing potential undergo a serum-based pregnancy test at screening.		Table 1 Table 2 Sections 4.3, 7.2.8, 7.2.11
Definition of prior and concomitant medications has been expanded to include invasive and diagnostic procedures.		Table 1 Table 2 Section 5
Additional information on selection of teduglutide dosing regimen and duration in the study has been inserted.		Section 2.1
Frequency of Data Monitoring Committee meetings has been specified.		Sections 3.1 and 9.4.1
Definition of screening period has been clarified.		Section 3.2

Inflammatory bowel disease that requires chronic systemic immunosuppressant therapy for symptom control has been removed from the list of excluded disease and illness in Exclusion Criterion #24.	Section 4.2 (Table 3)
Definition of acceptable methods of contraception has been revised to reflect available methods in Japan.	Section 4.3
List of prohibited prior therapy has been revised to remove experimental antibody treatment, as it is now included in the revised exclusion criterion #11.	Section 5.3
Requirement that teduglutide should be administered in the morning has been removed.	Section 6.2
Language on labeling, packaging, and drug accountability has been clarified.	Sections 6.3 and 6.4
Reviewing subject diaries has been included in the subject compliance with dosing check. Clarification that attempts should be made by the investigator to contact the sponsor or designee prior to dose interruption has been added.	Section 6.5
Requirement has been added that subjects who are re-screened must be re-consented.	Section 7.1.1
Timeframe for a subject to be considered enrolled in the study has been clarified.	Sections 7.1.2 and 9.6
Demographics and other baseline characteristics have been clarified.	Section 7.2.4
Windows for PK blood collection have been extended; possibility to collect week 4 timepoint at any future visit if needed has been added.	Section 7.2.5
PT/INR testing has been added at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected thereafter.	Table 1 Table 2 Section 7.2.8
For children in diapers, urine specimen collection should be attempted as part of the safety lab assessments, but lack of urinalysis will not constitute a protocol deviation.	Table 1 Table 2 Section 7.2.8
Timeframe of follow-up for subjects with blood samples testing positive for anti-teduglutide antibodies at week 28 or EOS has been clarified.	Synopsis Table 1 Table 2 Section 7.2.10
Need for a subject with a positive fecal occult blood testing at week 12 without a readily identifiable cause by physical examination to undergo a colonoscopy or sigmoidoscopy is now open to discussion with the Shire medical monitor or designee.	Table 1 Table 2 Section 7.2.14.3
Need for children younger than 12 years to undergo a colonoscopy or sigmoidoscopy if they test positive for fecal occult blood at screening and the cause is not identified by physical examination has been specified.	Section 7.2.14.4
GI symptoms history worksheet has been renamed GI-specific symptoms history diary, and details on recording and reviewing symptoms have been added.	Table 1 Table 2 Section 7.2.15.1
"Other nutrition (regular diet and drink)" has been removed from the Intake diary.	Section 7.2.15.2
Output diary data collection will continue to occur over a 48-hour period of PN/IV and EN stability before every site visit. Between site visits, the output diary collection will only be required within 1 week of	Table 1 Table 2 Section 7.2.15.3

implementing a change in the PN/IV prescription.	
Severity categorization has been updated to specify that the severity of AEs listed in Table 6 that may lead to dose interruption based on known risks of teduglutide will also be evaluated using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria.	Section 8.1.1
Definition of an overdose to teduglutide has been revised.	Section 8.1.7
Adverse events of special interest have been redefined and procedures for reporting them have been added.	Section 8.3
More information has been provided on criteria for dose interruption of individual subjects. Dose discontinuation has been made absolute for an AE known to be a risk associated with teduglutide administration (Table 6) that is of NCI CTCAE severity ≥Grade 3 and considered to be related to investigational product; cases of severe hypersensitivity that are determined to be related to investigational product; DILI that is related to investigational product; and pregnancy. SAEs related to investigational product are potential but not absolute reasons for dose discontinuation.	Sections 8.4, 8.4.1, and 8.4.2
Criteria for DILI have been added.	Section 8.4.2
Criteria for early termination of the study have been clarified.	Section 8.5
Clarification that original diary data should be entered into the eCRF and take precedence over data collected over the phone.	Section 9.1
Definition of PK analysis population has been added.	Section 9.6
Pharmacokinetic analyses methods and parameters have been clarified.	Synopsis Section 9.10.1
Protocol history has been added in Appendix 1.	Appendix 1
Guidelines for nutritional support management during the study have been clarified.	Appendix 2

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

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

Pharmacovigilance SAE Reporting:

FAX: [redacted] or [redacted] (Japan domestic line only)
or
Email: [redacted]

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

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

For protocol- or safety-related issues between 8:00 to 20:00 US Eastern Standard Time, the investigator may contact the Shire medical monitor:

[redacted], MD, PhD
[redacted], Clinical Medicine
Office Phone: [redacted]
Mobile Phone: [redacted]
Email: [redacted]
Fax: [redacted]

In-country Clinical Caretaker:

[redacted], [redacted]:
Quintiles Transnational Japan K.K
Phone: [redacted]
Email: [redacted]
Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

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

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-inf}	AUC of zero to infinity
AUC_{0-t}	AUC from zero to the last measurable concentration
AUC_{ss}	AUC at steady state
BMI	body mass index
C_{max}	maximum plasma concentration
$C_{max,ss}$	C_{max} at steady state
$C_{min, ss}$	minimum plasma concentration at steady state
CL/F	apparent clearance
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EC	ethics committee
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	US Food and Drug Administration

GCP	Good Clinical Practice
GI	gastrointestinal
GLP-2	glucagon-like peptide 2
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NCI	National Cancer Institute
PD	pharmacodynamic
PK	pharmacokinetic
PN	parenteral nutrition
PN/EN	parenteral nutrition/ intravenous fluids and enteral nutrition
PN/IV	parenteral nutrition/intravenous fluids
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2}$	terminal-phase half-life
t_{max}	time to C_{max}
UGI/SBFT	upper GI series with small bowel follow-through
ULN	upper limit of normal
US	United States
$V_{\lambda z}/F$	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP633-302 **Drug:** Teduglutide

Study Title:

A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

Number of subjects:

Planned enrollment is approximately 5 subjects.

Sites and Regions: Approximately 5 investigational sites in Japan are planned.

Study Duration:

There will be, at a minimum, a 2-week screening period followed by 24 weeks of treatment. The end of study (EOS) visit will be scheduled at week 28, 4 weeks after the end of treatment (EOT) visit (week 24).

Investigational Product, Dose, and Mode of Administration:

During the treatment period, a dose of 0.05 mg/kg/day of teduglutide will be administered once daily subcutaneously (SC) to the subjects. The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with Shire medical monitor or designee.

Objective(s):

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in pediatric subjects (1 year through 15 years of age) with short bowel syndrome (SBS) who are dependent on parenteral support.

Study Design:

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide.

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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The EOS visit will be scheduled at week 28, 4 weeks following EOT. Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and to be provided in the protocol) for decisions regarding parenteral nutrition/intravenous fluids (PN/IV) support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

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 continue 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.

Safety and tolerability results will be evaluated by a Data Monitoring Committee periodically during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible

subjects could receive teduglutide.

Study Inclusion and Exclusion Criteria:

Subjects who satisfy the following inclusion and exclusion criteria will be enrolled in the study.

Inclusion Criteria

1. Informed consent by a parent or legally-authorized representative prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product

Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤ 10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic glucagon-like peptide-2 (GLP-2)
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening

15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

    For subjects with Gilbert's disease:
    d. Indirect (unconjugated) bilirubin ≥2x ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2
22. Parent(s)/legally-authorized representative(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Pharmacokinetic Variables:

Blood samples for drug concentrations will be collected at the baseline visit (predose, at 1 and 6 hours postdose) and at week 4 visit (predose, 2 and 4 hours postdose). If blood samples are not/cannot be collected at week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product.

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

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

Efficacy/Pharmacodynamic Assessments:

The efficacy/PD endpoints include:

- Change (absolute and percent change) from baseline in PN/IV support (volume and calories), citrulline, and enteral nutritional support (volume and calories), separately, at each visit

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

Safety Assessments:
Safety and tolerability will be assessed by evaluating the following:

- Adverse events, including those pertaining to GI symptoms.
- Physical examinations, including body weight, height (or length), head circumference (up to 36 months of age), and trends on growth charts
- Vital signs, including temperature, heart rate, blood pressure
- Electrocardiograms (ECGs)
- Laboratory safety data (ie, biochemistry, hematology, coagulation, urinalysis)
- Urine output
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through

Safety and tolerability will be evaluated by a Data Monitoring Committee during the study period.

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.

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

Continuous variables 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.

Efficacy/PD data will include change in PN/IV support, enteral nutritional support, plasma citrulline, and hours per day and days per week of PN/IV support, and will be summarized by visit.

Safety data will include clinical laboratory tests results; measurement of body weight, height (or length), and head circumferences (if applicable); vital signs; concomitant medications; and ECG monitoring; and will be summarized by visit. Adverse events will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Date of Original Protocol: 18 Dec 2015

Date of Most Recent Protocol Amendment (if applicable): 27 Apr 2016

STUDY SCHEDULES

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	**≥-14**	**0**	**7 ±2**	**14 ±2**	**21 ±3**	**28 ±3**	**35 ±3**	**42 ±3**	**49 ±3**	**56 ±3**	**63 ±3**	**70 ±3**	**77 ±3**	**84 ±3**
Informed consent/assent[a]	X													
Eligibility	X	X												
Demographics	X													
Medical /surgical history	X													
Electrocardiogram	X													X
SBS history	X													
Upper GI with small bowel follow-through and abdominal ultrasound[b]	X													
Fecal occult blood testing[c]	X													X
Colonoscopy/ sigmoidoscopy[c]	(X)													(X)
Provide GI-specific symptoms history diary	X													
Review GI-specific symptoms history diary		X												
Dispense investigational product[d]		X	X	X		X		X		X		X		X
Pharmacokinetic sampling		X[e]				X[f]								
Safety laboratory tests[g]	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Pregnancy testing[h]	X	X	X	X		X		X		X		X		X

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	**≥-14**	**0**	**7 ±2**	**14 ±2**	**21 ±3**	**28 ±3**	**35 ±3**	**42 ±3**	**49 ±3**	**56 ±3**	**63 ±3**	**70 ±3**	**77 ±3**	**84 ±3**
Plasma citrulline[i]		X												X
Antibodies to teduglutide[j]		X												
Provide intake and output diaries	X	X	X	X		X		X		X		X		X
Review diaries and nutritional support[k]		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[l]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Physical examination/ vital signs/weight	X	X	X	X		X		X		X		X		X
Height (or length) and head circumference[m]	X	X				X				X				X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.

(X)=as needed; eCRF=electronic case report form; EN=enteral nutrition; GI=gastrointestinal; PK=pharmacokinetic; PT/INR=prothrombin time/international normalized ratio; PN/IV=parenteral nutrition/intravenous fluids; SBS=short bowel syndrome; SC=subcutaneous; UGI/SBFT= upper GI series with small bowel follow through

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

[b] If the subject has undergone an UGI/SBFT and/or an abdominal ultrasound within the 6 months before visit 1 (screening), then those test results will be acceptable for the screening assessments. If the subject has not had these procedures within the 6 months before visit 1 (screening), then the procedure(s) will be performed any time after providing informed consent with the results available and reviewed before the baseline visit (day 0).

[c] All subjects enrolled will have a fecal occult blood test after providing consent/assent. Subjects with positive fecal occult blood test at screening for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy. Colonoscopy or sigmoidoscopy will be conducted at screening on all subjects 12 years of age and older; however if the screening fecal occult blood test is negative and the subject has undergone the procedure within 1 year before visit 1 (screening), then that result will be acceptable for the screening assessment (Section 7.2.14.4). Subjects with positive fecal occult blood test results at week 12 for which a cause is not identified by a physical exam will be discussed with the Shire medical monitor or designee (Section 7.2.14.3).

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	≥-14	0	7 ±2	14 ±2	21 ±3	28 ±3	35 ±3	42 ±3	49 ±3	56 ±3	63 ±3	70 ±3	77 ±3	84 ±3

[d] 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) must be specified and recorded in the eCRF. The dose of study medication may be adjusted at week 12.

[e] Baseline (visit 2) samples for PK analysis will be drawn predose, and 1 and 6 hours postdose (Section 7.2.5).

[f] Week 4 (visit 6) samples for PK analysis will be drawn predose, and 2 and 4 hours postdose (Section 7.2.5).

[g] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately 5-7 days following any adjustment to the PN/IV prescription. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[h] All female subjects of child-bearing potential will be tested for pregnancy: serum testing at screening; urine testing thereafter.

[i] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9).

[j] Blood sample for antibody testing is to be collected at study site prior to first investigational product administration. Blood samples may be drawn from a central line or peripheral access (Section 7.2.10).

[k] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[l] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[m] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET) a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Dispense investigational product			X			X			X					
Provide intake and output diaries			X			X			X			X		
Review diaries and nutritional support[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[c]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety laboratory tests[d]	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	X
Pregnancy testing[e]			X			X			X			X		X
Plasma citrulline[f]												X		X
Antibodies to teduglutide[g]												X		X
Physical examination/ vital signs/weight			X			X			X			X		X
Height (or length) and head circumference[h]			X			X			X			X		X
Fecal occult blood testing[i]												X		
Colonoscopy/ sigmoidoscopy[i]												(X)		
Electrocardiogram												X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET) a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Concomitant medication/ procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.

(X)=as needed; EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; PN/IV=parenteral nutrition/intravenous fluid

[a] If a subject terminates from the study prematurely, all EOT procedures should be done at the time of termination and a follow-up visit should be scheduled 4 weeks later.

[b] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[c] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[d] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately 5-7 days following any adjustment to the PN/IV prescription. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[e] All female subjects of child-bearing potential will be tested for pregnancy (urine testing).

[f] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9).

[g] Blood draw to test for antibodies to teduglutide before the last dose of teduglutide, at least 14 hours after the previous dose of teduglutide. If a blood sample is positive for antibodies at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

[h] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

[i] Subjects with positive fecal occult blood test at week 24 (EOT)/ET for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a confirmatory colonoscopy or sigmoidoscopy (Section 7.2.14.3).

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal disease that results in major surgical resections of the small intestine. In children, most cases of short bowel syndrome begin in infancy. Common causes of SBS in children include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis. (Duro et al. 2008; Squires et al. 2012) Similar to adults, new-onset SBS in older children usually stems from Crohn's disease, trauma, and cancer. The diminished absorptive capacity for fluids and nutrients often results in dependence on parenteral nutrition or intravenous fluids (PN/IV) to maintain energy and fluid and electrolyte homeostasis.

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

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

For this reason, research in the pediatric arena is focused on children with PN/IV-dependent SBS. Given intestinal adaption in younger children, the unmet medical need is the greatest in children who are 1 year of age and older. It is highly unlikely that children with less than 10% of the expected length of small intestine reach enteral independence. These subjects reach a plateau in their ability to advance oral/enteral feeds or decrease PN/IV support (ie, are "stuck") and are not expected to achieve spontaneous adaptation. Subjects who have not progressed to full enteral adaptation by 12 months after their intestinal insults are very unlikely to demonstrate spontaneous improvement in their enteral function. (Sigalet et al. 2011)

1.2 Product Background and Clinical Information

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

There are no approved pharmacological therapies that promote intestinal adaptation in children with SBS. In the US and Europe, a GLP-2 analog called teduglutide is approved for the treatment of SBS in adult patients who are dependent on PN/IV support.

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. (Tappenden et al. 2013; Thymann et al. 2014)

Clinical Studies

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

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

Study CL0600-020 was a randomized, double-blind, placebo-controlled study in which subjects were randomized to teduglutide 0.05 mg/kg/day or placebo on a 1:1 ratio. The first stage of the study included a screening and optimization period and a stabilization period that demonstrated stable administration of PN/IV volume for a minimum of 4 weeks up to a maximum of 8 weeks. The second stage was a dosing period of 24 weeks. Subjects on 0.05 mg/kg/day teduglutide achieved a higher responder rate (defined as a 20% to 100% reduction from baseline in PN/IV volume at weeks 20 and 24) than the placebo-treated subjects (27/43 subjects [62.8%] versus

13/43 subjects [30.2%], respectively). This difference was clinically and statistically significant in both the intent-to-treat (ITT) (p=0.002) and per-protocol ($p < 0.001$) populations. Generally, the incidence of treatment-emergent AEs was distributed similarly across all treatment groups. The treatment-emergent AEs with a higher incidence in the teduglutide group were mainly of GI origin. A long-term, open-label extension study (CL0600-021) assessed safety and efficacy for up to 24 additional months (ie, up to 30 months of exposure for subjects who received teduglutide in Study CL0600-020). Overall, 30 of 43 subjects who received teduglutide in Study CL0600-020 and entered Study CL0600-021 completed a total of 30 months of treatment with teduglutide. Of these, 28 subjects (93%) achieved a 20% or greater reduction of 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 CL0600-020. PN/IV use was reduced by at least 1 day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 3.11 L/week from baseline at the start of Study CL0600-021 (a 28% reduction). Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. Of the 12 subjects entering Study CL0600-021 directly, 6 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 4.0 L/week (a 39.4% reduction from baseline at the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of parenteral support.

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

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

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

Additional information is provided in the investigator's brochure.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Clinical Study

Teduglutide was designated as an orphan drug indicated for SBS in Japan on 20 Nov 2014. Based on national surveys, it is estimated that the number of subjects with SBS who are dependent on parenteral nutrition/intravenous fluid (PN/IV) is less than 1000 in Japan. (Kitajima et al. 2013; Takagi et al. 1995; Takehara 2001) Among the 195 SBS subjects in the 2011 survey, 99 (51%) developed SBS at <1 years old. Early intervention could potentially improve intestinal adaptation and decrease the need for parenteral support in these patients.

The current study proposes to investigate the safe and appropriate use of teduglutide in the Japanese pediatric population for the purpose of providing pharmacokinetic, pharmacodynamic, and safety data. This protocol was developed similarly to the planned EU/US study, TED-C14-006, 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*. The TED-C14-006 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 teduglutide dose of 0.05 mg/kg daily is supported by results from the completed 12-week pediatric study. Teduglutide is approved for adult use in the US and EU at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric study (TED-C13-003, *A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support*) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population pharmacokinetics (PK) modeling and simulations were conducted to determine the effective dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phases 1, 2, and 3 studies as well as the pediatric study (TED-C13-003); they suggested that the dose in pediatric subjects is likely to be the same as the dose in adults. (O'Keefe et al. 2006) The duration of teduglutide treatment in study SHP633-302 mirrors that of the TED-C14-006 study, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period.

The aim of teduglutide treatment is to increase absorptive capacity in order to yield decreases in parenteral support. In addition, the experts anticipated that there would be several direct benefits from decreased parenteral support and advances in enteral feeds, 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.

2.2 Objective(s)

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and PK of teduglutide in pediatric subjects (1 year through 15 years of age) with SBS who are dependent on parenteral support. See Sections 9.8 and 9.10.1 for further details of the endpoints being measured, and Section 9.9 for safety variables.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. 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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The end of study (EOS) visit will be scheduled at week 28, 4 weeks following end of treatment (EOT). Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support. The Study Schedules are displayed at the beginning of this protocol.

A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and provided in Appendix 2 and Appendix 3, respectively) 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. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

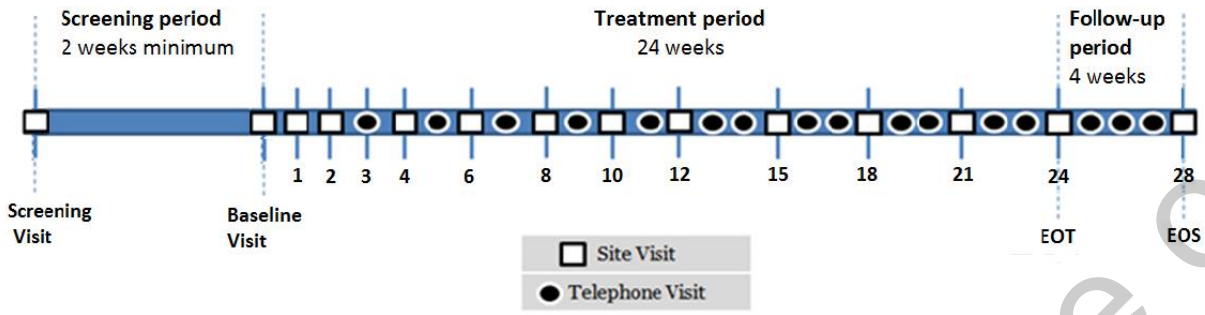
At the conclusion of the follow-up period (week 28), if subjects are determined to have positive/specific antibodies, they will be asked to return for a follow-up visit 3 months post EOT for another antibody sample. If the subjects continue to have positive/specific antibodies at 3 months post EOT, they will be asked to return for follow-up visit(s) up to 6 months post-treatment in order to determine their antibody status.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) which will convene approximately every 3 months during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible subjects could receive teduglutide.

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

Figure 1 Study Diagram



EOS=end of study; EOT=end of treatment

3.2 Study Duration

There will be, at a minimum, a 2-week screening period from the time of the screening visit to the baseline visit, followed by 24 weeks of treatment. Attempts should be made to limit the screening period to 4 weeks. The EOS visit will be scheduled at week 28, 4 weeks after the EOT visit (week 24).

The start of the clinical phase is defined as first subject consented. The end of the clinical phase is defined as the last visit of the last subject.

3.3 Sites and Regions

This study will be conducted at approximately 5 investigational sites in Japan.

4 STUDY POPULATION

Approximately 5 pediatric Japanese subjects, male and female children and adolescents aged 1 year through 15 years, will be enrolled.

4.1 Inclusion Criteria

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

1. Informed consent by a parent or legally-authorized representative prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product

4.2 Exclusion Criteria

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

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

6. Evidence of clinically significant obstruction on upper GI series done within 6 months prior to screening
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic GLP-2
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2x ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2

22. Parent(s)/legally-authorized representative(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Table 3 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	• Active IBD which requires chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months • Tufting or autoimmune enteropathy or microvillus inclusion disease • Untreated pre-malignant or malignant change in the GI tract identified by upper GI series, biopsy or polypectomy • Known polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome) • Intestinal or other major surgery scheduled within the time frame of the study • Chronic active pancreatitis • Cholecystitis
Immune	• Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency)
Psychiatric	• Alcohol or drug abuse 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)

GI=gastrointestinal; IBD=inflammatory bowel disease

4.3 Reproductive Potential

Sexually active females of childbearing potential must be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 4 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception if they become sexually active during the period of the study and 4 weeks following the last dose of investigational product.

Female children and adolescent subjects should be either:

Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or

Females of childbearing potential with a negative serum β-HCG pregnancy test at the screening visit (visit 1) and a negative urine β-HCG pregnancy test prior to enrollment. Females of childbearing potential must agree to abstain from sexual activity (ie, true abstinence) that could result in pregnancy or agree to use medically acceptable methods of contraception at all times during the study and 4 weeks following the last dose of investigational product.

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

4.4 Discontinuation of Subjects

4.4.1 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified without prejudice to further treatment. However, a discussion should be held by the investigator and the Shire medical monitor or designee prior to the subject discontinuing or withdrawing.

4.4.2 Reasons for Discontinuation

- Reasons for discontinuation may include but are not limited to:
- Adverse event
- Death
- Failure to meet enrollment criteria
- Lost to follow-up
- Non-compliance with investigational product
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor

- Study terminated by sponsor
- Technical problems
- Withdrawal by parent/legally-authorized representative
- Withdrawal by subject

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 8.1.

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

4.4.3 Subjects "Lost to follow-up" Prior to Last Scheduled Visit

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

5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including non-prescription herbal treatments, vitamins, invasive and diagnostic procedures) received within 14 days prior to the screening visit (visit 1) and through the end of study (ie, including the protocol-defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Treatment

Prior treatment includes all treatment received within 14 days of the first dose of investigational product, but discontinued before the first dose of investigational product.

5.2 Concomitant Treatment

Concomitant medications are those that continue after the start of investigational product or are newly introduced after the start of treatment through the end of study. In all instances the start date of prior and concomitant therapies must be recorded to the extent possible.

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, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

Changes in any medication and/or dosage will be recorded on the eCRF. See also nutritional support in Section 7.2.15.2.

5.3 Prohibited Treatment

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 following prior therapies are excluded within the timeframes noted (see Section 4.2).

Prior Therapy	Time Restriction Prior to Screening
Native/synthetic glucagon-like peptide-2	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

Teduglutide for subcutaneous (SC) injection is provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide as a lyophilized powder that must be reconstituted using 0.5 mL with sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the investigator's brochure.

6.1.1 Blinding of the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

A dose of 0.05 mg/kg/day of teduglutide will be administered once daily to the subjects for 24 weeks. The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with the Shire medical monitor or designee.

Following reconstitution, teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. If a dose is delayed, that day's dose should be administered as soon as possible, but consecutive doses should be separated by at least 12 hours.

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 investigational product can be found in the Instructions for Use. Each day, the injection site should be rotated.

6.2.1 Allocation of Subjects to Treatment

This is an open-label study; all subjects will receive teduglutide 0.05 mg/kg/day as described in Section 6.2. Subject numbers are assigned to all subjects as consent/assent to take part in the study is provided. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. These numbers will be used to identify the subjects throughout the study period. Once a number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling and Packaging

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

The pre-filled sterile water for injection syringes used for the reconstitution of the investigational product will also be provided. The pre-filled sterile water for injection syringes will be labeled in accordance with the applicable regulatory requirements. The dosing syringes and needles for reconstitution will be provided separately.

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

6.3.2 Storage

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2 and 8^{o}C until dispensed to a subject. The pre-filled sterile water for injection syringes will be stored at a temperature between 2 and 25°C. Once dispensed/supplied to a subject, the investigational product can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25^{o}C). Parent/legally-authorized representative will be instructed to keep the subject's investigational product and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the investigational product may be refrigerated.

6.4 Drug Accountability

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

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

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

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

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

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

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

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

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

See the Pharmacy Manual for additional information.

6.5 Treatment Compliance

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

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

Compliance is considered to be achieved if the subject has 80% of the planned doses administered. Subjects falling outside of these parameters will not be included in the per-protocol efficacy analyses (see Section 9.6).

7 STUDY PROCEDURES

7.1 Study Schedule

Subject evaluations will be performed during the indicated days and weeks of the study as provided in the Study Schedules.

All data collected are to be recorded on the appropriate eCRF.

Details for study procedures including sample collection are described in the Operations Manual for this study.

7.1.1 Screening

All subjects' parents/legally-authorized representatives must sign an informed consent form and, if applicable, subjects must sign an informed assent form prior to initiation of any study-related procedure. All subjects will be screened for a minimum of 2 weeks. Attempts should be made to limit the screening period to 4 weeks.

Subjects will be designated as a screen failure if they fail to meet all inclusion criteria and/or meet any of the exclusion criteria. Screen failures will not be administered investigation product.

At the discretion of the investigator, subjects who fail screening may be re-screened one time with prior sponsor approval. In the event of re-screening, a new subject number will be assigned to the subject and the subject will also be re-consented.

7.1.2 Treatment Period

Subjects who meet all eligibility criteria at screening, and eligibility criteria are confirmed at visit 2/baseline, will be enrolled in the study and will receive the first dose of investigational product at the baseline visit (visit 2). Subjects will enter a 24-week treatment period consisting of either visits or scheduled weekly telephone contacts as outlined in the Section 3.1.

7.1.3 Follow-up Period

During the 4-week follow-up period, weekly telephone visits will be conducted on week 25 to week 27 followed by the EOS visit (week 28). Similar to assessments performed during the treatment period, phone visits during follow-up will include review of intake diaries, and adjustment of nutritional support as needed (see Section 3.1). Procedures to be performed at the EOS visit (week 28) are specified in the Study Schedules; subjects will be queried on serious adverse events (SAEs), AEs, and concomitant treatments, and all AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

7.2 Study Evaluations and Procedures

7.2.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent (and, when applicable, informed assent) must be obtained from the subject's parent(s) or legally authorized representative(s) and from the subject (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject, the subject's parent(s), or the subject's legally authorized representative by the investigator or designee in accordance with the guidelines described in Section 10.3.1. Documentation and filing of informed consent documents should be completed according to Section 10.2.

7.2.2 Study Entrance Criteria

At screening, each subject will be reviewed for eligibility against the study entrance criteria by the investigator or designee. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.2.3 Confirmation of Study Eligibility

Subject eligibility according to the study inclusion and exclusion criteria will be confirmed at baseline by the investigator or designee on the basis of review of the study entrance criteria.

7.2.4 Demographics and Other Baseline Characteristics

Demographic and/or other baseline variables obtained at the screening and/or baseline visits 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 (including surgical history)
- SBS history, including remnant anatomy
- GI-specific symptoms history (Section 7.2.15.1)
- Physical examination, including body weight, height (or length), and head circumference (up to 36 months of age), and trends on growth charts
- Vital signs including temperature, heart rate, and blood pressure
- Prior medications (medications used within 14 days prior to screening and discontinued prior to the first dose of investigational product), including drug name, dose, route, reason for use, and therapy dates. Medications used during the treatment period (after the first dose of investigational product) will be recorded as concomitant medications.
- Electrocardiogram (ECG) (12-lead) variables include general findings (normal/ abnormal, not clinically significant/ abnormal, clinically significant). The cause of any clinically significant ECG will be specified.
- Laboratory test results: biochemistry, hematology, coagulation, and urinalysis
- Plasma citrulline levels
- Presence of antibodies to teduglutide and titer level, if present
- Gastrointestinal imaging/testing (upper GI series with small bowel follow-through [UGI/SBFT], abdominal ultrasound, colonoscopy or sigmoidoscopy, fecal occult blood)

- Pregnancy testing for females of childbearing potential
- Nutritional support prescriptions (eg, PN/IV and enteral nutrition [EN] volume and calories, PN/IV hours per day and days per week) (Section 7.2.15.2)
- Nutritional support diary data (Section 7.2.15.3)

7.2.5 Pharmacokinetic Assessments

Pharmacokinetic assessments are listed in Section 9.10.1.

Blood samples for teduglutide concentrations will be collected at the baseline and week 4 visits. If blood samples are not/cannot be collected at week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product. A schedule of PK sample collection is provided in Table 4. Instructions for sample collection and handling are included in the Laboratory Manual.

Table 4 Blood Sample Collection Schedule for Pharmacokinetic Testing

Study week	Baseline			Week 4		
Visit Number	2			6		
Hour	0[a]	1	6	0[a]	2	4

[a] Prior to investigational product administration

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

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose (at the week 4 draw).
- 1-hour postdose draw: ±10 minutes
- 2-hour postdose draw: ±10 minutes
- 4-hour postdose draw: ±30 minutes
- 6-hour postdose draw: ±30 minutes

At PK timepoints, the date and time of investigational product administration and blood collection must be recorded on the eCRF.

7.2.6 Physical Examination (Including Height and Weight)

Physical examinations will be performed, and body weight, height (or length), and head circumference (up to 36 months of age) measured according to the Study Schedules.

Physical examinations will be performed by the investigator during the study to assess the subject's physical status. New clinically significant abnormalities that are detected or diagnosed after study evaluations have begun (after signing of the informed consent) should be recorded on the appropriate AE page of the eCRF.

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

Body mass index (BMI) and z-scores for weight, height (or length), head circumference, and BMI will be calculated by the sponsor.

7.2.7 Vital Signs

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

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

7.2.8 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing according to the Study Schedules. Subjects should be in a seated or supine position during blood collection.

Laboratory collections required at intervals that do not coincide with site visits (safety laboratory assessments eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site.

Clinical laboratory tests will include the following (see Table 5):

Table 5 List of Laboratory Tests

Hematology: Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count RBC morphology, if needed White blood cell count with differential Coagulation: Prothrombin time/International normalized ratio will be measured in all subjects at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected (Section 8.4.2) Urinalysis: Blood Glucose Leucocytes Microscopic analysis pH and osmolality Protein Sodium Specific gravity **Pregnancy tests** (females of childbearing potential): Serum β-HCG (screening) Urine β-HCG (all other visits)	Biochemistry: Albumin Alkaline phosphatase Alanine aminotransferase Amylase Aspartate aminotransferase Bicarbonate Bilirubin (total and indirect) Blood urea nitrogen Calcium (total) Chloride Cholesterol Citrulline (plasma) C-reactive protein Creatinine Estimated glomerular filtration rate (Schwartz formula) Gamma-glutamyl transferase Glucose Lipase Magnesium Phosphorus Potassium Sodium Triglycerides Uric acid

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

7.2.9 Plasma Citrulline

Plasma citrulline levels will be measured as a biomarker of enterocyte mass. Blood samples will be collected 2 to 4 hours postprandial, whenever possible, at the timepoints specified in the Study Schedules. Samples may be drawn from a central line or peripheral access and processed according to instructions in the Laboratory Manual.

7.2.10 Antibody Assessments

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the baseline visit (day 0) and at least 14 hours after the previous dose at the EOT visit (week 24 or early termination); samples may be drawn from a central line

or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, week 28 or EOS).

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

7.2.11 Pregnancy Testing

Any female subject of childbearing potential (Section 4.3) must have negative pregnancy tests to enroll or continue in the study. Pregnancy tests will be performed at screening (serum β-HCG testing) and at all site visits (urine β-HCG testing).

7.2.12 Volume of Blood

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

The amount of blood to be drawn may vary according to instructions provided by the manufacturer or laboratory for an individual assessment. When more than one blood assessment is to be done at the same timepoint, the assessments should be combined if they require the same type of tube.

7.2.13 Electrocardiogram

Twelve-lead ECGs will be performed in accordance with the clinical site's standard practice(s) as indicated in the Study Schedules. Electrocardiogram recordings will be read locally by an experienced physician. Results (normal; abnormal, not clinically significant; and abnormal, clinically significant with a description of the abnormality) will be recorded on the eCRF.

7.2.14 Gastrointestinal-specific Testing

Gastrointestinal testing will be performed as needed for all subjects during the screening period, as indicated in sections 7.2.14.1 to 7.2.14.4. Follow-up testing will be performed as needed according to the guidelines noted in sections 7.2.14.1 to 7.2.14.4 and the Study Schedules.

7.2.14.1 Upper Gastrointestinal Series with Contrast

An UGI/SBFT will be performed following the ingestion of barium contrast material during the screening period. Results from procedures performed within 6 months prior to visit 1 will also be acceptable.

7.2.14.2 Abdominal Ultrasound

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

7.2.14.3 Fecal Occult Blood Testing

Fecal occult blood testing will be performed at screening, week 12, and week 24 (EOT).

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

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

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

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

7.2.14.4 Colonoscopy/Sigmoidoscopy

Subjects who are 12 years and older will undergo a colonoscopy or sigmoidoscopy at screening. If the fecal occult blood testing is negative at screening and the procedure was performed within 1 year before the screening visit (visit 1), then those prior results are acceptable for the screening assessment.

Children younger than 12 years will undergo the procedure if they test positive for fecal occult blood at screening and the cause is not identified by physical examination (see Section 7.2.14.3).

Requirements for colonoscopy or sigmoidoscopy in response to positive fecal occult blood testing at weeks 12 or 24 are presented in Section 7.2.14.3.

7.2.15 Other Study Procedures

7.2.15.1 GI-specific Symptoms History

GI symptoms during the screening period will be recorded by the subject/parent/legally-authorized representative in a GI-specific symptoms history diary on a daily basis. At the baseline visit, the investigator will review the GI-symptoms diary and summarize the findings.

7.2.15.2 Nutritional Support

Nutritional support includes PN/IV and EN. Advances in enteral nutrition and/or reductions to PN/IV support will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2 and Appendix 3, respectively.

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

7.2.15.3 Diaries

The subject/parent/legally-authorized representative will complete the appropriate fields of the PN/IV and EN (formula) sections of the intake diary.

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

PN/IV volume and infusion duration

EN (formula) volume

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

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

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

      At the discretion of the investigator, the parent may be asked to collect the first void after the daily PN/IV infusion to measure specific gravity.
- Stool data (includes diapers with mixed urine and stool)
    - *Toilet-trained subjects (who do not wear diapers)*
      Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see output diary)
    - *Nontoilet-trained subjects (who wear diapers)*
      Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (see output diary). Stool volume will be calculated using the formula: 1 g (scale weight) = 1 mL or 1 cc

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

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

8 ADVERSE AND SERIOUS ADVERSE EVENT ASSESSMENTS

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

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

All AEs are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

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

8.1.1 Severity Categorization

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

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

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

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

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

8.1.4 Symptoms of the Disease Under Study

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

8.1.5 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent/assent is signed until the defined follow-up period stated in Section 3.2.

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

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

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

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol as well as the Shire

Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Administration of a dose greater than the allocated dose of investigational product or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

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

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

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

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

8.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2 and must be reported to Quintiles Transnational Japan K.K within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

Quintiles Transnational Japan K.K is responsible for notifying the relevant regulatory authorities/central institutional review boards (IRBs)/ethics committees (ECs) of related, unexpected SAEs. In addition the sponsor and/or designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the teduglutide program.

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

8.3 Adverse Events of Special Interest

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

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

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system

- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

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

8.4 Dose Interruption of Individual Subjects

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

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

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to the investigational product. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE listed in Table 6 that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to the investigational product administration (see Section 8.4.1)
- Confirmed drug-induced liver injury (DILI) related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Known Risks of Teduglutide

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

Investigators and the DMC should be guided by the descriptions of Grade 3 and 4 events, as they relate to identified risks associated with the administration of teduglutide (see Table 6).

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	>5.0 to 20.0x ULN	>20.0x ULN
Blood bilirubin increased	>3.0 to 10.0x ULN	>10.0x ULN
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increaseda	>2.0 to 5.0x ULN	>5.0x ULN
Lipase increaseda	>2.0 to 5.0x ULN	>5.0x ULN

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

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

ULN=upper limit of normal

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

8.4.2 Dose Interruption Criteria Based on Drug-induced Liver Injury

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

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

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. INR should be measured with this set of verification laboratory assessments and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin M [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure

associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

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

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

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

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

or

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

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

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

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

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Shire Global Pharmacovigilance and Risk Management database.

9.3 Statistical Analysis Process

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

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. Accordingly, no claims of significance will be made for any of the data.

Continuous variables 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.

All statistical analyses will be performed using SAS®.

9.4 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis or adaptive design.

9.4.1 Data Monitoring Committee

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

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

Safety and tolerability results will be evaluated by a DMC which will convene approximately 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), based on subject enrollment. The DMC review will include all cumulative safety data from study assessment through the end of each review period.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility of this orphan population in children in Japan, rather than power calculation.

9.6 Study Population

Subjects are considered enrolled in the study when they meet all eligibility criteria at screening and eligibility criteria are confirmed at visit 2/baseline.

The ITT population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least 1 administration of investigational product with any safety follow-up. The primary population analyzed for efficacy/PD will be the ITT population. An additional per-protocol population analysis will also

be performed as secondary/sensitivity analysis. The per-protocol population is defined as the subset of subjects in the ITT population without a major protocol deviation. Details will be prospectively defined in the final SAP prior to database lock.

The PK analysis population is defined as all subjects in the safety analysis population for whom the primary PK data are considered sufficient and interpretable.

9.7 Demographics and Baseline Characteristics

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

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

Medical history (including surgical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

9.8 Efficacy/Pharmacodynamic Analyses

The efficacy/PD endpoints include:

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

No formal statistical test will be performed due the limited sample size.

Continuous variables 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.

9.9 Safety Analyses

The safety and tolerability variables include:

- Adverse events, including those pertaining to GI symptoms
- Body weight, height (or length), head circumference (up to 36 months of age), and trends on growth charts
- Vital signs, including temperature, heart rate, blood pressure
- Electrocardiograms
- Laboratory safety data (ie, biochemistry, hematology, coagulation, urinalysis) including the following lab tests at all site visits and interim safety labs to detect hepatoxicity signals: AST, ALT, ALP, and bilirubin
- Urine output (measured volume)
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, UGI/SBFT

Adverse events will be coded using MedDRA. Treatment-emergent AEs will be summarized by system organ class and preferred term. The number and percentage of subjects with AEs, SAEs, AEs that lead to discontinuation, investigational product-related AEs (determined by the investigator), and AEs that resulted in a fatal outcome will be summarized. AEs will also be summarized with regard to intensity and relationship to investigational product. For AEs of special interest, the CTCAE grading system will be used as described in Section 8.4.1.

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

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

9.10 Other Analyses

9.10.1 Pharmacokinetic Analyses

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

- Area under the plasma concentration-time curve (AUC) of zero to infinity ($_{0–inf}$)
- AUC from zero to the last measurable concentration (AUC_{0-t})
- AUC at steady state (AUC_{ss})
- Maximum plasma concentration (C_{max})
- C_{max} at steady state ($C_{max,ss}$)

- Minimum plasma concentration at steady state ($C_{min,ss}$)
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{\lambda z}/F$)

Descriptive statistics for PK parameters (mean, median, standard deviation, minimum and maximum values, geometric mean) will be calculated.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Public Posting of Study Information

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

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

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms

must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded solely onto the eCRF.

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

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

Original source data to be reviewed during this study will include, but are not limited to subject's medical file, subject diaries, and original clinical laboratory reports, and imaging reports. All key data must be recorded in the subject's medical records.

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

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

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the Pharmaceuticals and Medical Devices Agency) or an auditor.

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

10.2.3.3 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator or designee to obtain written informed consent from all subjects or parents/legally-authorized representatives, and assent from subjects where applicable, prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's parent or legally-authorized representative, as applicable, is requested to sign and date

the informed consent form/assent, or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent/assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's parent or legally-authorized representative, as applicable. This document requires translation into the local language. Signed consent/assent forms must remain in each subject's study file and must be available for verification at any time.

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

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

10.3.2 Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent/assent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation. Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

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

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

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

10.4 Privacy and Confidentiality

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

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

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

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

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

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

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to

submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

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

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

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12 APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	18 Dec 2015	Global
Amendment 1	27 Apr 2016	Global

Appendix 2 Guidelines for Nutritional Support Management During the Study (SHP633-302)

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

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

Appendix 3 Weaning Algorithms

Figure A-1 Weaning Algorithm for Subjects Who Are Not Toilet-trained and in Diapers

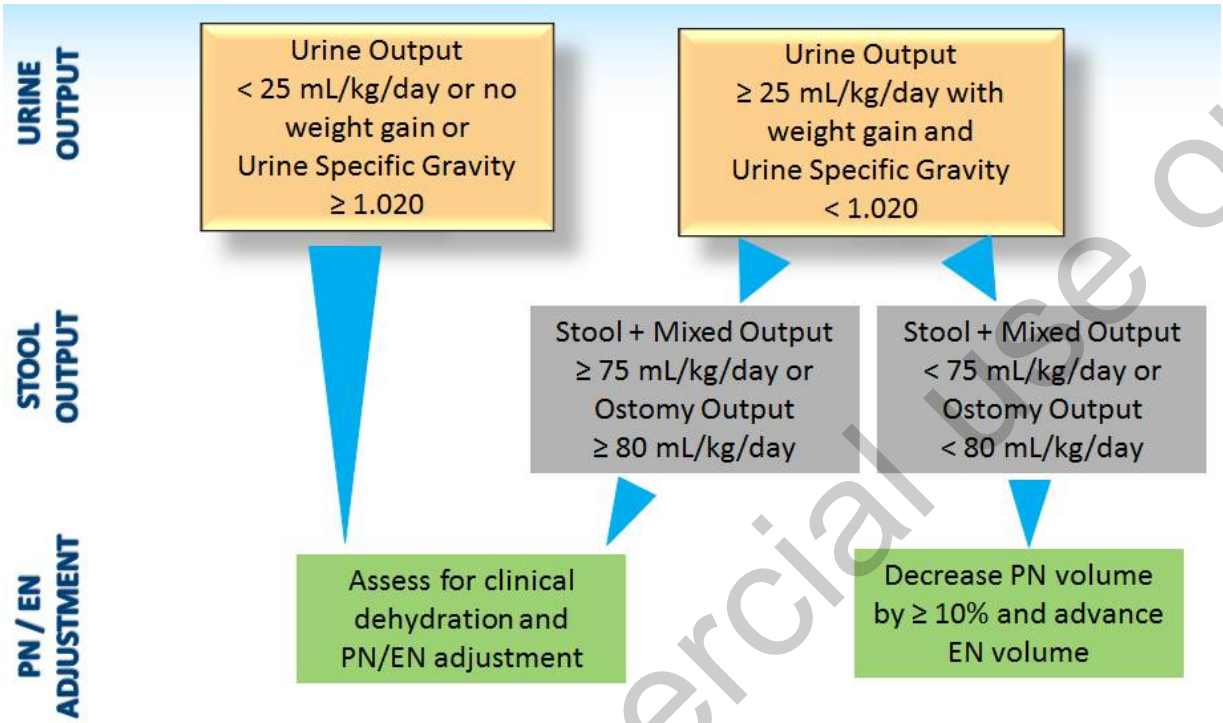


Figure A-2 Subjects Who Are Toilet-trained and Not in Diapers

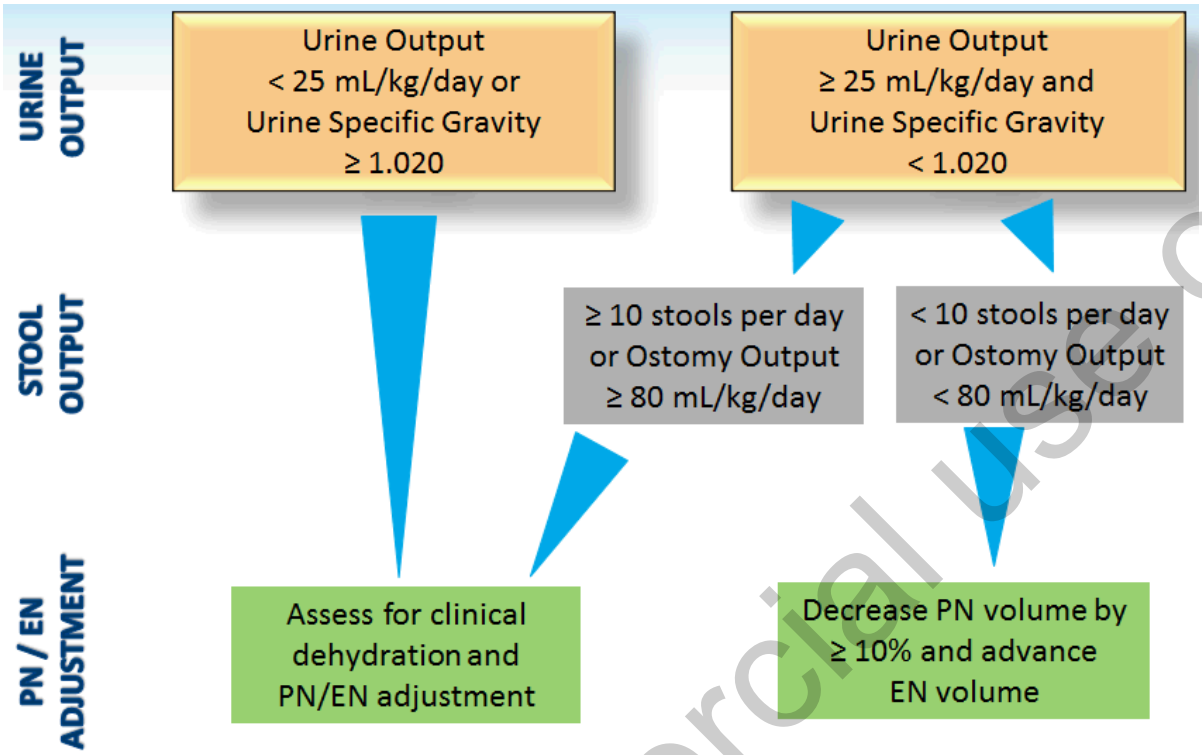
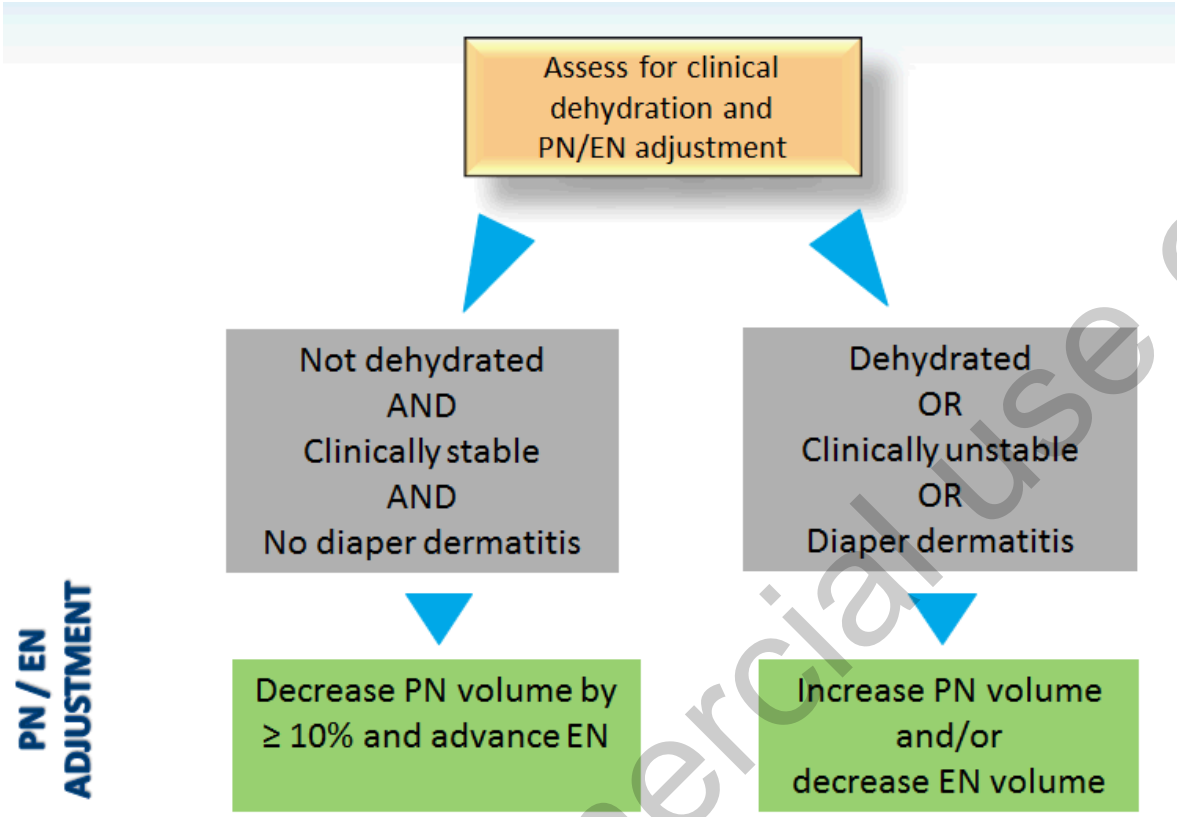


Figure A-3 Clinical Dehydration Assessment and PN/EN Adjustment



CLINICAL TRIAL PROTOCOL: SHP633-302

TITLE:	A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support
NUMBER:	SHP633-302
PHASE:	3
DRUG:	Teduglutide
IND:	058213
OTHER NO.:	NA
INDICATION:	Short bowel syndrome
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Amendment 2: 06 Jun 2017 Amendment 1: 27 Apr 2016 Original Protocol: 18 Dec 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

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

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-302.

Title: A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

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

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

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

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

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

Investigator Name and Address:

(please hand print or type)

Signature: Date:

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** **06 Jun 2017**	**Global**
Description of Change		**Section(s) Affected by Change**
The Pharmacovigilance SAE Reporting fax number and email address have been updated. A sentence has been removed from the emergency contact information to eliminate a redundancy with the information provided under the Pharmacovigilance SAE Reporting heading (Protocol Administrative Change Memo #2, dated 24 Aug 2016). The title of Andrew Grimm MD PhD is now Medical Director and his email address has been changed.		Protocol Signature Page Emergency Contact Information
Urine osmolality (Protocol Administrative Change Memo #1, dated 10 Aug 2016) and urine sodium have been removed from the list of urinalysis parameters to be tested. Neither parameters are needed as safety parameters nor required for the decision to adjust a subject's nutritional support.		Table 5
Clarification that biological therapy prohibited during teduglutide treatment and within 6 months prior to the pretreatment visit refers to biological therapy used to treat inflammatory bowel disease.		Section 5.3
Clarification that subjects, and/or any designated person who will be administering the investigational product, will be trained on investigational product preparation and administration before the first dose of teduglutide or the implementation of any change in ancillary kit components.		Section 6.2
Language on contents of ancillary kits has been revised.		Section 6.3.1

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event, the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to Quintiles Transnational Japan K.K using the details below.

Pharmacovigilance SAE Reporting:

FAX: [redacted] or [redacted] (Japan domestic line only)
or
Email: [redacted]

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

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

For protocol- or safety-related issues between 8:00 to 20:00 US Eastern Standard Time, the investigator may contact the Shire medical monitor:

[redacted], MD, PhD
[redacted], Global Clinical Development
Office Phone: [redacted]
Mobile Phone: [redacted]
Email: [redacted]
Fax: [redacted]

[redacted], [redacted]:
Quintiles Transnational Japan K.K
Phone: [redacted]
Email: [redacted]
Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

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

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-inf}	AUC of zero to infinity
AUC_{0-t}	AUC from zero to the last measurable concentration
AUC_{ss}	AUC at steady state
BMI	body mass index
C_{max}	maximum plasma concentration
$C_{max,ss}$	C_{max} at steady state
$C_{min, ss}$	minimum plasma concentration at steady state
CL/F	apparent clearance
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EC	ethics committee
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	US Food and Drug Administration

GCP	Good Clinical Practice
GI	gastrointestinal
GLP-2	glucagon-like peptide 2
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NCI	National Cancer Institute
PD	pharmacodynamic
PK	pharmacokinetic
PN	parenteral nutrition
PN/EN	parenteral nutrition/ intravenous fluids and enteral nutrition
PN/IV	parenteral nutrition/intravenous fluids
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2}$	terminal-phase half-life
t_{max}	time to C_{max}
UGI/SBFT	upper GI series with small bowel follow-through
ULN	upper limit of normal
US	United States
$V_{\lambda z}/F$	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP633-302 **Drug:** Teduglutide

Study Title:

A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

Number of subjects:

Planned enrollment is approximately 5 subjects.

Sites and Regions: Approximately 5 investigational sites in Japan are planned.

Study Duration:

There will be, at a minimum, a 2-week screening period followed by 24 weeks of treatment. The end of study (EOS) visit will be scheduled at week 28, 4 weeks after the end of treatment (EOT) visit (week 24).

Investigational Product, Dose, and Mode of Administration:

During the treatment period, a dose of 0.05 mg/kg/day of teduglutide will be administered once daily subcutaneously (SC) to the subjects. The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with Shire medical monitor or designee.

Objective(s):

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in pediatric subjects (1 year through 15 years of age) with short bowel syndrome (SBS) who are dependent on parenteral support.

Study Design:

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide.

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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The EOS visit will be scheduled at week 28, 4 weeks following EOT. Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and to be provided in the protocol) for decisions regarding parenteral nutrition/intravenous fluids (PN/IV) support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

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 continue 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.

Safety and tolerability results will be evaluated by a Data Monitoring Committee periodically during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible subjects could receive teduglutide.

Study Inclusion and Exclusion Criteria:

Subjects who satisfy the following inclusion and exclusion criteria will be enrolled in the study.

Inclusion Criteria

1. Informed consent by a parent or legally-authorized representative prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product

Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤ 10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic glucagon-like peptide-2 (GLP-2)
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening

14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2x ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2
22. Parent(s)/legally-authorized representative(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Pharmacokinetic Variables:

Blood samples for drug concentrations will be collected at the baseline visit (predose, at 1 and 6 hours postdose) and at week 4 visit (predose, 2 and 4 hours postdose). If blood samples are not/cannot be collected at week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product.

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

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

Efficacy/Pharmacodynamic Assessments:

The efficacy/PD endpoints include:

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

Safety Assessments:

Safety and tolerability will be assessed by evaluating the following:

- Adverse events, including those pertaining to GI symptoms.
- Physical examinations, including body weight, height (or length), head circumference (up to 36 months of age), and trends on growth charts
- Vital signs, including temperature, heart rate, blood pressure
- Electrocardiograms (ECGs)
- Laboratory safety data (ie, biochemistry, hematology, coagulation, urinalysis)
- Urine output
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through

Safety and tolerability will be evaluated by a Data Monitoring Committee during the study period.

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.

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

Continuous variables 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.

Efficacy/PD data will include change in PN/IV support, enteral nutritional support, plasma citrulline, and hours per day and days per week of PN/IV support, and will be summarized by visit.

Safety data will include clinical laboratory tests results; measurement of body weight, height (or length), and head circumferences (if applicable); vital signs; concomitant medications; and ECG monitoring; and will be summarized by visit. Adverse events will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Date of Original Protocol: 18 Dec 2015

Date of Most Recent Protocol Amendment (if applicable): 27 Apr 2016

STUDY SCHEDULES

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	**≥-14**	**0**	**7 ±2**	**14 ±2**	**21 ±3**	**28 ±3**	**35 ±3**	**42 ±3**	**49 ±3**	**56 ±3**	**63 ±3**	**70 ±3**	**77 ±3**	**84 ±3**
Informed consent/assent[a]	X													
Eligibility	X	X												
Demographics	X													
Medical /surgical history	X													
Electrocardiogram	X													X
SBS history	X													
Upper GI with small bowel follow-through and abdominal ultrasound[b]	X													
Fecal occult blood testing[c]	X													X
Colonoscopy/ sigmoidoscopy[c]	(X)													(X)
Provide GI-specific symptoms history diary	X													
Review GI-specific symptoms history diary		X												
Dispense investigational product[d]		X	X	X		X		X		X		X		X
Pharmacokinetic sampling		X[e]				X[f]								
Safety laboratory tests[g]	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Pregnancy testing[h]	X	X	X	X		X		X		X		X		X

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	**≥-14**	**0**	**7 ±2**	**14 ±2**	**21 ±3**	**28 ±3**	**35 ±3**	**42 ±3**	**49 ±3**	**56 ±3**	**63 ±3**	**70 ±3**	**77 ±3**	**84 ±3**
Plasma citrulline[i]		X												X
Antibodies to teduglutide[j]		X												
Provide intake and output diaries	X	X	X	X		X		X		X		X		X
Review diaries and nutritional support[k]		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[l]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Physical examination/ vital signs/weight	X	X	X	X		X		X		X		X		X
Height (or length) and head circumference[m]	X	X				X				X				X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.

(X)=as needed; eCRF=electronic case report form; EN=enteral nutrition; GI=gastrointestinal; PK=pharmacokinetic; PT/INR=prothrombin time/international normalized ratio; PN/IV=parenteral nutrition/intravenous fluids; SBS=short bowel syndrome; SC=subcutaneous; UGI/SBFT= upper GI series with small bowel follow through

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

[b] If the subject has undergone an UGI/SBFT and/or an abdominal ultrasound within the 6 months before visit 1 (screening), then those test results will be acceptable for the screening assessments. If the subject has not had these procedures within the 6 months before visit 1 (screening), then the procedure(s) will be performed any time after providing informed consent with the results available and reviewed before the baseline visit (day 0).

[c] All subjects enrolled will have a fecal occult blood test after providing consent/assent. Subjects with positive fecal occult blood test at screening for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy. Colonoscopy or sigmoidoscopy will be conducted at screening on all subjects 12 years of age and older; however if the screening fecal occult blood test is negative and the subject has undergone the procedure within 1 year before visit 1 (screening), then that result will be acceptable for the screening assessment (Section 7.2.14.4). Subjects with positive fecal occult blood test results at week 12 for which a cause is not identified by a physical exam will be discussed with the Shire medical monitor or designee (Section 7.2.14.3).

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	≥-14	0	7 ±2	14 ±2	21 ±3	28 ±3	35 ±3	42 ±3	49 ±3	56 ±3	63 ±3	70 ±3	77 ±3	84 ±3

[d] 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) must be specified and recorded in the eCRF. The dose of study medication may be adjusted at week 12.

[e] Baseline (visit 2) samples for PK analysis will be drawn predose, and 1 and 6 hours postdose (Section 7.2.5).

[f] Week 4 (visit 6) samples for PK analysis will be drawn predose, and 2 and 4 hours postdose (Section 7.2.5).

[g] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately 5-7 days following any adjustment to the PN/IV prescription. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[h] All female subjects of child-bearing potential will be tested for pregnancy: serum testing at screening; urine testing thereafter.

[i] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9).

[j] Blood sample for antibody testing is to be collected at study site prior to first investigational product administration. Blood samples may be drawn from a central line or peripheral access (Section 7.2.10).

[k] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[l] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[m] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET) a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Dispense investigational product			X			X			X					
Provide intake and output diaries			X			X			X			X		
Review diaries and nutritional support[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[c]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety laboratory tests[d]	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	X
Pregnancy testing[e]			X			X			X			X		X
Plasma citrulline[f]												X		X
Antibodies to teduglutide[g]												X		X
Physical examination/ vital signs/weight			X			X			X			X		X
Height (or length) and head circumference[h]			X			X			X			X		X
Fecal occult blood testing[i]												X		
Colonoscopy/ sigmoidoscopy[i]												(X)		
Electrocardiogram												X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET) a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Concomitant medication/ procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.

(X)=as needed; EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; PN/IV=parenteral nutrition/intravenous fluid

[a] If a subject terminates from the study prematurely, all EOT procedures should be done at the time of termination and a follow-up visit should be scheduled 4 weeks later.

[b] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[c] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[d] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately 5-7 days following any adjustment to the PN/IV prescription. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[e] All female subjects of child-bearing potential will be tested for pregnancy (urine testing).

[f] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9).

[g] Blood draw to test for antibodies to teduglutide before the last dose of teduglutide, at least 14 hours after the previous dose of teduglutide. If a blood sample is positive for antibodies at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

[h] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

[i] Subjects with positive fecal occult blood test at week 24 (EOT)/ET for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a confirmatory colonoscopy or sigmoidoscopy (Section 7.2.14.3).

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal disease that results in major surgical resections of the small intestine. In children, most cases of short bowel syndrome begin in infancy. Common causes of SBS in children include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis. (Duro et al. 2008; Squires et al. 2012) Similar to adults, new-onset SBS in older children usually stems from Crohn's disease, trauma, and cancer. The diminished absorptive capacity for fluids and nutrients often results in dependence on parenteral nutrition or intravenous fluids (PN/IV) to maintain energy and fluid and electrolyte homeostasis.

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

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

For this reason, research in the pediatric arena is focused on children with PN/IV-dependent SBS. Given intestinal adaption in younger children, the unmet medical need is the greatest in children who are 1 year of age and older. It is highly unlikely that children with less than 10% of the expected length of small intestine reach enteral independence. These subjects reach a plateau in their ability to advance oral/enteral feeds or decrease PN/IV support (ie, are "stuck") and are not expected to achieve spontaneous adaptation. Subjects who have not progressed to full enteral adaptation by 12 months after their intestinal insults are very unlikely to demonstrate spontaneous improvement in their enteral function. (Sigalet et al. 2011)

1.2 Product Background and Clinical Information

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

There are no approved pharmacological therapies that promote intestinal adaptation in children with SBS. In the US and Europe, a GLP-2 analog called teduglutide is approved for the treatment of SBS in adult patients who are dependent on PN/IV support.

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. (Thymann et al. 2014; Tappenden et al. 2013)

Clinical Studies

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

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

Study CL0600-020 was a randomized, double-blind, placebo-controlled study in which subjects were randomized to teduglutide 0.05 mg/kg/day or placebo on a 1:1 ratio. The first stage of the study included a screening and optimization period and a stabilization period that demonstrated stable administration of PN/IV volume for a minimum of 4 weeks up to a maximum of 8 weeks. The second stage was a dosing period of 24 weeks. Subjects on 0.05 mg/kg/day teduglutide achieved a higher responder rate (defined as a 20% to 100% reduction from baseline in PN/IV volume at weeks 20 and 24) than the placebo-treated subjects (27/43 subjects [62.8%] versus 13/43 subjects [30.2%], respectively).

This difference was clinically and statistically significant in both the intent-to-treat (ITT) ($p=0.002$) and per-protocol ($p < 0.001$) populations. Generally, the incidence of treatment-emergent AEs was distributed similarly across all treatment groups. The treatment-emergent AEs with a higher incidence in the teduglutide group were mainly of GI origin. A long-term, open-label extension study (CL0600-021) assessed safety and efficacy for up to 24 additional months (ie, up to 30 months of exposure for subjects who received teduglutide in Study CL0600-020). Overall, 30 of 43 subjects who received teduglutide in Study CL0600-020 and entered Study CL0600-021 completed a total of 30 months of treatment with teduglutide. Of these, 28 subjects (93%) achieved a 20% or greater reduction of 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 CL0600-020. PN/IV use was reduced by at least 1 day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 3.11 L/week from baseline at the start of Study CL0600-021 (a 28% reduction). Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. Of the 12 subjects entering Study CL0600-021 directly, 6 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 4.0 L/week (a 39.4% reduction from baseline at the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of parenteral support.

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

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

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

Additional information is provided in the investigator's brochure.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Clinical Study

Teduglutide was designated as an orphan drug indicated for SBS in Japan on 20 Nov 2014. Based on national surveys, it is estimated that the number of subjects with SBS who are dependent on parenteral nutrition/intravenous fluid (PN/IV) is less than 1000 in Japan. (Takagi et al. 1995; Takehara 2001; Kitajima et al. 2013) Among the 195 SBS subjects in the 2011 survey, 99 (51%) developed SBS at <1 years old. Early intervention could potentially improve intestinal adaptation and decrease the need for parenteral support in these patients.

The current study proposes to investigate the safe and appropriate use of teduglutide in the Japanese pediatric population for the purpose of providing pharmacokinetic, pharmacodynamic, and safety data. This protocol was developed similarly to the planned EU/US study, TED-C14-006, 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*. The TED-C14-006 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 teduglutide dose of 0.05 mg/kg daily is supported by results from the completed 12-week pediatric study. Teduglutide is approved for adult use in the US and EU at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric study (TED-C13-003, *A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support*) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population pharmacokinetics (PK) modeling and simulations were conducted to determine the effective dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phases 1, 2, and 3 studies as well as the pediatric study (TED-C13-003); they suggested that the dose in pediatric subjects is likely to be the same as the dose in adults. (O'Keefe et al. 2006) The duration of teduglutide treatment in study SHP633-302 mirrors that of the TED-C14-006 study, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period.

The aim of teduglutide treatment is to increase absorptive capacity in order to yield decreases in parenteral support. In addition, the experts anticipated that there would be several direct benefits from decreased parenteral support and advances in enteral feeds, 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.

2.2 Objective(s)

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and PK of teduglutide in pediatric subjects (1 year through 15 years of age) with SBS who are dependent on parenteral support. See Sections 9.8 and 9.10.1 for further details of the endpoints being measured, and Section 9.9 for safety variables.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. 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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The end of study (EOS) visit will be scheduled at week 28, 4 weeks following end of treatment (EOT). Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support. The Study Schedules (Table 1 and Table 2) are displayed at the beginning of this protocol.

A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and provided in Appendix 2 and Appendix 3, respectively) 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. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

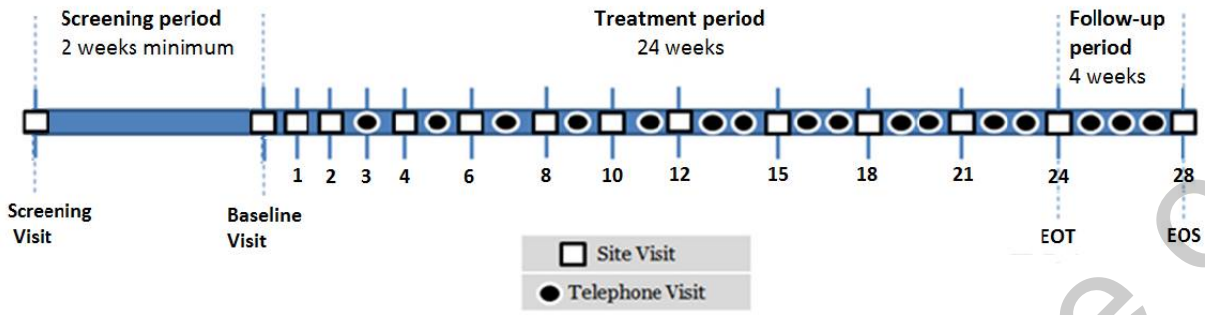
At the conclusion of the follow-up period (week 28), if subjects are determined to have positive/specific antibodies, they will be asked to return for a follow-up visit 3 months post EOT for another antibody sample. If the subjects continue to have positive/specific antibodies at 3 months post EOT, they will be asked to return for follow-up visit(s) up to 6 months post-treatment in order to determine their antibody status.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) which will convene approximately every 3 months during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible subjects could receive teduglutide.

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

Figure 1 Study Diagram



EOS=end of study; EOT=end of treatment

3.2 Study Duration

There will be, at a minimum, a 2-week screening period from the time of the screening visit to the baseline visit, followed by 24 weeks of treatment. Attempts should be made to limit the screening period to 4 weeks. The EOS visit will be scheduled at week 28, 4 weeks after the EOT visit (week 24).

The start of the clinical phase is defined as first subject consented. The end of the clinical phase is defined as the last visit of the last subject.

3.3 Sites and Regions

This study will be conducted at approximately 5 investigational sites in Japan.

4 STUDY POPULATION

Approximately 5 pediatric Japanese subjects, male and female children and adolescents aged 1 year through 15 years, will be enrolled.

4.1 Inclusion Criteria

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

1. Informed consent by a parent or legally-authorized representative prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product

4.2 Exclusion Criteria

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

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper GI series done within 6 months prior to screening

7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic GLP-2
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2x ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2

22. Parent(s)/legally-authorized representative(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Table 3 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	• Active IBD which requires chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months • Tufting or autoimmune enteropathy or microvillus inclusion disease • Untreated pre-malignant or malignant change in the GI tract identified by upper GI series, biopsy or polypectomy • Known polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome) • Intestinal or other major surgery scheduled within the time frame of the study • Chronic active pancreatitis • Cholecystitis
Immune	• Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency)
Psychiatric	• Alcohol or drug abuse 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)

GI=gastrointestinal; IBD=inflammatory bowel disease

4.3 Reproductive Potential

Sexually active females of childbearing potential must be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 4 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception if they become sexually active during the period of the study and 4 weeks following the last dose of investigational product.

Female children and adolescent subjects should be either:

Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or

Females of childbearing potential with a negative serum β-HCG pregnancy test at the screening visit (visit 1) and a negative urine β-HCG pregnancy test prior to enrollment. Females of childbearing potential must agree to abstain from sexual activity (ie, true abstinence) that could result in pregnancy or agree to use medically acceptable methods of contraception at all times during the study and 4 weeks following the last dose of investigational product.

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

4.4 Discontinuation of Subjects

4.4.1 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified without prejudice to further treatment. However, a discussion should be held by the investigator and the Shire medical monitor or designee prior to the subject discontinuing or withdrawing.

4.4.2 Reasons for Discontinuation

- Reasons for discontinuation may include but are not limited to:
- Adverse event
- Death
- Failure to meet enrollment criteria
- Lost to follow-up
- Non-compliance with investigational product
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor

- Study terminated by sponsor
- Technical problems
- Withdrawal by parent/legally-authorized representative
- Withdrawal by subject

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 8.1.

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

4.4.3 Subjects "Lost to follow-up" Prior to Last Scheduled Visit

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

5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including non-prescription herbal treatments, vitamins, invasive and diagnostic procedures) received within 14 days prior to the screening visit (visit 1) and through the end of study (ie, including the protocol-defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Treatment

Prior treatment includes all treatment received within 14 days of the first dose of investigational product, but discontinued before the first dose of investigational product.

5.2 Concomitant Treatment

Concomitant medications are those that continue after the start of investigational product or are newly introduced after the start of treatment through the end of study. In all instances the start date of prior and concomitant therapies must be recorded to the extent possible.

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, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

Changes in any medication and/or dosage will be recorded on the eCRF. See also nutritional support in Section 7.2.15.2.

5.3 Prohibited Treatment

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 following prior therapies are excluded within the timeframes noted (see Section 4.2).

Prior Therapy	Time Restriction Prior to Screening
Native/synthetic glucagon-like peptide-2	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy used to treat inflammatory bowel disease (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

Teduglutide for subcutaneous (SC) injection is provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide as a lyophilized powder that must be reconstituted using 0.5 mL with sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the investigator's brochure.

6.1.1 Blinding of the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

A dose of 0.05 mg/kg/day of teduglutide will be administered once daily to the subjects for 24 weeks. The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with the Shire medical monitor or designee.

Before the first dose of teduglutide or implementation of any change in ancillary kit components, subjects and/or any designated person who will be administering the investigational product will be trained by the investigator or a qualified designee on investigational product preparation and administration. After being trained, the trainee must perform the entire procedure correctly using the provided training materials and without coaching, including demonstration of proper technique for injecting the placebo into an injection simulation device. Subjects should not be injected with the placebo.

Following reconstitution, teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. If a dose is delayed, that day's dose should be administered as soon as possible, but consecutive doses should be separated by at least 12 hours.

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 investigational product can be found in the Instructions for Use. Each day, the injection site should be rotated.

6.2.1 Allocation of Subjects to Treatment

This is an open-label study; all subjects will receive teduglutide 0.05 mg/kg/day as described in Section 6.2. Subject numbers are assigned to all subjects as consent/assent to take part in the study is provided. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. These numbers will be used to identify the subjects throughout the study period. Once a number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling and Packaging

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

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

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

6.3.2 Storage

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2 and 8°C until dispensed to a subject. The pre-filled sterile water for injection syringes will be stored at a temperature between 2 and 25°C. Once dispensed/supplied to a subject, the investigational product can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25°C). Parent/legally-authorized representative will be instructed to keep the subject's investigational product and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the investigational product may be refrigerated.

6.4 Drug Accountability

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

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

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

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

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

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

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

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

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

See the Pharmacy Manual for additional information.

6.5 Treatment Compliance

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

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

Compliance is considered to be achieved if the subject has 80% of the planned doses administered. Subjects falling outside of these parameters will not be included in the per-protocol efficacy analyses (see Section 9.6).

7 STUDY PROCEDURES

7.1 Study Schedule

Subject evaluations will be performed during the indicated days and weeks of the study as provided in the Study Schedules (Table 1 and Table 2).

All data collected are to be recorded on the appropriate eCRF.

Details for study procedures including sample collection are described in the Operations Manual for this study.

7.1.1 Screening

All subjects' parents/legally-authorized representatives must sign an informed consent form and, if applicable, subjects must sign an informed assent form prior to initiation of any study-related procedure. All subjects will be screened for a minimum of 2 weeks. Attempts should be made to limit the screening period to 4 weeks.

Subjects will be designated as a screen failure if they fail to meet all inclusion criteria and/or meet any of the exclusion criteria. Screen failures will not be administered investigation product.

At the discretion of the investigator, subjects who fail screening may be re-screened one time with prior sponsor approval. In the event of re-screening, a new subject number will be assigned to the subject and the subject will also be re-consented.

7.1.2 Treatment Period

Subjects who meet all eligibility criteria at screening, and eligibility criteria are confirmed at visit 2/baseline, will be enrolled in the study and will receive the first dose of investigational product at the baseline visit (visit 2). Subjects will enter a 24-week treatment period consisting of either visits or scheduled weekly telephone contacts as outlined in the Section 3.1.

7.1.3 Follow-up Period

During the 4-week follow-up period, weekly telephone visits will be conducted on week 25 to week 27 followed by the EOS visit (week 28). Similar to assessments performed during the treatment period, phone visits during follow-up will include review of intake diaries, and adjustment of nutritional support as needed (see Section 3.1). Procedures to be performed at the EOS visit (week 28) are specified in the Study Schedules (Table 1 and Table 2); subjects will be queried on serious adverse events (SAEs), AEs, and concomitant treatments, and all AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

7.2 Study Evaluations and Procedures

7.2.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent (and, when applicable, informed assent) must be obtained from the subject's parent(s) or legally authorized representative(s) and from the subject (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject, the subject's parent(s), or the subject's legally authorized representative by the investigator or designee in accordance with the guidelines described in Section 10.3.1. Documentation and filing of informed consent documents should be completed according to Section 10.2.

7.2.2 Study Entrance Criteria

At screening, each subject will be reviewed for eligibility against the study entrance criteria by the investigator or designee. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.2.3 Confirmation of Study Eligibility

Subject eligibility according to the study inclusion and exclusion criteria will be confirmed at baseline by the investigator or designee on the basis of review of the study entrance criteria.

7.2.4 Demographics and Other Baseline Characteristics

Demographic and/or other baseline variables obtained at the screening and/or baseline visits 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 (including surgical history)
- SBS history, including remnant anatomy
- GI-specific symptoms history (Section 7.2.15.1)
- Physical examination, including body weight, height (or length), and head circumference (up to 36 months of age), and trends on growth charts
- Vital signs including temperature, heart rate, and blood pressure
- Prior medications (medications used within 14 days prior to screening and discontinued prior to the first dose of investigational product), including drug name, dose, route, reason for use, and therapy dates. Medications used during the treatment period (after the first dose of investigational product) will be recorded as concomitant medications.
- Electrocardiogram (ECG) (12-lead) variables include general findings (normal/ abnormal, not clinically significant/ abnormal, clinically significant). The cause of any clinically significant ECG will be specified.
- Laboratory test results: biochemistry, hematology, coagulation, and urinalysis
- Plasma citrulline levels
- Presence of antibodies to teduglutide and titer level, if present
- Gastrointestinal imaging/testing (upper GI series with small bowel follow-through [UGI/SBFT], abdominal ultrasound, colonoscopy or sigmoidoscopy, fecal occult blood)

- Pregnancy testing for females of childbearing potential
- Nutritional support prescriptions (eg, PN/IV and enteral nutrition [EN] volume and calories, PN/IV hours per day and days per week) (Section 7.2.15.2)
- Nutritional support diary data (Section 7.2.15.3)

7.2.5 Pharmacokinetic Assessments

Pharmacokinetic assessments are listed in Section 9.10.1.

Blood samples for teduglutide concentrations will be collected at the baseline and week 4 visits. If blood samples are not/cannot be collected at week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product. A schedule of PK sample collection is provided in Table 4. Instructions for sample collection and handling are included in the Laboratory Manual.

Table 4 Blood Sample Collection Schedule for Pharmacokinetic Testing

Study week	Baseline			Week 4		
Visit Number	2			6		
Hour	0[a]	1	6	0[a]	2	4

[a] Prior to investigational product administration

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

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose (at the week 4 draw).
- 1-hour postdose draw: ±10 minutes
- 2-hour postdose draw: ±10 minutes
- 4-hour postdose draw: ±30 minutes
- 6-hour postdose draw: ±30 minutes

At PK timepoints, the date and time of investigational product administration and blood collection must be recorded on the eCRF.

7.2.6 Physical Examination (Including Height and Weight)

Physical examinations will be performed, and body weight, height (or length), and head circumference (up to 36 months of age) measured according to the Study Schedules (Table 1 and Table 2).

Physical examinations will be performed by the investigator during the study to assess the subject's physical status. New clinically significant abnormalities that are detected or diagnosed after study evaluations have begun (after signing of the informed consent) should be recorded on the appropriate AE page of the eCRF.

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

Body mass index (BMI) and z-scores for weight, height (or length), head circumference, and BMI will be calculated by the sponsor.

7.2.7 Vital Signs

Vital signs will be measured according to the Study Schedules (Table 1 and Table 2). Measurements will include body temperature (°C), heart rate (beats per minute), and systolic and diastolic blood pressure (mmHg). Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study).

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

7.2.8 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing according to the Study Schedules (Table 1 and Table 2). Subjects should be in a seated or supine position during blood collection.

Laboratory collections required at intervals that do not coincide with site visits (safety laboratory assessments eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site.

Clinical laboratory tests will include the following (see Table 5):

Table 5 List of Laboratory Tests

Hematology:	Biochemistry:
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Platelet count	Alanine aminotransferase
Red blood cell (RBC) count	Amylase
RBC morphology, if needed	Aspartate aminotransferase
White blood cell count with differential	Bicarbonate
Coagulation:	Bilirubin (total and indirect)
Prothrombin time/International normalized ratio will be measured in all subjects at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected (Section 8.4.2)	Blood urea nitrogen
	Calcium (total)
	Chloride
	Cholesterol
	Citrulline (plasma)

Table 5 List of Laboratory Tests

Urinalysis:	C-reactive protein
Blood	Creatinine
Glucose	Estimated glomerular filtration rate
Leucocytes	(Schwartz formula)
Microscopic analysis	Gamma-glutamyl transferase
pH	Glucose
Protein	Lipase
Specific gravity	Magnesium
Pregnancy tests (females of childbearing potential):	Phosphorus
Serum β-HCG (screening)	Potassium
Urine β-HCG (all other visits)	Sodium
	Triglycerides
	Uric acid

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

7.2.9 Plasma Citrulline

Plasma citrulline levels will be measured as a biomarker of enterocyte mass. Blood samples will be collected 2 to 4 hours postprandial, whenever possible, at the timepoints specified in the Study Schedules (Table 1 and Table 2). Samples may be drawn from a central line or peripheral access and processed according to instructions in the Laboratory Manual.

7.2.10 Antibody Assessments

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the baseline visit (day 0) and at least 14 hours after the previous dose at the EOT visit (week 24 or early termination); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, week 28 or EOS).

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

7.2.11 Pregnancy Testing

Any female subject of childbearing potential (Section 4.3) must have negative pregnancy tests to enroll or continue in the study. Pregnancy tests will be performed at screening (serum β-HCG testing) and at all site visits (urine β-HCG testing).

7.2.12 Volume of Blood

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

The amount of blood to be drawn may vary according to instructions provided by the manufacturer or laboratory for an individual assessment. When more than one blood assessment is to be done at the same timepoint, the assessments should be combined if they require the same type of tube.

7.2.13 Electrocardiogram

Twelve-lead ECGs will be performed in accordance with the clinical site's standard practice(s) as indicated in the Study Schedules (Table 1 and Table 2). Electrocardiogram recordings will be read locally by an experienced physician. Results (normal; abnormal, not clinically significant; and abnormal, clinically significant with a description of the abnormality) will be recorded on the eCRF.

7.2.14 Gastrointestinal-specific Testing

Gastrointestinal testing will be performed as needed for all subjects during the screening period, as indicated in sections 7.2.14.1 to 7.2.14.4. Follow-up testing will be performed as needed according to the guidelines noted in sections 7.2.14.1 to 7.2.14.4 and the Study Schedules (Table 1 and Table 2).

7.2.14.1 Upper Gastrointestinal Series with Contrast

An UGI/SBFT will be performed following the ingestion of barium contrast material during the screening period. Results from procedures performed within 6 months prior to visit 1 will also be acceptable.

7.2.14.2 Abdominal Ultrasound

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

7.2.14.3 Fecal Occult Blood Testing

Fecal occult blood testing will be performed at screening, week 12, and week 24 (EOT).

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

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

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

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

7.2.14.4 Colonoscopy/Sigmoidoscopy

Subjects who are 12 years and older will undergo a colonoscopy or sigmoidoscopy at screening. If the fecal occult blood testing is negative at screening and the procedure was performed within 1 year before the screening visit (visit 1), then those prior results are acceptable for the screening assessment.

Children younger than 12 years will undergo the procedure if they test positive for fecal occult blood at screening and the cause is not identified by physical examination (see Section 7.2.14.3).

Requirements for colonoscopy or sigmoidoscopy in response to positive fecal occult blood testing at weeks 12 or 24 are presented in Section 7.2.14.3.

7.2.15 Other Study Procedures

7.2.15.1 GI-specific Symptoms History

GI symptoms during the screening period will be recorded by the subject/parent/legally-authorized representative in a GI-specific symptoms history diary on a daily basis. At the baseline visit, the investigator will review the GI-symptoms diary and summarize the findings.

7.2.15.2 Nutritional Support

Nutritional support includes PN/IV and EN. Advances in enteral nutrition and/or reductions to PN/IV support will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2 and Appendix 3, respectively.

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

7.2.15.3 Diaries

The subject/parent/legally-authorized representative will complete the appropriate fields of the PN/IV and EN (formula) sections of the intake diary.

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

PN/IV volume and infusion duration

EN (formula) volume

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

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

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

      At the discretion of the investigator, the parent may be asked to collect the first void after the daily PN/IV infusion to measure specific gravity.
- Stool data (includes diapers with mixed urine and stool)
    - *Toilet-trained subjects (who do not wear diapers)*
      Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see output diary)
    - *Nontoilet-trained subjects (who wear diapers)*
      Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (see output diary). Stool volume will be calculated using the formula: 1 g (scale weight) = 1 mL or 1 cc

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

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

8 ADVERSE AND SERIOUS ADVERSE EVENT ASSESSMENTS

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

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

All AEs are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

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

8.1.1 Severity Categorization

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

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

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

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

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

8.1.4 Symptoms of the Disease Under Study

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

8.1.5 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent/assent is signed until the defined follow-up period stated in Section 3.2.

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

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

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

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

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Administration of a dose greater than the allocated dose of investigational product or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

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

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to Quintiles Transnational Japan K.K within 24 hours of the first awareness of the event.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

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

8.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2 and must be reported to Quintiles Transnational Japan K.K within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

Quintiles Transnational Japan K.K is responsible for notifying the relevant regulatory authorities/central institutional review boards (IRBs)/ethics committees (ECs) of related, unexpected SAEs. In addition the sponsor and/or designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the teduglutide program.

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

8.3 Adverse Events of Special Interest

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

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

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

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

8.4 Dose Interruption of Individual Subjects

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

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

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to the investigational product. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE listed in Table 6 that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to the investigational product administration (see Section 8.4.1)
- Confirmed drug-induced liver injury (DILI) related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Known Risks of Teduglutide

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

Investigators and the DMC should be guided by the descriptions of Grade 3 and 4 events, as they relate to identified risks associated with the administration of teduglutide (see Table 6).

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	>5.0 to 20.0x ULN	>20.0x ULN
Blood bilirubin increased	>3.0 to 10.0x ULN	>10.0x ULN
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Lipase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

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

ULN=upper limit of normal

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

8.4.2 Dose Interruption Criteria Based on Drug-induced Liver Injury

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

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

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. INR should be measured with this set of verification laboratory assessments and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin M [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

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

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

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

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

or

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

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

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

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

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Shire Global Pharmacovigilance and Risk Management database.

9.3 Statistical Analysis Process

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

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. Accordingly, no claims of significance will be made for any of the data.

Continuous variables 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.

All statistical analyses will be performed using SAS®.

9.4 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis or adaptive design.

9.4.1 Data Monitoring Committee

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

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

Safety and tolerability results will be evaluated by a DMC which will convene approximately 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), based on subject enrollment. The DMC review will include all cumulative safety data from study assessment through the end of each review period.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility of this orphan population in children in Japan, rather than power calculation.

9.6 Study Population

Subjects are considered enrolled in the study when they meet all eligibility criteria at screening and eligibility criteria are confirmed at visit 2/baseline.

The ITT population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least 1 administration of investigational product with any safety follow-up. The primary population analyzed for efficacy/PD will be the ITT population.

An additional per-protocol population analysis will also be performed as secondary/sensitivity analysis. The per-protocol population is defined as the subset of subjects in the ITT population without a major protocol deviation. Details will be prospectively defined in the final SAP prior to database lock.

The PK analysis population is defined as all subjects in the safety analysis population for whom the primary PK data are considered sufficient and interpretable.

9.7 Demographics and Baseline Characteristics

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

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

Medical history (including surgical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

9.8 Efficacy/Pharmacodynamic Analyses

The efficacy/PD endpoints include:

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

No formal statistical test will be performed due the limited sample size.

Continuous variables 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.

9.9 Safety Analyses

The safety and tolerability variables include:

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

Adverse events will be coded using MedDRA. Treatment-emergent AEs will be summarized by system organ class and preferred term. The number and percentage of subjects with AEs, SAEs, AEs that lead to discontinuation, investigational product-related AEs (determined by the investigator), and AEs that resulted in a fatal outcome will be summarized. AEs will also be summarized with regard to intensity and relationship to investigational product. For AEs of special interest, the CTCAE grading system will be used as described in Section 8.4.1.

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

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

9.10 Other Analyses

9.10.1 Pharmacokinetic Analyses

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

- Area under the plasma concentration-time curve (AUC) of zero to infinity ($_{0–inf}$)
- AUC from zero to the last measurable concentration (AUC_{0-t})

- AUC at steady state (AUC_{ss})
- Maximum plasma concentration (C_{max})
- C_{max} at steady state ($C_{max,ss}$)
- Minimum plasma concentration at steady state ($C_{min,ss}$)
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{\lambda z}/F$)

Descriptive statistics for PK parameters (mean, median, standard deviation, minimum and maximum values, geometric mean) will be calculated.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Public Posting of Study Information

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

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

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

Original source data to be reviewed during this study will include, but are not limited to subject's medical file, subject diaries, and original clinical laboratory reports, and imaging reports. All key data must be recorded in the subject's medical records.

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

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

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the Pharmaceuticals and Medical Devices Agency) or an auditor.

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

10.2.3.3 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator or designee to obtain written informed consent from all subjects or parents/legally-authorized representatives, and assent from subjects where applicable, prior to any study-related procedures including screening assessments.

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

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

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

10.3.2 Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent/assent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation. Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

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

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

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

10.4 Privacy and Confidentiality

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

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

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

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

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

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

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

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

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

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12 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	18 Dec 2015	Global
Amendment 1	27 Apr 2016	Global
Amendment 2	06 Jun 2017	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Age range for subjects has been specified. Subjects will be 1 year through 15 years of age.		Title page Protocol signature page Synopsis Sections 4 and 4.1
Emergency contact information has been updated.		Emergency Contact Information Sections 8.1.6, 8.2.2, 8.2.4
Clarification that departing from the nutritional support adjustment guidelines and weaning algorithms in Appendix 2 and Appendix 3, respectively, will not constitute a protocol deviation.		Synopsis Section 3.1
Statement added that subjects who complete the study may participate in a long-term extension study in which eligible subjects could receive teduglutide.		Synopsis Section 3.1
Inclusion and Exclusion criteria have been refined and clarified; there were no criteria added with the exception of the age of subject population which has been added as an inclusion criterion (was previously in introductory sentence).		Synopsis Sections 4.1 and 4.2
Exclusion Criterion #11 has been updated to indicate that a subject would be excluded from the study if the subject had participated in a clinical study of experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.		Synopsis Section 4.2
Efficacy/PD endpoints have been lumped together and clarified. The small population does not warrant primary versus secondary endpoints. The statistical method has been clarified.		Synopsis Section 9.8
Safety assessments and statistical methods have been clarified.		Synopsis Section 9.9
Study schedule of events tables have been revised to reflect the changes to the protocol and for clarity.		Table 1 Table 2
Any phone contacts may be replaced with unscheduled site visits if necessary.		Table 1 Table 2 Section 3.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Requirement added that female subjects of child-bearing potential undergo a serum-based pregnancy test at screening.		Table 1 Table 2 Sections 4.3, 7.2.8, 7.2.11
Definition of prior and concomitant medications has been expanded to include invasive and diagnostic procedures.		Table 1 Table 2 Section 5
Additional information on selection of teduglutide dosing regimen and duration in the study has been inserted.		Section 2.1
Frequency of Data Monitoring Committee meetings has been specified.		Sections 3.1 and 9.4.1
Definition of screening period has been clarified.		Section 3.2
Inflammatory bowel disease that requires chronic systemic immunosuppressant therapy for symptom control has been removed from the list of excluded disease and illness in Exclusion Criterion #24.		Section 4.2 (Table 3)
Definition of acceptable methods of contraception has been revised to reflect available methods in Japan.		Section 4.3
List of prohibited prior therapy has been revised to remove experimental antibody treatment, as it is now included in the revised exclusion criterion #11.		Section 5.3
Requirement that teduglutide should be administered in the morning has been removed.		Section 6.2
Language on labeling, packaging, and drug accountability has been clarified.		Sections 6.3 and 6.4
Reviewing subject diaries has been included in the subject compliance with dosing check. Clarification that attempts should be made by the investigator to contact the sponsor or designee prior to dose interruption has been added.		Section 6.5
Requirement has been added that subjects who are re-screened must be re-consented.		Section 7.1.1
Timeframe for a subject to be considered enrolled in the study has been clarified.		Sections 7.1.2 and 9.6
Demographics and other baseline characteristics have been clarified.		Section 7.2.4
Windows for PK blood collection have been extended; possibility to collect week 4 timepoint at any future visit if needed has been added.		Section 7.2.5
PT/INR testing has been added at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected thereafter.		Table 1 Table 2 Section 7.2.8
For children in diapers, urine specimen collection should be attempted as part of the safety lab assessments, but lack of urinalysis will not constitute a protocol deviation.		Table 1 Table 2 Section 7.2.8

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Timeframe of follow-up for subjects with blood samples testing positive for anti-teduglutide antibodies at week 28 or EOS has been clarified.		Synopsis Table 1 Table 2 Section 7.2.10
Need for a subject with a positive fecal occult blood testing at week 12 without a readily identifiable cause by physical examination to undergo a colonoscopy or sigmoidoscopy is now open to discussion with the Shire medical monitor or designee.		Table 1 Table 2 Section 7.2.14.3
Need for children younger than 12 years to undergo a colonoscopy or sigmoidoscopy if they test positive for fecal occult blood at screening and the cause is not identified by physical examination has been specified.		Section 7.2.14.4
GI symptoms history worksheet has been renamed GI-specific symptoms history diary, and details on recording and reviewing symptoms have been added.		Table 1 Table 2 Section 7.2.15.1
"Other nutrition (regular diet and drink)" has been removed from the Intake diary.		Section 7.2.15.2
Output diary data collection will continue to occur over a 48-hour period of PN/IV and EN stability before every site visit. Between site visits, the output diary collection will only be required within 1 week of implementing a change in the PN/IV prescription.		Table 1 Table 2 Section 7.2.15.3
Severity categorization has been updated to specify that the severity of AEs listed in Table 6 that may lead to dose interruption based on known risks of teduglutide will also be evaluated using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria.		Section 8.1.1
Definition of an overdose to teduglutide has been revised.		Section 8.1.7
Adverse events of special interest have been redefined and procedures for reporting them have been added.		Section 8.3
More information has been provided on criteria for dose interruption of individual subjects. Dose discontinuation has been made absolute for an AE known to be a risk associated with teduglutide administration (Table 6) that is of NCI CTCAE severity ≥Grade 3 and considered to be related to investigational product; cases of severe hypersensitivity that are determined to be related to investigational product; DILI that is related to investigational product; and pregnancy. SAEs related to investigational product are potential but not absolute reasons for dose discontinuation.		Sections 8.4, 8.4.1, and 8.4.2
Criteria for DILI have been added.		Section 8.4.2
Criteria for early termination of the study have been clarified.		Section 8.5
Clarification that original diary data should be entered into the eCRF and take precedence over data collected over the phone.		Section 9.1
Definition of PK analysis population has been added.		Section 9.6
Pharmacokinetic analyses methods and parameters have been clarified.		Synopsis Section 9.10.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Protocol history has been added in Appendix 1.		Appendix 1
Guidelines for nutritional support management during the study have been clarified.		Appendix 2

APPENDIX 2 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY (SHP633-302)

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

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

APPENDIX 3 WEANING ALGORITHMS

Figure A-1 Weaning Algorithm for Subjects Who Are Not Toilet-trained and in Diapers

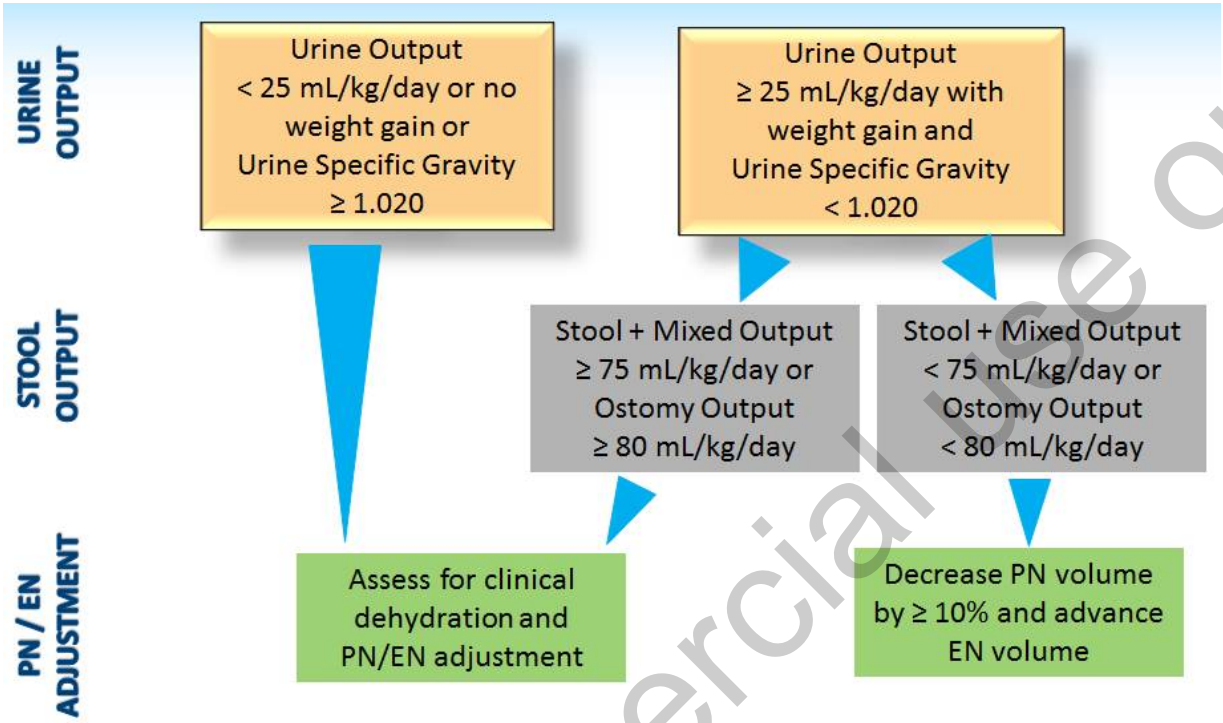


Figure A-2 Subjects Who Are Toilet-trained and Not in Diapers

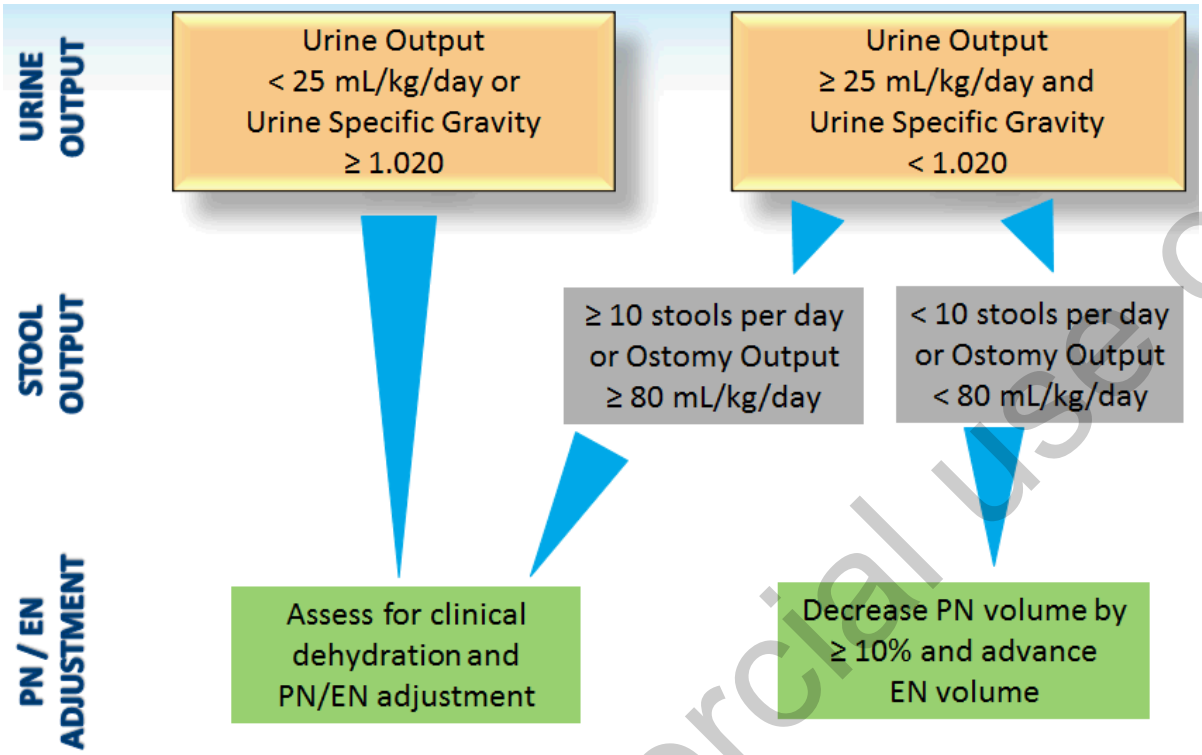
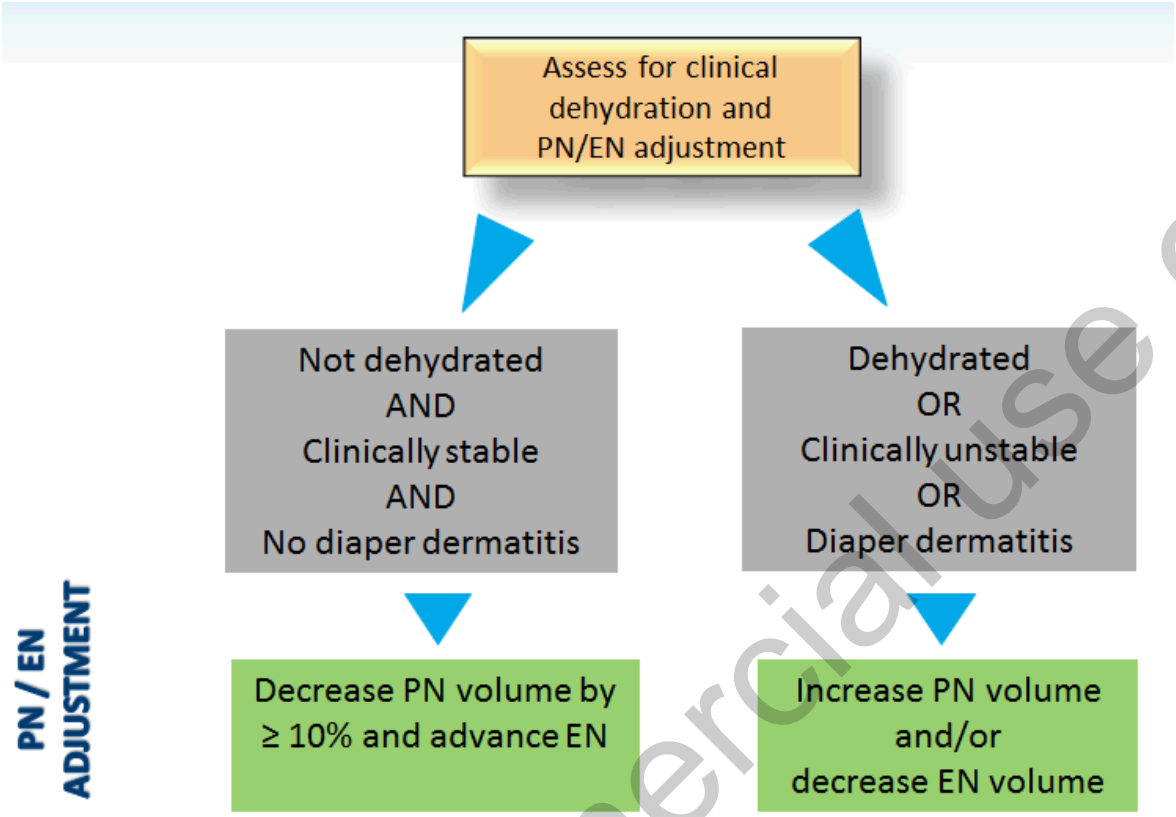


Figure A-3 Clinical Dehydration Assessment and PN/EN Adjustment



CLINICAL TRIAL PROTOCOL: SHP633-302

TITLE:	A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support
NUMBER:	SHP633-302
PHASE:	3
DRUG:	Teduglutide
IND:	058213
OTHER NO.:	NA
INDICATION:	Short bowel syndrome
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Amendment 3: 24 Jan 2018 Amendment 2: 06 Jun 2017 Amendment 1: 27 Apr 2016 Original Protocol: 18 Dec 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

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

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-302.

Title: A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

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

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

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

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

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

Investigator Name and Address:

(please hand print or type) _____

_____

Signature: _____ Date: _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date 24 Jan 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Updated the emergency contact information for the study.		Emergency Contact Information
Updated the product quality complaint section to address the drug delivery device.		Product Quality Complaints
Revised study drug administration language for clarity.		Section 6.1.2
As requested by PMDA, updated text to specify the process for training parent/guardian and measures to be taken to provide oversight on study drug administration.		Synopsis, Table 1, Section 6.1.2.1
Clarified that the study drug administration diary can be completed by study site staff.		Table 1, Section 6.4, Section 7.2.15.3
Added direct bilirubin to the list of laboratory tests.		Table 5
Replaced the term “legally authorized representative” with guardian.		Throughout protocol
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event, the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to Quintiles Transnational Japan K.K using the details below.

Pharmacovigilance SAE Reporting:

FAX: [redacted] or [redacted] (Japan domestic line only)
or
Email: [redacted]

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

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

For protocol- or safety-related issues between 8:00 to 20:00 US Eastern Standard Time, the investigator may contact the Shire medical monitor:

[redacted], PharmD, MSc
Lead Clinical Development Scientist
Office Phone: [redacted]
Mobile Phone: [redacted]
Email: [redacted]

[redacted], [redacted]:
Quintiles Transnational Japan K.K
Phone: [redacted]
Email: [redacted]
Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

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

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

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

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LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-inf}	AUC of zero to infinity
AUC_{0-t}	AUC from zero to the last measurable concentration
AUC_{ss}	AUC at steady state
BMI	body mass index
C_{max}	maximum plasma concentration
$C_{max,ss}$	C_{max} at steady state
$C_{min, ss}$	minimum plasma concentration at steady state
CL/F	apparent clearance
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EC	ethics committee
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	US Food and Drug Administration

GCP	Good Clinical Practice
GI	gastrointestinal
GLP-2	glucagon-like peptide 2
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NCI	National Cancer Institute
PD	pharmacodynamic
PK	pharmacokinetic
PN	parenteral nutrition
PN/EN	parenteral nutrition/ intravenous fluids and enteral nutrition
PN/IV	parenteral nutrition/intravenous fluids
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2}$	terminal-phase half-life
t_{max}	time to C_{max}
UGI/SBFT	upper GI series with small bowel follow-through
ULN	upper limit of normal
US	United States
$V_{\lambda z}/F$	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP633-302 **Drug:** Teduglutide

Study Title:

A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 1 Year through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

Number of subjects:

Planned enrollment is approximately 5 subjects.

Sites and Regions: Approximately 5 investigational sites in Japan are planned.

Study Duration:

There will be, at a minimum, a 2-week screening period followed by 24 weeks of treatment. The end of study (EOS) visit will be scheduled at week 28, 4 weeks after the end of treatment (EOT) visit (week 24).

Investigational Product, Dose, and Mode of Administration:

During the treatment period, a dose of 0.05 mg/kg/day of teduglutide will be administered once daily subcutaneously (SC) to the subjects.

The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with Shire medical monitor or designee.

The first dose of teduglutide will be administered by a study physician. The processes for training the parent/guardian to administer teduglutide and for providing oversight of study drug administration are described in the Site Training Guide.

Objective(s):

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in pediatric subjects (1 year through 15 years of age) with short bowel syndrome (SBS) who are dependent on parenteral support.

Study Design:

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide.

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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The EOS visit will be scheduled at week 28, 4 weeks following EOT. Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and to be provided in the protocol) for decisions regarding parenteral nutrition/intravenous fluids (PN/IV) support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

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 continue 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.

Safety and tolerability results will be evaluated by a Data Monitoring Committee periodically during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible subjects could receive teduglutide.

Study Inclusion and Exclusion Criteria:

Subjects who satisfy the following inclusion and exclusion criteria will be enrolled in the study.

Inclusion Criteria

1. Informed consent by a parent or guardian prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product

Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤ 10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within

3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study

12. Previous use of teduglutide or native/synthetic glucagon-like peptide-2 (GLP-2)
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

    For subjects with Gilbert's disease:
    d. Indirect (unconjugated) bilirubin ≥2x ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2
22. Parent(s)/guardian(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Pharmacokinetic Variables:

Blood samples for drug concentrations will be collected at the baseline visit (predose, at 1 and 6 hours postdose) and at week 4 visit (predose, 2 and 4 hours postdose). If blood samples are not/cannot be collected at week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product.

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

- Area under the plasma concentration–time curve (AUC) of zero to infinity ($_{0–inf}$)
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Area under the concentration-time curve at steady-state (AUC_{ss})
- Maximum plasma concentration (C_{max})
- Maximum plasma concentration at steady-state ($C_{max,ss}$)
- Minimum plasma concentration at steady-state ($C_{min,ss}$)
- Time to C_{max} (t_{max})

- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{\lambda z}$/F)

Efficacy/Pharmacodynamic Assessments:

The efficacy/PD endpoints include:

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

Safety Assessments:

Safety and tolerability will be assessed by evaluating the following:

- Adverse events, including those pertaining to GI symptoms.
- Physical examinations, including body weight, height (or length), head circumference (up to 36 months of age), and trends on growth charts
- Vital signs, including temperature, heart rate, blood pressure
- Electrocardiograms (ECGs)
- Laboratory safety data (ie, biochemistry, hematology, coagulation, urinalysis)
- Urine output
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through

Safety and tolerability will be evaluated by a Data Monitoring Committee during the study period.

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.

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

Continuous variables 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.

Efficacy/PD data will include change in PN/IV support, enteral nutritional support, plasma citrulline, and hours per day and days per week of PN/IV support, and will be summarized by visit.

Safety data will include clinical laboratory tests results; measurement of body weight, height (or length), and head circumferences (if applicable); vital signs; concomitant medications; and ECG monitoring; and will be summarized by visit. Adverse events will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

STUDY SCHEDULES

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	≥-14	0		7 ±2	14 ±2	21 ±3	28 ±3	35 ±3	42 ±3	49 ±3	56 ±3	63 ±3	70 ±3	77 ±3	84 ±3
Informed consent/assent[a]	X														
Eligibility	X	X													
Demographics	X														
Medical /surgical history	X														
Electrocardiogram	X														X
SBS history	X														
Upper GI with small bowel follow-through and abdominal ultrasound[b]	X														
Fecal occult blood testing[c]	X														X
Colonoscopy/ sigmoidoscopy[c]	(X)														(X)
Provide GI-specific symptoms history diary	X														
Review GI-specific symptoms history diary		X													
Dispense investigational product[d]		X		X	X		X		X		X		X		X
Confirm administration proficiency		X^n	X^n	X^n				X							X

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	**≥-14**	**0**	**7 ±2**	**14 ±2**	**21 ±3**	**28 ±3**	**35 ±3**	**42 ±3**	**49 ±3**	**56 ±3**	**63 ±3**	**70 ±3**	**77 ±3**	**84 ±3**
Pharmacokinetic sampling		X[e]				X[f]								
Safety laboratory tests[g]	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Pregnancy testing[h]	X	X	X	X		X		X		X		X		X
Plasma citrulline[i]		X												X
Antibodies to teduglutide[j]		X												
Provide intake and output diaries	X	X	X	X		X		X		X		X		X
Review diaries and nutritional support[k]		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[l]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Physical examination/ vital signs/weight	X	X	X	X		X		X		X		X		X
Height (or length) and head circumference[m]	X	X				X				X				X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit.
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.
(X)=as needed; eCRF=electronic case report form; EN=enteral nutrition; GI=gastrointestinal; PK=pharmacokinetic; PT/INR=prothrombin time/international normalized ratio; PN/IV=parenteral nutrition/intravenous fluids; SBS=short bowel syndrome; SC=subcutaneous; UGI/SBFT= upper GI series with small bowel follow through

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	≥-14	0	7 ±2	14 ±2	21 ±3	28 ±3	35 ±3	42 ±3	49 ±3	56 ±3	63 ±3	70 ±3	77 ±3	84 ±3

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

[b] If the subject has undergone an UGI/SBFT and/or an abdominal ultrasound within the 6 months before visit 1 (screening), then those test results will be acceptable for the screening assessments. If the subject has not had these procedures within the 6 months before visit 1 (screening), then the procedure(s) will be performed any time after providing informed consent with the results available and reviewed before the baseline visit (day 0).

[c] All subjects enrolled will have a fecal occult blood test after providing consent/assent. Subjects with positive fecal occult blood test at screening for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy. Colonoscopy or sigmoidoscopy will be conducted at screening on all subjects 12 years of age and older; however if the screening fecal occult blood test is negative and the subject has undergone the procedure within 1 year before visit 1 (screening), then that result will be acceptable for the screening assessment (Section 7.2.14.4). Subjects with positive fecal occult blood test results at week 12 for which a cause is not identified by a physical exam will be discussed with the Shire medical monitor or designee (Section 7.2.14.3).

[d] 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) must be specified and recorded in the eCRF. The dose of study medication may be adjusted at week 12.

[e] Baseline (visit 2) samples for PK analysis will be drawn predose, and 1 and 6 hours postdose (Section 7.2.5).

[f] Week 4 (visit 6) samples for PK analysis will be drawn predose, and 2 and 4 hours postdose (Section 7.2.5).

[g] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately 5-7 days following any adjustment to the PN/IV prescription. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[h] All female subjects of child-bearing potential will be tested for pregnancy: serum testing at screening; urine testing thereafter.

[i] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9).

[j] Blood sample for antibody testing is to be collected at study site prior to first investigational product administration. Blood samples may be drawn from a central line or peripheral access (Section 7.2.10).

[k] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study by the subject or parent/guardian/study site staff (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[l] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[m] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

[n] The first dose of teduglutide will be administered by a study physician. The study physician must observe the parent/guardian administer the study drug in compliance with the study drug administration checklist at least twice before the parent/guardian is allowed to administer the drug without direct observation by the physician. Refer to Section 6.1.2.1.

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET)a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Dispense investigational product			X			X			X					
Provide intake and output diaries			X			X			X			X		
Review diaries and nutritional support[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[c]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety laboratory tests[d]	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	X
Pregnancy testing[e]			X			X			X			X		X
Plasma citrulline[f]												X		X
Antibodies to teduglutide[g]												X		X
Physical examination/ vital signs/weight			X			X			X			X		X
Height (or length) and head circumference[h]			X			X			X			X		X
Fecal occult blood testing[i]												X		
Colonoscopy/ sigmoidoscopy[i]												(X)		
Electrocardiogram												X		X

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET)a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/ procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.
(X)=as needed; EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; PN/IV=parenteral nutrition/intravenous fluid

[a] If a subject terminates from the study prematurely, all EOT procedures should be done at the time of termination and a follow-up visit should be scheduled 4 weeks later.

[b] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[c] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[d] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately 5-7 days following any adjustment to the PN/IV prescription. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[e] All female subjects of child-bearing potential will be tested for pregnancy (urine testing).

[f] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9).

[g] Blood draw to test for antibodies to teduglutide before the last dose of teduglutide, at least 14 hours after the previous dose of teduglutide. If a blood sample is positive for antibodies at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

[h] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

[i] Subjects with positive fecal occult blood test at week 24 (EOT)/ET for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a confirmatory colonoscopy or sigmoidoscopy (Section 7.2.14.3).

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal disease that results in major surgical resections of the small intestine. In children, most cases of short bowel syndrome begin in infancy. Common causes of SBS in children include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis. (Duro et al. 2008; Squires et al. 2012) Similar to adults, new-onset SBS in older children usually stems from Crohn's disease, trauma, and cancer. The diminished absorptive capacity for fluids and nutrients often results in dependence on parenteral nutrition or intravenous fluids (PN/IV) to maintain energy and fluid and electrolyte homeostasis.

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

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

For this reason, research in the pediatric arena is focused on children with PN/IV-dependent SBS. Given intestinal adaption in younger children, the unmet medical need is the greatest in children who are 1 year of age and older. It is highly unlikely that children with less than 10% of the expected length of small intestine reach enteral independence. These subjects reach a plateau in their ability to advance oral/enteral feeds or decrease PN/IV support (ie, are "stuck") and are not expected to achieve spontaneous adaptation. Subjects who have not progressed to full enteral adaptation by 12 months after their intestinal insults are very unlikely to demonstrate spontaneous improvement in their enteral function. (Sigalet et al. 2011)

1.2 Product Background and Clinical Information

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

There are no approved pharmacological therapies that promote intestinal adaptation in children with SBS. In the US and Europe, a GLP-2 analog called teduglutide is approved for the treatment of SBS in adult patients who are dependent on PN/IV support.

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. (Thymann et al. 2014; Tappenden et al. 2013)

Clinical Studies

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

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

Study CL0600-020 was a randomized, double-blind, placebo-controlled study in which subjects were randomized to teduglutide 0.05 mg/kg/day or placebo on a 1:1 ratio. The first stage of the study included a screening and optimization period and a stabilization period that demonstrated stable administration of PN/IV volume for a minimum of 4 weeks up to a maximum of 8 weeks. The second stage was a dosing period of 24 weeks. Subjects on 0.05 mg/kg/day teduglutide achieved a higher responder rate (defined as a 20% to 100% reduction from baseline in PN/IV volume at weeks 20 and 24) than the placebo-treated subjects (27/43 subjects [62.8%] versus

13/43 subjects [30.2%], respectively).
This difference was clinically and statistically significant in both the intent-to-treat (ITT) ($p=0.002$) and per-protocol ($p < 0.001$) populations. Generally, the incidence of treatment-emergent AEs was distributed similarly across all treatment groups. The treatment-emergent AEs with a higher incidence in the teduglutide group were mainly of GI origin. A long-term, open-label extension study (CL0600-021) assessed safety and efficacy for up to 24 additional months (ie, up to 30 months of exposure for subjects who received teduglutide in Study CL0600-020). Overall, 30 of 43 subjects who received teduglutide in Study CL0600-020 and entered Study CL0600-021 completed a total of 30 months of treatment with teduglutide. Of these, 28 subjects (93%) achieved a 20% or greater reduction of 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 CL0600-020. PN/IV use was reduced by at least 1 day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 3.11 L/week from baseline at the start of Study CL0600-021 (a 28% reduction). Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. Of the 12 subjects entering Study CL0600-021 directly, 6 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 4.0 L/week (a 39.4% reduction from baseline at the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of parenteral support.

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

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

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

Additional information is provided in the investigator's brochure.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Clinical Study

Teduglutide was designated as an orphan drug indicated for SBS in Japan on 20 Nov 2014. Based on national surveys, it is estimated that the number of subjects with SBS who are dependent on parenteral nutrition/intravenous fluid (PN/IV) is less than 1000 in Japan. (Takagi et al. 1995; Takehara 2001; Kitajima et al. 2013) Among the 195 SBS subjects in the 2011 survey, 99 (51%) developed SBS at <1 years old. Early intervention could potentially improve intestinal adaptation and decrease the need for parenteral support in these patients.

The current study proposes to investigate the safe and appropriate use of teduglutide in the Japanese pediatric population for the purpose of providing pharmacokinetic, pharmacodynamic, and safety data. This protocol was developed similarly to the planned EU/US study, TED-C14-006, 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*. The TED-C14-006 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 teduglutide dose of 0.05 mg/kg daily is supported by results from the completed 12-week pediatric study. Teduglutide is approved for adult use in the US and EU at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric study (TED-C13-003, *A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support*) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population pharmacokinetics (PK) modeling and simulations were conducted to determine the effective dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phases 1, 2, and 3 studies as well as the pediatric study (TED-C13-003); they suggested that the dose in pediatric subjects is likely to be the same as the dose in adults. (O'Keefe et al. 2006) The duration of teduglutide treatment in study SHP633-302 mirrors that of the TED-C14-006 study, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period.

The aim of teduglutide treatment is to increase absorptive capacity in order to yield decreases in parenteral support. In addition, the experts anticipated that there would be several direct benefits from decreased parenteral support and advances in enteral feeds, 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.

2.2 Objective(s)

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and PK of teduglutide in pediatric subjects (1 year through 15 years of age) with SBS who are dependent on parenteral support. See Sections 9.8 and 9.10.1 for further details of the endpoints being measured, and Section 9.9 for safety variables.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. 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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The end of study (EOS) visit will be scheduled at week 28, 4 weeks following end of treatment (EOT). Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support. The Study Schedules (Table 1 and Table 2) are displayed at the beginning of this protocol.

A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and provided in Appendix 2 and Appendix 3, respectively) 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. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

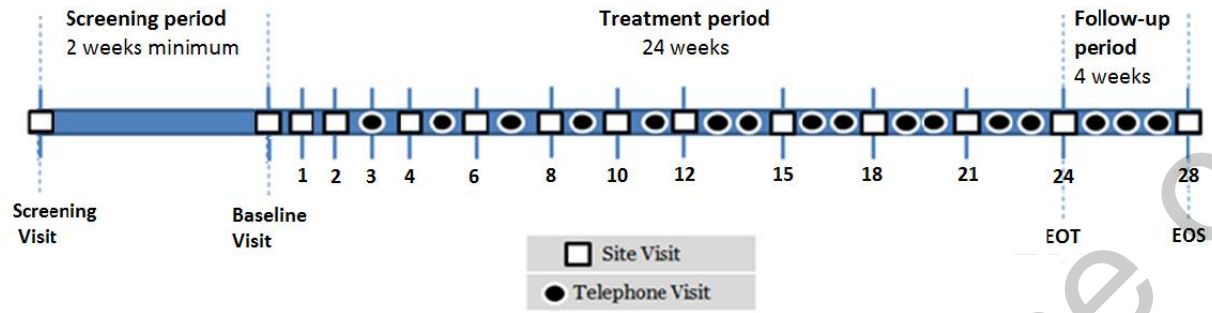
At the conclusion of the follow-up period (week 28), if subjects are determined to have positive/specific antibodies, they will be asked to return for a follow-up visit 3 months post EOT for another antibody sample. If the subjects continue to have positive/specific antibodies at 3 months post EOT, they will be asked to return for follow-up visit(s) up to 6 months post-treatment in order to determine their antibody status.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) which will convene approximately every 3 months during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible subjects could receive teduglutide.

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

Figure 1 Study Diagram



EOS=end of study; EOT=end of treatment

3.2 Study Duration

There will be, at a minimum, a 2-week screening period from the time of the screening visit to the baseline visit, followed by 24 weeks of treatment. Attempts should be made to limit the screening period to 4 weeks. The EOS visit will be scheduled at week 28, 4 weeks after the EOT visit (week 24).

The start of the clinical phase is defined as first subject consented. The end of the clinical phase is defined as the last visit of the last subject.

3.3 Sites and Regions

This study will be conducted at approximately 5 investigational sites in Japan.

4 STUDY POPULATION

Approximately 5 pediatric Japanese subjects, male and female children and adolescents aged 1 year through 15 years, will be enrolled.

4.1 Inclusion Criteria

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

1. Informed consent by a parent or guardian prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product

4.2 Exclusion Criteria

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

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on upper GI series done within 6 months prior to screening

7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic GLP-2
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 SBS-related or PN-related hospital admissions (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <10 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period, indicative by any of the following laboratory test results:
    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2x ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2

22. Parent(s)/guardian(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Table 3 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	• Active IBD which requires chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months • Tufting or autoimmune enteropathy or microvillus inclusion disease • Untreated pre-malignant or malignant change in the GI tract identified by upper GI series, biopsy or polypectomy • Known polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome) • Intestinal or other major surgery scheduled within the time frame of the study • Chronic active pancreatitis • Cholecystitis
Immune	• Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency)
Psychiatric	• Alcohol or drug abuse 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)

GI=gastrointestinal; IBD=inflammatory bowel disease

4.3 Reproductive Potential

Sexually active females of childbearing potential must be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 4 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception if they become sexually active during the period of the study and 4 weeks following the last dose of investigational product.

Female children and adolescent subjects should be either:

Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or

Females of childbearing potential with a negative serum β-HCG pregnancy test at the screening visit (visit 1) and a negative urine β-HCG pregnancy test prior to enrollment. Females of childbearing potential must agree to abstain from sexual activity (ie, true abstinence) that could result in pregnancy or agree to use medically acceptable methods of contraception at all times during the study and 4 weeks following the last dose of investigational product.

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

4.4 Discontinuation of Subjects

4.4.1 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified without prejudice to further treatment. However, a discussion should be held by the investigator and the Shire medical monitor or designee prior to the subject discontinuing or withdrawing.

4.4.2 Reasons for Discontinuation

- Reasons for discontinuation may include but are not limited to:
- Adverse event
- Death
- Failure to meet enrollment criteria
- Lost to follow-up
- Non-compliance with investigational product
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problems
- Withdrawal by parent/guardian

- Withdrawal by subject

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 8.1.

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

4.4.3 Subjects "Lost to follow-up" Prior to Last Scheduled Visit

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

5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including non-prescription herbal treatments, vitamins, invasive and diagnostic procedures) received within 14 days prior to the screening visit (visit 1) and through the end of study (ie, including the protocol-defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Treatment

Prior treatment includes all treatment received within 14 days of the first dose of investigational product, but discontinued before the first dose of investigational product.

5.2 Concomitant Treatment

Concomitant medications are those that continue after the start of investigational product or are newly introduced after the start of treatment through the end of study. In all instances the start date of prior and concomitant therapies must be recorded to the extent possible.

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, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

Changes in any medication and/or dosage will be recorded on the eCRF. See also nutritional support in Section 7.2.15.2.

5.3 Prohibited Treatment

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 following prior therapies are excluded within the timeframes noted (see Section 4.2).

Prior Therapy	Time Restriction Prior to Screening
Native/synthetic glucagon-like peptide-2	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy used to treat inflammatory bowel disease (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

Teduglutide for subcutaneous (SC) injection is provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide as a lyophilized powder that must be reconstituted using 0.5 mL with sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the investigator's brochure.

6.1.1 Blinding of the Treatment Assignment

Not applicable.

6.1.2 Administration of Investigational Product

A dose of 0.05 mg/kg/day of teduglutide will be administered once daily to the subjects for 24 weeks. The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with the Shire medical monitor or designee.

Following reconstitution, teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Each day, the injection site should be rotated. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later. Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

The subject should be dosed at approximately the same time each day. If a dose is delayed, that day's dose should be administered as soon as possible, but consecutive doses should be separated by at least 12 hours.

6.1.2.1 Administration by Parent/Guardian

The first dose of teduglutide will be administered by a study physician and the subject is observed for possible hypersensitivity reactions for at least 4 hours during their initial dosing visit.

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

After the study physician certifies that the parent/guardian can safely administer the study drug, subsequent doses may be administered by the parent/guardian at home without direct supervision by the physician. However, at selected study visits during the dosing period (refer to Table 1), administration of the study drug must be performed under direct supervision by the study physician, and the teduglutide administration checklist must be completed again. This ensures that the parent/guardian continues to administer the study drug correctly and safely throughout the dosing period.

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

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

Criteria to Initiate Teduglutide Administration by the Parent/Guardian:

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

Criteria to Discontinue Teduglutide Administration by the Parent/Guardian:

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

6.1.3 Allocation of Subjects to Treatment

This is an open-label study; all subjects will receive teduglutide 0.05 mg/kg/day as described in Section 6.1.2. Subject numbers are assigned to all subjects as consent/assent to take part in the study is provided. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. These numbers will be used to identify the subjects throughout the study period. Once a number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

6.2 Labeling, Packaging, and Storage

6.2.1 Labeling and Packaging

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

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

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

6.2.2 Storage

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2 and 8^{o}C until dispensed to a subject. The pre-filled sterile water for injection syringes will be stored at a temperature between 2 and 25°C. Once dispensed/supplied to a subject, the investigational product can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25^{o}C). Parent/guardian will be instructed to keep the subject's investigational product and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the investigational product may be refrigerated.

6.3 Drug Accountability

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

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

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

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

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

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

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

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

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

See the Pharmacy Manual for additional information.

6.4 Treatment Compliance

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

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

Compliance is considered to be achieved if the subject has 80% of the planned doses administered. Subjects falling outside of these parameters will not be included in the per-protocol efficacy analyses (see Section 9.6).

7 STUDY PROCEDURES

7.1 Study Schedule

Subject evaluations will be performed during the indicated days and weeks of the study as provided in the Study Schedules (Table 1 and Table 2).

All data collected are to be recorded on the appropriate eCRF.

Details for study procedures including sample collection are described in the Operations Manual for this study.

7.1.1 Screening

All subjects' parents/guardians must sign an informed consent form and, if applicable, subjects must sign an informed assent form prior to initiation of any study-related procedure. All subjects will be screened for a minimum of 2 weeks. Attempts should be made to limit the screening period to 4 weeks.

Subjects will be designated as a screen failure if they fail to meet all inclusion criteria and/or meet any of the exclusion criteria. Screen failures will not be administered investigation product.

At the discretion of the investigator, subjects who fail screening may be re-screened one time with prior sponsor approval. In the event of re-screening, a new subject number will be assigned to the subject and the subject will also be re-consented.

7.1.2 Treatment Period

Subjects who meet all eligibility criteria at screening, and eligibility criteria are confirmed at visit 2/baseline, will be enrolled in the study and will receive the first dose of investigational product at the baseline visit (visit 2). Subjects will enter a 24-week treatment period consisting of either visits or scheduled weekly telephone contacts as outlined in the Section 3.1.

7.1.3 Follow-up Period

During the 4-week follow-up period, weekly telephone visits will be conducted on week 25 to week 27 followed by the EOS visit (week 28). Similar to assessments performed during the treatment period, phone visits during follow-up will include review of intake diaries, and adjustment of nutritional support as needed (see Section 3.1). Procedures to be performed at the EOS visit (week 28) are specified in the Study Schedules (Table 1 and Table 2); subjects will be queried on serious adverse events (SAEs), AEs, and concomitant treatments, and all AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

7.2 Study Evaluations and Procedures

7.2.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent (and, when applicable, informed assent) must be obtained from the subject's parent(s) or guardian(s) and from the subject (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject, the subject's parent(s), or the subject's guardian(s) by the investigator or designee in accordance with the guidelines described in Section 10.3.1. Documentation and filing of informed consent documents should be completed according to Section 10.2.

7.2.2 Study Entrance Criteria

At screening, each subject will be reviewed for eligibility against the study entrance criteria by the investigator or designee. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.2.3 Confirmation of Study Eligibility

Subject eligibility according to the study inclusion and exclusion criteria will be confirmed at baseline by the investigator or designee on the basis of review of the study entrance criteria.

7.2.4 Demographics and Other Baseline Characteristics

Demographic and/or other baseline variables obtained at the screening and/or baseline visits 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 (including surgical history)
- SBS history, including remnant anatomy
- GI-specific symptoms history (Section 7.2.15.1)
- Physical examination, including body weight, height (or length), and head circumference (up to 36 months of age), and trends on growth charts
- Vital signs including temperature, heart rate, and blood pressure
- Prior medications (medications used within 14 days prior to screening and discontinued prior to the first dose of investigational product), including drug name, dose, route, reason for use, and therapy dates. Medications used during the treatment period (after the first dose of investigational product) will be recorded as concomitant medications.
- Electrocardiogram (ECG) (12-lead) variables include general findings (normal/ abnormal, not clinically significant/ abnormal, clinically significant). The cause of any clinically significant ECG will be specified.

- Laboratory test results: biochemistry, hematology, coagulation, and urinalysis
- Plasma citrulline levels
- Presence of antibodies to teduglutide and titer level, if present
- Gastrointestinal imaging/testing (upper GI series with small bowel follow-through [UGI/SBFT], abdominal ultrasound, colonoscopy or sigmoidoscopy, fecal occult blood)
- Pregnancy testing for females of childbearing potential
- Nutritional support prescriptions (eg, PN/IV and enteral nutrition [EN] volume and calories, PN/IV hours per day and days per week) (Section 7.2.15.2)
- Nutritional support diary data (Section 7.2.15.3)

7.2.5 Pharmacokinetic Assessments

Pharmacokinetic assessments are listed in Section 9.10.1.

Blood samples for teduglutide concentrations will be collected at the baseline and week 4 visits. If blood samples are not/cannot be collected at week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product. A schedule of PK sample collection is provided in Table 4. Instructions for sample collection and handling are included in the Laboratory Manual.

Table 4 Blood Sample Collection Schedule for Pharmacokinetic Testing

Study week	Baseline			Week 4		
Visit Number	2			6		
Hour	0[a]	1	6	0[a]	2	4

[a] Prior to investigational product administration

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

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose (at the week 4 draw).
- 1-hour postdose draw: ±10 minutes
- 2-hour postdose draw: ±10 minutes
- 4-hour postdose draw: ±30 minutes
- 6-hour postdose draw: ±30 minutes

At PK timepoints, the date and time of investigational product administration and blood collection must be recorded on the eCRF.

7.2.6 Physical Examination (Including Height and Weight)

Physical examinations will be performed, and body weight, height (or length), and head circumference (up to 36 months of age) measured according to the Study Schedules (Table 1 and Table 2).

Physical examinations will be performed by the investigator during the study to assess the subject's physical status. New clinically significant abnormalities that are detected or diagnosed after study evaluations have begun (after signing of the informed consent) should be recorded on the appropriate AE page of the eCRF.

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

Body mass index (BMI) and z-scores for weight, height (or length), head circumference, and BMI will be calculated by the sponsor.

7.2.7 Vital Signs

Vital signs will be measured according to the Study Schedules (Table 1 and Table 2). Measurements will include body temperature (°C), heart rate (beats per minute), and systolic and diastolic blood pressure (mmHg). Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study).

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

7.2.8 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing according to the Study Schedules (Table 1 and Table 2). Subjects should be in a seated or supine position during blood collection.

Laboratory collections required at intervals that do not coincide with site visits (safety laboratory assessments eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site.

Clinical laboratory tests will include the following (see Table 5):

Table 5 List of Laboratory Tests

Hematology:	Biochemistry:
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Platelet count	Alanine aminotransferase

Table 5 List of Laboratory Tests

Red blood cell (RBC) count	Amylase
RBC morphology, if needed	Aspartate aminotransferase
White blood cell count with differential	Bicarbonate
Coagulation:	Bilirubin (total, direct, and indirect)
Prothrombin time/International normalized ratio will be measured in all subjects at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected (Section 8.4.2)	Blood urea nitrogen
	Calcium (total)
	Chloride
Urinalysis:	Cholesterol
Blood	Citrulline (plasma)
Glucose	C-reactive protein
Leucocytes	Creatinine
Microscopic analysis	Estimated glomerular filtration rate (Schwartz formula)
pH	Gamma-glutamyl transferase
Protein	Glucose
Specific gravity	Lipase
Pregnancy tests (females of childbearing potential):	Magnesium
Serum β-HCG (screening)	Phosphorus
Urine β-HCG (all other visits)	Potassium
	Sodium
	Triglycerides
	Uric acid

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

7.2.9 Plasma Citrulline

Plasma citrulline levels will be measured as a biomarker of enterocyte mass. Blood samples will be collected 2 to 4 hours postprandial, whenever possible, at the timepoints specified in the Study Schedules (Table 1 and Table 2). Samples may be drawn from a central line or peripheral access and processed according to instructions in the Laboratory Manual.

7.2.10 Antibody Assessments

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the baseline visit (day 0) and at least 14 hours after the previous dose at the EOT visit (week 24 or early termination); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, week 28 or EOS).

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

7.2.11 Pregnancy Testing

Any female subject of childbearing potential (Section 4.3) must have negative pregnancy tests to enroll or continue in the study. Pregnancy tests will be performed at screening (serum β-HCG testing) and at all site visits (urine β-HCG testing).

7.2.12 Volume of Blood

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

The amount of blood to be drawn may vary according to instructions provided by the manufacturer or laboratory for an individual assessment. When more than one blood assessment is to be done at the same timepoint, the assessments should be combined if they require the same type of tube.

7.2.13 Electrocardiogram

Twelve-lead ECGs will be performed in accordance with the clinical site's standard practice(s) as indicated in the Study Schedules (Table 1 and Table 2). Electrocardiogram recordings will be read locally by an experienced physician. Results (normal; abnormal, not clinically significant; and abnormal, clinically significant with a description of the abnormality) will be recorded on the eCRF.

7.2.14 Gastrointestinal-specific Testing

Gastrointestinal testing will be performed as needed for all subjects during the screening period, as indicated in sections 7.2.14.1 to 7.2.14.4. Follow-up testing will be performed as needed according to the guidelines noted in sections 7.2.14.1 to 7.2.14.4 and the Study Schedules (Table 1 and Table 2).

7.2.14.1 Upper Gastrointestinal Series with Contrast

An UGI/SBFT will be performed following the ingestion of barium contrast material during the screening period. Results from procedures performed within 6 months prior to visit 1 will also be acceptable.

7.2.14.2 Abdominal Ultrasound

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

7.2.14.3 Fecal Occult Blood Testing

Fecal occult blood testing will be performed at screening, week 12, and week 24 (EOT).

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

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

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

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

7.2.14.4 Colonoscopy/Sigmoidoscopy

Subjects who are 12 years and older will undergo a colonoscopy or sigmoidoscopy at screening. If the fecal occult blood testing is negative at screening and the procedure was performed within 1 year before the screening visit (visit 1), then those prior results are acceptable for the screening assessment.

Children younger than 12 years will undergo the procedure if they test positive for fecal occult blood at screening and the cause is not identified by physical examination (see Section 7.2.14.3).

Requirements for colonoscopy or sigmoidoscopy in response to positive fecal occult blood testing at weeks 12 or 24 are presented in Section 7.2.14.3.

7.2.15 Other Study Procedures

7.2.15.1 GI-specific Symptoms History

GI symptoms during the screening period will be recorded by the subject/parent/guaridan representative in a GI-specific symptoms history diary on a daily basis. At the baseline visit, the investigator will review the GI-symptoms diary and summarize the findings.

7.2.15.2 Nutritional Support

Nutritional support includes PN/IV and EN. Advances in enteral nutrition and/or reductions to PN/IV support will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2 and Appendix 3, respectively.

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

7.2.15.3 Diaries

The subject/parent/guardian/study site staff will complete the appropriate fields of the PN/IV and EN (formula) sections of the intake diary.

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

PN/IV volume and infusion duration

EN (formula) volume

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

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

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

      At the discretion of the investigator, the parent may be asked to collect the first void after the daily PN/IV infusion to measure specific gravity.
- Stool data (includes diapers with mixed urine and stool)
    - *Toilet-trained subjects (who do not wear diapers)*
      Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see output diary)
    - *Nontoilet-trained subjects (who wear diapers)*
      Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (see output diary). Stool volume will be calculated using the formula: 1 g (scale weight) = 1 mL or 1 cc

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

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

8 ADVERSE AND SERIOUS ADVERSE EVENT ASSESSMENTS

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

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

All AEs are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

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

8.1.1 Severity Categorization

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

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

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

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

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

8.1.4 Symptoms of the Disease Under Study

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

8.1.5 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent/assent is signed until the defined follow-up period stated in Section 3.2.

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

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

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

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

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Administration of a dose greater than the allocated dose of investigational product or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

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

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

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

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

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

8.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2 and must be reported to Quintiles Transnational Japan K.K within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

Quintiles Transnational Japan K.K is responsible for notifying the relevant regulatory authorities/central institutional review boards (IRBs)/ethics committees (ECs) of related, unexpected SAEs. In addition the sponsor and/or designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the teduglutide program.

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

8.3 Adverse Events of Special Interest

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

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

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

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

8.4 Dose Interruption of Individual Subjects

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

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

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to the investigational product. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE listed in Table 6 that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to the investigational product administration (see Section 8.4.1)
- Confirmed drug-induced liver injury (DILI) related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Known Risks of Teduglutide

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

Investigators and the DMC should be guided by the descriptions of Grade 3 and 4 events, as they relate to identified risks associated with the administration of teduglutide (see Table 6).

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	>5.0 to 20.0x ULN	>20.0x ULN
Blood bilirubin increased	>3.0 to 10.0x ULN	>10.0x ULN
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Lipase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

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

8.4.2 Dose Interruption Criteria Based on Drug-induced Liver Injury

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

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

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. INR should be measured with this set of verification laboratory assessments and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin M [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

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

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

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

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

or

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

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

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

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

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Shire Global Pharmacovigilance and Risk Management database.

9.3 Statistical Analysis Process

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

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. Accordingly, no claims of significance will be made for any of the data.

Continuous variables 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.

All statistical analyses will be performed using SAS®.

9.4 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis or adaptive design.

9.4.1 Data Monitoring Committee

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

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

Safety and tolerability results will be evaluated by a DMC which will convene approximately 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), based on subject enrollment. The DMC review will include all cumulative safety data from study assessment through the end of each review period.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility of this orphan population in children in Japan, rather than power calculation.

9.6 Study Population

Subjects are considered enrolled in the study when they meet all eligibility criteria at screening and eligibility criteria are confirmed at visit 2/baseline.

The ITT population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least 1 administration of investigational product with any safety follow-up. The primary population analyzed for

efficacy/PD will be the ITT population.
An additional per-protocol population analysis will also be performed as secondary/sensitivity analysis. The per-protocol population is defined as the subset of subjects in the ITT population without a major protocol deviation. Details will be prospectively defined in the final SAP prior to database lock.

The PK analysis population is defined as all subjects in the safety analysis population for whom the primary PK data are considered sufficient and interpretable.

9.7 Demographics and Baseline Characteristics

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

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

Medical history (including surgical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

9.8 Efficacy/Pharmacodynamic Analyses

The efficacy/PD endpoints include:

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

No formal statistical test will be performed due the limited sample size.

Continuous variables 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.

9.9 Safety Analyses

The safety and tolerability variables include:

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

Adverse events will be coded using MedDRA. Treatment-emergent AEs will be summarized by system organ class and preferred term. The number and percentage of subjects with AEs, SAEs, AEs that lead to discontinuation, investigational product-related AEs (determined by the investigator), and AEs that resulted in a fatal outcome will be summarized. AEs will also be summarized with regard to intensity and relationship to investigational product. For AEs of special interest, the CTCAE grading system will be used as described in Section 8.4.1.

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

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

9.10 Other Analyses

9.10.1 Pharmacokinetic Analyses

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

- Area under the plasma concentration-time curve (AUC) of zero to infinity ($_{0–inf}$)
- AUC from zero to the last measurable concentration (AUC_{0-t})

- AUC at steady state (AUC_{ss})
- Maximum plasma concentration (C_{max})
- C_{max} at steady state ($C_{max,ss}$)
- Minimum plasma concentration at steady state ($C_{min,ss}$)
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{\lambda z}/F$)

Descriptive statistics for PK parameters (mean, median, standard deviation, minimum and maximum values, geometric mean) will be calculated.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Public Posting of Study Information

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

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

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

Original source data to be reviewed during this study will include, but are not limited to subject's medical file, subject diaries, and original clinical laboratory reports, and imaging reports. All key data must be recorded in the subject's medical records.

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

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

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the Pharmaceuticals and Medical Devices Agency) or an auditor.

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

10.2.3.3 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator or designee to obtain written informed consent from all subjects or parents/guardians, and assent from subjects where applicable, prior to any study-

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

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

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

10.3.2 Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent/assent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation. Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

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

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

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

10.4 Privacy and Confidentiality

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

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

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

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

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

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

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

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

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

11 LIST OF REFERENCES

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12 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	18 Dec 2015	Global
Amendment 1	27 Apr 2016	Global
Amendment 2	06 Jun 2017	Global
Amendment 3	24 Jan 2018	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date 06 Jun 2017**	**Global**
Description of Change		**Section(s) Affected by Change**
The Pharmacovigilance SAE Reporting fax number and email address have been updated. A sentence has been removed from the emergency contact information to eliminate a redundancy with the information provided under the Pharmacovigilance SAE Reporting heading (Protocol Administrative Change Memo #2, dated 24 Aug 2016). The title of Andrew Grimm MD PhD is now Medical Director and his email address has been changed.		Protocol Signature Page Emergency Contact Information
Urine osmolality (Protocol Administrative Change Memo #1, dated 10 Aug 2016) and urine sodium have been removed from the list of urinalysis parameters to be tested. Neither parameters are needed as safety parameters nor required for the decision to adjust a subject's nutritional support.		Table 5
Clarification that biological therapy prohibited during teduglutide treatment and within 6 months prior to the pretreatment visit refers to biological therapy used to treat inflammatory bowel disease.		Section 5.3
Clarification that subjects, and/or any designated person who will be administering the investigational product, will be trained on investigational product preparation and administration before the first dose of teduglutide or the implementation of any change in ancillary kit components.		Section 6.1.2
Language on contents of ancillary kits has been revised.		Section 6.2.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Age range for subjects has been specified. Subjects will be 1 year through 15 years of age.		Title page Protocol signature page Synopsis Sections 4 and 4.1
Emergency contact information has been updated.		Emergency Contact Information Sections 8.1.6, 8.2.2, 8.2.4
Clarification that departing from the nutritional support adjustment guidelines and weaning algorithms in Appendix 2 and Appendix 3, respectively, will not constitute a protocol deviation.		Synopsis Section 3.1
Statement added that subjects who complete the study may participate in a long-term extension study in which eligible subjects could receive teduglutide.		Synopsis Section 3.1
Inclusion and Exclusion criteria have been refined and clarified; there were no criteria added with the exception of the age of subject population which has been added as an inclusion criterion (was previously in introductory sentence).		Synopsis Sections 4.1 and 4.2
Exclusion Criterion #11 has been updated to indicate that a subject would be excluded from the study if the subject had participated in a clinical study of experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.		Synopsis Section 4.2
Efficacy/PD endpoints have been lumped together and clarified. The small population does not warrant primary versus secondary endpoints. The statistical method has been clarified.		Synopsis Section 9.8
Safety assessments and statistical methods have been clarified.		Synopsis Section 9.9
Study schedule of events tables have been revised to reflect the changes to the protocol and for clarity.		Table 1 Table 2
Any phone contacts may be replaced with unscheduled site visits if necessary.		Table 1 Table 2 Section 3.1
Requirement added that female subjects of child-bearing potential undergo a serum-based pregnancy test at screening.		Table 1 Table 2 Sections 4.3, 7.2.8, 7.2.11
Definition of prior and concomitant medications has been expanded to include invasive and diagnostic procedures.		Table 1 Table 2 Section 5
Additional information on selection of teduglutide dosing regimen and duration in the study has been inserted.		Section 2.1
Frequency of Data Monitoring Committee meetings has been specified.		Sections 3.1 and 9.4.1
Definition of screening period has been clarified.		Section 3.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Inflammatory bowel disease that requires chronic systemic immunosuppressant therapy for symptom control has been removed from the list of excluded disease and illness in Exclusion Criterion #24.		Section 4.2 (Table 3)
Definition of acceptable methods of contraception has been revised to reflect available methods in Japan.		Section 4.3
List of prohibited prior therapy has been revised to remove experimental antibody treatment, as it is now included in the revised exclusion criterion #11.		Section 5.3
Requirement that teduglutide should be administered in the morning has been removed.		Section 6.2
Language on labeling, packaging, and drug accountability has been clarified.		Sections 6.3 and 6.4
Reviewing subject diaries has been included in the subject compliance with dosing check. Clarification that attempts should be made by the investigator to contact the sponsor or designee prior to dose interruption has been added.		Section 6.5
Requirement has been added that subjects who are re-screened must be re-consented.		Section 7.1.1
Timeframe for a subject to be considered enrolled in the study has been clarified.		Sections 7.1.2 and 9.6
Demographics and other baseline characteristics have been clarified.		Section 7.2.4
Windows for PK blood collection have been extended; possibility to collect week 4 timepoint at any future visit if needed has been added.		Section 7.2.5
PT/INR testing has been added at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected thereafter.		Table 1 Table 2 Section 7.2.8
For children in diapers, urine specimen collection should be attempted as part of the safety lab assessments, but lack of urinalysis will not constitute a protocol deviation.		Table 1 Table 2 Section 7.2.8
Timeframe of follow-up for subjects with blood samples testing positive for anti-teduglutide antibodies at week 28 or EOS has been clarified.		Synopsis Table 1 Table 2 Section 7.2.10
Need for a subject with a positive fecal occult blood testing at week 12 without a readily identifiable cause by physical examination to undergo a colonoscopy or sigmoidoscopy is now open to discussion with the Shire medical monitor or designee.		Table 1 Table 2 Section 7.2.14.3
Need for children younger than 12 years to undergo a colonoscopy or sigmoidoscopy if they test positive for fecal occult blood at screening and the cause is not identified by physical examination has been specified.		Section 7.2.14.4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
GI symptoms history worksheet has been renamed GI-specific symptoms history diary, and details on recording and reviewing symptoms have been added.		Table 1 Table 2 Section 7.2.15.1
"Other nutrition (regular diet and drink)" has been removed from the Intake diary.		Section 7.2.15.2
Output diary data collection will continue to occur over a 48-hour period of PN/IV and EN stability before every site visit. Between site visits, the output diary collection will only be required within 1 week of implementing a change in the PN/IV prescription.		Table 1 Table 2 Section 7.2.15.3
Severity categorization has been updated to specify that the severity of AEs listed in Table 6 that may lead to dose interruption based on known risks of teduglutide will also be evaluated using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria.		Section 8.1.1
Definition of an overdose to teduglutide has been revised.		Section 8.1.7
Adverse events of special interest have been redefined and procedures for reporting them have been added.		Section 8.3
More information has been provided on criteria for dose interruption of individual subjects. Dose discontinuation has been made absolute for an AE known to be a risk associated with teduglutide administration (Table 6) that is of NCI CTCAE severity ≥Grade 3 and considered to be related to investigational product; cases of severe hypersensitivity that are determined to be related to investigational product; DILI that is related to investigational product; and pregnancy. SAEs related to investigational product are potential but not absolute reasons for dose discontinuation.		Sections 8.4, 8.4.1, and 8.4.2
Criteria for DILI have been added.		Section 8.4.2
Criteria for early termination of the study have been clarified.		Section 8.5
Clarification that original diary data should be entered into the eCRF and take precedence over data collected over the phone.		Section 9.1
Definition of PK analysis population has been added.		Section 9.6
Pharmacokinetic analyses methods and parameters have been clarified.		Synopsis Section 9.10.1
Protocol history has been added in Appendix 1.		Appendix 1
Guidelines for nutritional support management during the study have been clarified.		Appendix 2

APPENDIX 2 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY (SHP633-302)

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

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

APPENDIX 3 WEANING ALGORITHMS

Figure A-1 Weaning Algorithm for Subjects Who Are Not Toilet-trained and in Diapers

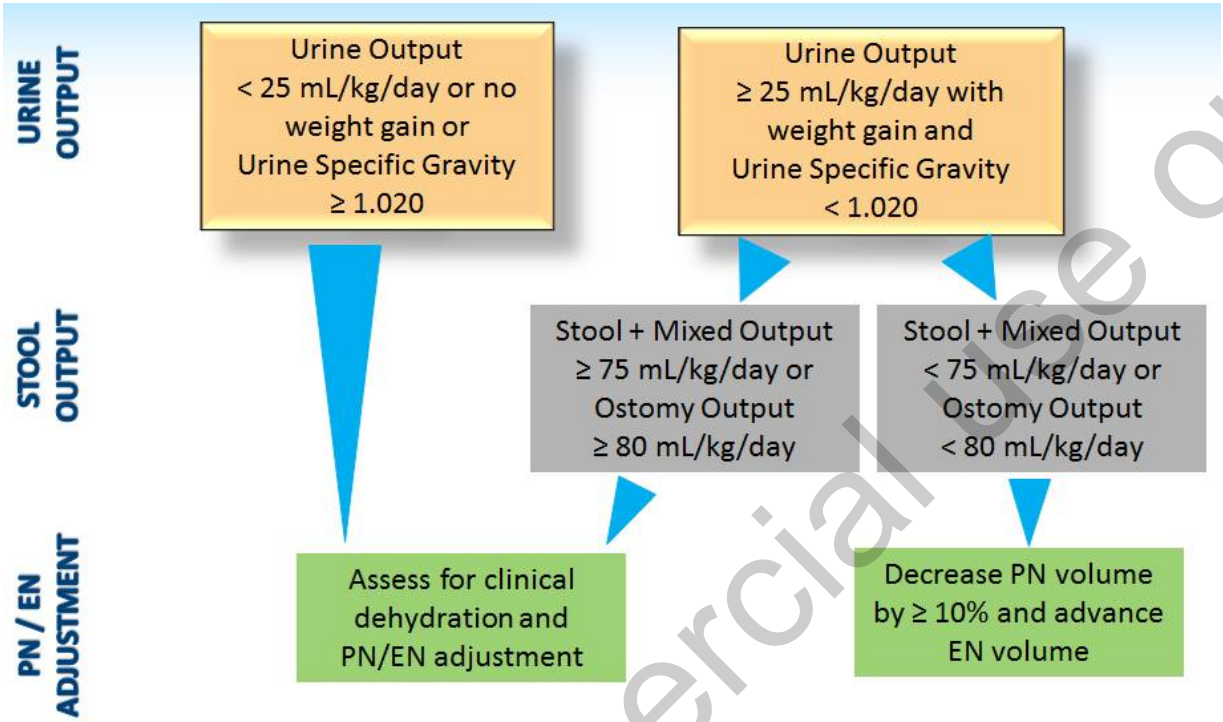


Figure A-2 Subjects Who Are Toilet-trained and Not in Diapers

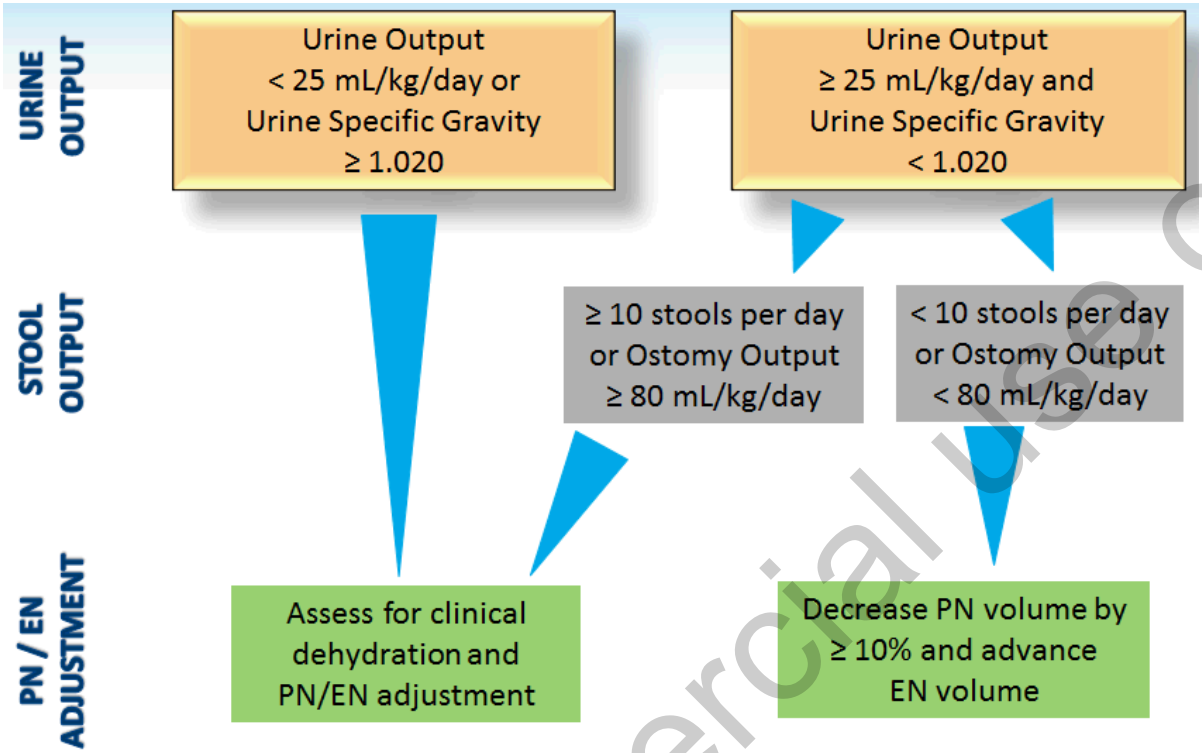
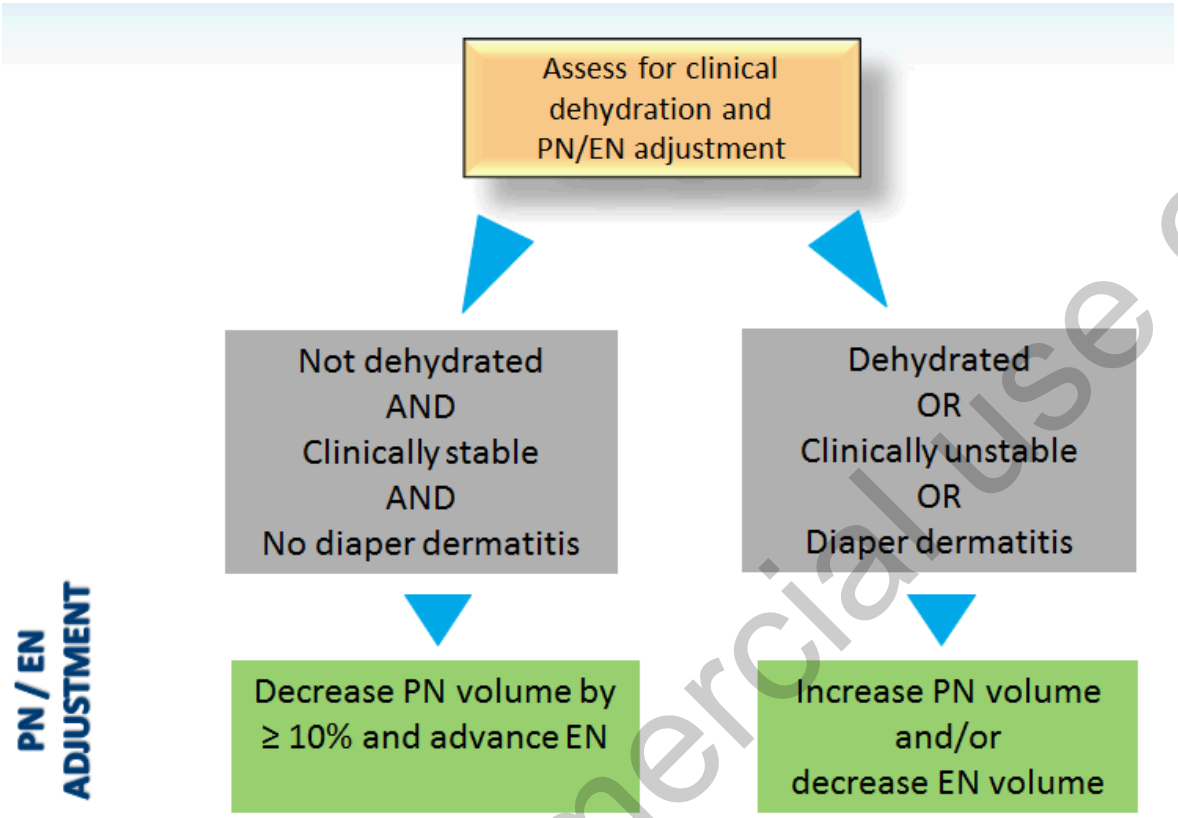


Figure A-3 Clinical Dehydration Assessment and PN/EN Adjustment



CLINICAL TRIAL PROTOCOL: SHP633-302

TITLE:	A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support
NUMBER:	SHP633-302
PHASE:	3
DRUG:	Teduglutide
IND:	058213
OTHER NO.:	NA
INDICATION:	Short bowel syndrome
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA [redacted]
PROTOCOL HISTORY:	Amendment 4: 12 Jun 2018 Amendment 3: 24 Jan 2018 Amendment 2: 06 Jun 2017 Amendment 1: 27 Apr 2016 Original Protocol: 18 Dec 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

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

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-302.

Title: A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

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

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

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

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

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

Investigator Name and Address:

(please hand print or type) _____

_____

Signature: _____ Date: _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **Amendment 4**	**Amendment Date** **12 Jun 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Added enrollment of a minimum of 2 infants (4 to <12 months corrected gestational age) to the protocol due to medical need.		Title Page; Protocol Signature Page, Study Synopsis, Section 2.2, Section 3.1, Section 4, Section 4.1
Changed Quintiles Transnational Japan K.K. to IQVIA Services Japan K.K to reflect a corporate name change.		Emergency Contact Information, Section 8.1.6, Section 8.2.2, Section 8.2.4, Section 8.2.7, Section 8.3
Clarified that planned enrollment is a minimum of 5 subjects aged 1 through 15 years.		Study Synopsis, Section 4
Updated Inclusion Criterion #6 to define stable PN/IV for infants.		Study Synopsis, Section 4.1
Updated Exclusion Criterion #6 to clarify that the subject will be excluded if there is evidence of a clinically significant obstruction in the most recent upper gastrointestinal series done within 6 months prior to screening.		Study Synopsis, Table 1, Section 4.2, Section 7.2.14.1
Updated Exclusion Criterion #9 to specify that subjects with known cancer predisposition syndrome will also be excluded.		Study Synopsis, Section 4.2
Updated Exclusion Criteria #17 & 18 to remove references to hospitalizations in order not to exclude infants who are frequently chronically hospitalized.		Study Synopsis, Section 4.2
Updated Exclusion Criterion #19 to exclude subjects <5 kg.		Study Synopsis, Section 4.2
Added infant specific laboratory values to Exclusion Criterion #20. Removed the criteria for Gilbert's disease as it was redundant.		Study Synopsis, Section 4.2
Specified that fecal occult blood testing was not required for infants.		Study Synopsis, Table 1, Section 7.2.4, Section 7.2.14.3
Specified that abdominal ultrasound was not required for infants.		Study Synopsis, Table 1, Section 7.2.4, Section 7.2.14.2
Specified that colonoscopy or sigmoidoscopy was not required for infants and that an upper endoscopy may be performed along with any colonoscopy at the discretion of the investigator.		Study Synopsis, Table 1, Table 2, Section 7.2.4, Section 7.2.14.4
Specified that PK samples may be reduced in smaller children for who blood sampling may impose an unacceptable phlebotomy volume.		Table 1, Section 7.2.5
Specified that results for infant subjects will be analyzed separately from those over 12 months of age.		Study Synopsis, Section 9.3
A planned interim analysis after completion of study participation of children 1-15 years of age has been added.		Section 9.4.1
Updated the details of the population PK analysis to be conducted.		Study Synopsis, Section 9.10.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **Amendment 4**	**Amendment Date** **12 Jun 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Specified that safety labs at phone visits are at the discretion of the investigator for infants.		Table 1, Table 2, Section 7.2.8
Specified that plasma citrulline will not be collected from infants.		Table 1, Table 2, Section 7.2.4, Section 7.2.9
Added the contact information for the monitoring personnel.		Appendix 4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event, the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to IQVIA Services Japan K.K. using the details below.

Pharmacovigilance SAE Reporting:

FAX: [redacted] or [redacted] (Japan domestic line only)
or
Email: [redacted]

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

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

For protocol- or safety-related issues between 8:00 to 20:00 US Eastern Standard Time, the investigator may contact the Shire medical monitor:

[redacted], MD, PhD, FAAP
Clinical Development Physician
Phone: [redacted]
Mobile: [redacted]
Email: [redacted]

In-country Clinical Caretaker:

[redacted]:
IQVIA Services Japan K.K.
Phone: [redacted]
Email: [redacted]
Fax: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

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

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

Telephone numbers (provided for reference, if needed):

Shire, Lexington, MA (USA)
[redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{ss}	AUC at steady state
BMI	body mass index
$C_{max,ss}$	C_{max} at steady state
$C_{min,ss}$	minimum plasma concentration at steady state
CL/F	apparent clearance
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
EC	ethics committee
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-2	glucagon-like peptide 2
IBD	inflammatory bowel disease

ICH	International Conference on Harmonisation
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NCI	National Cancer Institute
PD	pharmacodynamic
PK	pharmacokinetic
PN	parenteral nutrition
PN/EN	parenteral nutrition/ intravenous fluids and enteral nutrition
PN/IV	parenteral nutrition/intravenous fluids
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
$t_{1/2}$	terminal-phase half-life
t_{max}	time to C_{max}
UGI/SBFT	upper GI series with small bowel follow-through
ULN	upper limit of normal
US	United States
$V_{\lambda z}/F$	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP633-302 **Drug:** Teduglutide

Study Title:

A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

Number of subjects:

Planned enrollment is a minimum of 5 subjects aged 1 through 15 years and a minimum of 2 subjects of 4 to <12 months corrected gestational age.

Sites and Regions: Approximately 5 investigational sites in Japan are planned.

Study Duration:

There will be, at a minimum, a 2-week screening period followed by 24 weeks of treatment. The end of study (EOS) visit will be scheduled at week 28, 4 weeks after the end of treatment (EOT) visit (week 24).

Investigational Product, Dose, and Mode of Administration:

During the treatment period, a dose of 0.05 mg/kg/day of teduglutide will be administered once daily subcutaneously (SC) to the subjects.

The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with Shire medical monitor or designee.

The first dose of teduglutide will be administered by a study physician. The processes for training the parent/guardian to administer teduglutide and for providing oversight of study drug administration are described in the Site Training Guide.

Objective(s):

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in pediatric subjects (4 months through 15 years of age) with short bowel syndrome (SBS) who are dependent on parenteral support.

Study Design:

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. The study population will include two cohorts: infants 4-<12 months corrected gestational age and children 1-15 years of age.

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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The EOS visit will be scheduled at week 28, 4 weeks following EOT. Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and to be provided in the protocol) for decisions regarding parenteral nutrition/intravenous fluids (PN/IV) support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

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 continue 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.

Safety and tolerability results will be evaluated by a Data Monitoring Committee periodically during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible subjects could receive teduglutide.

Study Inclusion and Exclusion Criteria:

Subjects who satisfy the following inclusion and exclusion criteria will be enrolled in the study.

Inclusion Criteria

1. Informed consent by a parent or guardian prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female infant 4-<12 months corrected gestational age or child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as:

   For infants 4 to <12 months corrected gestational age:

   Inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 1 month prior to and during screening, as assessed by the investigator.

   For children 1 to 15 years of age:

   Inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator.

   Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product

Exclusion Criteria

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support
4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on the most recent upper gastrointestinal (GI) series done within 6 months prior to screening
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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 nonaggressive and surgically resected cancer. Subjects with known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of GI cancer (including hepatobiliary and pancreatic cancer) will also be excluded.
10. Pregnant or lactating female subjects
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic glucagon-like peptide-2 (GLP-2)
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 serious complications of SBS (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. A serious complication that affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <5 kg at screening and baseline visits
20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period:

    For infants 4 to <12 months corrected gestational age at least 2 of any of the following parameter:

    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/μL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
    e. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 μmol/L) over a 2 week period

    For children 1 to 15 years of age:

    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN
21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate below 50 mL/min/1.73 m^2
22. Parent(s)/guardian(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Pharmacokinetic Variables:

Blood samples for drug concentrations will be collected at the baseline visit (predose, at 1 and 6 hours postdose) and at week 4 visit (predose, 2 and 4 hours postdose). If blood samples are not/cannot be collected at week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product.

The following PK parameters will be derived using a population PK modeling approach and reported separately:

- Area under the concentration-time curve at steady-state ($AUC_{tau,ss}$)

- Maximum plasma concentration at steady-state ($C_{max,ss}$)
- Minimum plasma concentration at steady-state ($C_{min,ss}$)
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{\lambda z}/F$)

Efficacy/Pharmacodynamic Assessments:

The efficacy/PD endpoints include:

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

Safety Assessments:

Safety and tolerability will be assessed by evaluating the following:

- Adverse events, including those pertaining to GI symptoms.
- Physical examinations, including body weight, height (or length), head circumference (up to 36 months of age), and trends on growth charts
- Vital signs, including temperature, heart rate, blood pressure
- Electrocardiograms (ECGs)
- Laboratory safety data (ie, biochemistry, hematology, coagulation, urinalysis)
- Urine output
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- For children 1 to 15 years of age: GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through (UGI/SBFT).
  For infants 4 to <12 months corrected gestational age: UGI/SBFT.

Safety and tolerability will be evaluated by a Data Monitoring Committee during the study period.

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.

Pharmacokinetic parameters will be estimated based on measured teduglutide plasma concentrations using a population PK modeling approach and reported separately.

Continuous variables 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.

Efficacy/PD data will include change in PN/IV support, enteral nutritional support, plasma citrulline, and hours per day and days per week of PN/IV support, and will be summarized by visit.

Safety data will include clinical laboratory tests results; measurement of body weight, height (or length), and head circumferences (if applicable); vital signs; concomitant medications; and ECG monitoring; and will be summarized by visit. Adverse events will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Data will be analyzed and presented by subject cohorts. The infant cohort will be analyzed in a manner analogous to the pediatric cohort unless specified otherwise.

STUDY SCHEDULES

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	**≥-14**	**0**		**7 ±2**	**14 ±2**	**21 ±3**	**28 ±3**	**35 ±3**	**42 ±3**	**49 ±3**	**56 ±3**	**63 ±3**	**70 ±3**	**77 ±3**	**84 ±3**
Informed consent/assent[a]	X														
Eligibility	X	X													
Demographics	X														
Medical /surgical history	X														
Electrocardiogram	X														X
SBS history	X														
Upper GI with small bowel follow-through and abdominal ultrasound[b]	X														
Fecal occult blood testing[c]	X														X
Colonoscopy/ sigmoidoscopy[c]	(X)														(X)
Provide GI-specific symptoms history diary	X														
Review GI-specific symptoms history diary		X													
Dispense investigational product[d]		X		X	X		X		X		X		X		X
Confirm administration proficiency		X^n	X^n	X^n			X								X

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	**≥-14**	**0**	**7 ±2**	**14 ±2**	**21 ±3**	**28 ±3**	**35 ±3**	**42 ±3**	**49 ±3**	**56 ±3**	**63 ±3**	**70 ±3**	**77 ±3**	**84 ±3**
Pharmacokinetic sampling		X[e]				X[f]								
Safety laboratory tests[g]	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Pregnancy testing[h]	X	X	X	X		X		X		X		X		X
Plasma citrulline[i]		X												X
Antibodies to teduglutide[j]		X												
Provide intake and output diaries	X	X	X	X		X		X		X		X		X
Review diaries and nutritional support[k]		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[l]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Physical examination/ vital signs/weight	X	X	X	X		X		X		X		X		X
Height (or length) and head circumference[m]	X	X				X				X				X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(X)=as needed; eCRF=electronic case report form; EN=enteral nutrition; FOBT=fecal occult blood testing; GI=gastrointestinal; PK=pharmacokinetic; PT/INR=prothrombin time/international normalized ratio; PN/IV=parenteral nutrition/intravenous fluids; SBS=short bowel syndrome; SC=subcutaneous; UGI/SBFT= upper GI series with small bowel follow through

Table 1 Study Schedule of Events – Screening to Week 12

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 ±window (days)	≥-14	0	7 ±2	14 ±2	21 ±3	28 ±3	35 ±3	42 ±3	49 ±3	56 ±3	63 ±3	70 ±3	77 ±3	84 ±3

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

[b] If the subject has undergone an UGI/SBFT and/or an abdominal ultrasound within the 6 months before visit 1 (screening), then those test results will be acceptable for the screening assessments. However, if the most recent UGI/SBFT prior to screening shows evidence of obstruction, the UGI/SBFT should be repeated during screening. The procedure(s) are to be performed any time after providing informed consent with the results available and reviewed before the baseline visit (day 0). Abdominal ultrasound will not be performed for infant subjects.

[c] Fecal occult blood test (FOBT) and colonoscopy are not to be performed for infant subjects. Subjects over 12 months of age will have FOBT after providing consent/assent. Those with positive FOBT at screening for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy. Colonoscopy or sigmoidoscopy will be conducted at screening on all subjects 12 years of age and older; however if the screening FOBT is negative and the subject has undergone the procedure within 1 year before visit 1 (screening), then that result will be acceptable for the screening assessment (Section 7.2.14.4). Positive FOBT results at week 12 should be discussed with the medical monitor. Upper endoscopy may be performed along with any colonoscopy at the discretion of the investigator (Section 7.2.14.3).

[d] 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) must be specified and recorded in the eCRF. The dose of study medication may be adjusted at week 12.

[e] Baseline (visit 2) samples for PK analysis will be drawn predose, and 1 hour ± 10 minutes and 6 hours ± 30 minutes postdose (Section 7.2.5).

[f] Week 4 (visit 6) samples for PK analysis will be drawn predose, and 2 hours± 10 minutes and 4 hours± 30 minutes postdose (Section 7.2.5). If blood samples are not/cannot be collected at Week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product. In smaller children for whom blood sampling may impose unacceptable phlebotomy volume, the number of PK samples may be reduced.

[g] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. For children over 12 months of age, safety labs must be performed approximately 5 to 7 days following any adjustment to the PN/IV prescription. For infants, safety labs at phone visits are at the discretion of the investigatory. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[h] All female subjects of child-bearing potential will be tested for pregnancy: serum testing at screening; urine testing thereafter.

[i] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9). Plasma citrulline will not be collected from infant subjects.

[j] Blood sample for antibody testing is to be collected at study site prior to first investigational product administration. Blood samples may be drawn from a central line or peripheral access (Section 7.2.10).

[k] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study by the subject or parent/guardian/study site staff (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[l] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[m] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

[n] The first dose of teduglutide will be administered by a study physician. The study physician must observe the parent/guardian administer the study drug in compliance with the study drug administration checklist at least twice before the parent/guardian is allowed to administer the drug without direct observation by the physician. Refer to Section 6.1.2.1.

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit.
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET)a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Dispense investigational product			X			X			X					
Provide intake and output diaries			X			X			X			X		
Review diaries and nutritional support[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support[c]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety laboratory tests[d]	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	(X)	X	(X)	X
Pregnancy testing[e]			X			X			X			X		X
Plasma citrulline[f]												X		X
Antibodies to teduglutide[g]												X		X
Physical examination/ vital signs/weight			X			X			X			X		X
Height (or length) and head circumference[h]			X			X			X			X		X
Fecal occult blood testing[i]												X		
Colonoscopy/ sigmoidoscopy[i]												(X)		
Electrocardiogram												X		X

Table 2 Study Schedule of Events – Weeks 13 to 28

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/ET)a	Weeks 25, 26, 27	Week 28 (or EOS)
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-29**	**30**
Visit type	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Phone**	**Site**	**Phone**	**Site**
Study day ±window (days)	**91 ±3**	**98 ±3**	**105 ±3**	**112 ±3**	**119 ±3**	**126 ±3**	**133 ±3**	**140 ±3**	**147 ±3**	**154 ±3**	**161 ±3**	**168 ±3**	**175, 182, 189 ±3**	**196 ±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/ procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(X)=as needed; EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; PN/IV=parenteral nutrition/intravenous fluid

[a] If a subject terminates from the study prematurely, all EOT procedures should be done at the time of termination and a follow-up visit should be scheduled 4 weeks later.

[b] The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 7.2.15.3). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every site visit and within 1 week of each change in PN/IV prescription. (Section 7.2.15.3 for more details). Nutritional support includes PN/IV and EN (formula) (Section 7.2.15.2).

[c] Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Appendix 2 and Appendix 3, respectively.

[d] Safety lab assessments at site visits will consist of biochemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits (eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. For children over 12 months of age, safety labs must be performed approximately 5 to 7 days following any adjustment to the PN/IV prescription. For infants, safety labs at phone visits are at the discretion of the investigator. PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

[e] All female subjects of child-bearing potential will be tested for pregnancy (urine testing).

[f] Blood samples for measuring citrulline levels will be collected 2 to 4 hours postprandial, whenever possible, and may be drawn from a central line or from peripheral access (Section 7.2.9). Plasma citrulline will not be collected from infant subjects.

[g] Blood draw to test for antibodies to teduglutide before the last dose of teduglutide, at least 14 hours after the previous dose of teduglutide. If a blood sample is positive for antibodies at week 28 or EOS, then the subject will be retested 3 months after EOT. If that sample is positive, then the subject will be retested 6 months after EOT.

[h] Head circumference will be measured in subjects 36 months of age and younger (Section 7.2.6).

[i] Fecal occult blood test (FOBT) and colonoscopy are not to be performed for infant subjects enrolled. Subjects over 12 months of age with positive FOBT at week 24 (EOT)/ET for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a confirmatory colonoscopy or sigmoidoscopy. Upper endoscopy may be performed along with any colonoscopy at the discretion of the investigator (Section 7.2.14.3).

Note: A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit
Unshaded columns indicate that the site will contact the subject by telephone; shaded columns indicate the subject visits to the site.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal disease which results in major surgical resections of the small intestine. In children, most cases of SBS begin in infancy. Common causes of SBS in children include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis. (Duro et al., 2008; Squires et al., 2012) Similar to adults, new-onset SBS in older children usually stems from Crohn's disease, trauma, and cancer. The diminished absorptive capacity for fluids and nutrients often results in dependence on parenteral nutrition or intravenous fluids (PN/IV) to maintain energy and fluid and electrolyte homeostasis.

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

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

For this reason, research in the pediatric arena is focused on children with PN/IV-dependent SBS. Given intestinal adaption in younger children, the unmet medical need is the greatest in children who are 1 year of age and older. It is highly unlikely that children with less than 10% of the expected length of small intestine reach enteral independence. These subjects reach a plateau in their ability to advance oral/enteral feeds or decrease PN/IV support (ie, are "stuck") and are not expected to achieve spontaneous adaptation. Subjects who have not progressed to full enteral adaptation by 12 months after their intestinal insults are very unlikely to demonstrate spontaneous improvement in their enteral function. (Sigalet et al., 2011)

1.2 Product Background and Clinical Information

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

There are no approved pharmacological therapies that promote intestinal adaptation in children with SBS. In the US and Europe, a GLP-2 analog called teduglutide is approved for the treatment of SBS in adult patients who are dependent on PN/IV support.

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. (Thymann et al., 2014; Tappenden et al., 2013)

Clinical Studies

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

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

Study CL0600-020 was a randomized, double-blind, placebo-controlled study in which subjects were randomized to teduglutide 0.05 mg/kg/day or placebo on a 1:1 ratio. The first stage of the study included a screening and optimization period and a stabilization period that demonstrated stable administration of PN/IV volume for a minimum of 4 weeks up to a maximum of 8 weeks. The second stage was a dosing period of 24 weeks. Subjects on 0.05 mg/kg/day teduglutide achieved a higher responder rate (defined as a 20% to 100% reduction from baseline in PN/IV

volume at weeks 20 and 24) than the placebo-treated subjects (27/43 subjects [62.8%] versus 13/43 subjects [30.2%], respectively).

This difference was clinically and statistically significant in both the intent-to-treat (ITT) ($p=0.002$) and per-protocol ($p < 0.001$) populations. Generally, the incidence of treatment-emergent AEs was distributed similarly across all treatment groups. The treatment-emergent AEs with a higher incidence in the teduglutide group were mainly of GI origin. A long-term, open-label extension study (CL0600-021) assessed safety and efficacy for up to 24 additional months (ie, up to 30 months of exposure for subjects who received teduglutide in Study CL0600-020). Overall, 30 of 43 subjects who received teduglutide in Study CL0600-020 and entered Study CL0600-021 completed a total of 30 months of treatment with teduglutide. Of these, 28 subjects (93%) achieved a 20% or greater reduction of 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 CL0600-020. PN/IV use was reduced by at least 1 day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 3.11 L/week from baseline at the start of Study CL0600-021 (a 28% reduction). Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. Of the 12 subjects entering Study CL0600-021 directly, 6 completed 24 months of treatment with teduglutide. The mean reduction in PN/IV volume was 4.0 L/week (a 39.4% reduction from baseline at the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of parenteral support.

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

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

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

Additional information is provided in the investigator's brochure.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Clinical Study

Teduglutide was designated as an orphan drug indicated for SBS in Japan on 20 Nov 2014. Based on national surveys, it is estimated that the number of subjects with SBS who are dependent on parenteral nutrition/intravenous fluid (PN/IV) is less than 1000 in Japan. (Takagi et al., 1995; Takehara, 2001; Kitajima et al., 2013) Among the 195 SBS subjects in the 2011 survey, 99 (51%) developed SBS at <1 years old. Early intervention could potentially improve intestinal adaptation and decrease the need for parenteral support in these patients.

The current study proposes to investigate the safe and appropriate use of teduglutide in the Japanese pediatric population for the purpose of providing pharmacokinetic (PK), pharmacodynamic (PD), and safety data. This protocol was developed similarly to the planned EU/US study, TED-C14-006, 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. The TED-C14-006 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 teduglutide dose of 0.05 mg/kg daily is supported by results from the completed 12-week pediatric study. Teduglutide is approved for adult use in the US and EU at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric study (TED-C13-003, A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population PK modeling and simulations were conducted to determine the effective dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phases 1, 2, and 3 studies as well as the pediatric study (TED-C13-003); they suggested that the dose in pediatric subjects is likely to be the same as the dose in adults. (O'Keefe et al., 2006) The duration of teduglutide treatment in study SHP633-302 mirrors that of the TED-C14-006 study, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period.

The aim of teduglutide treatment is to increase absorptive capacity in order to yield decreases in parenteral support. In addition, the experts anticipated that there would be several direct benefits from decreased parenteral support and advances in enteral feeds, 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.

2.2 Objective(s)

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and PD, and PK of teduglutide in pediatric subjects (4 months through 15 years of age) with SBS who are dependent on parenteral support. See Sections 9.8 and 9.10.1 for further details of the endpoints being measured, and Section 9.9 for safety variables.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. The study population will include 2 cohorts: infants 4-<12 months corrected gestational age and children 1-15 years of age.

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. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks (weeks 1 and 2), and then every other week through week 12 (weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at weeks 15, 18, 21, and 24). Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The end of study (EOS) visit will be scheduled at week 28, 4 weeks following end of treatment (EOT). Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support. The Study Schedules (Table 1 and Table 2) are displayed at the beginning of this protocol.

A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and provided in Appendix 2 and Appendix 3, respectively) 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. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

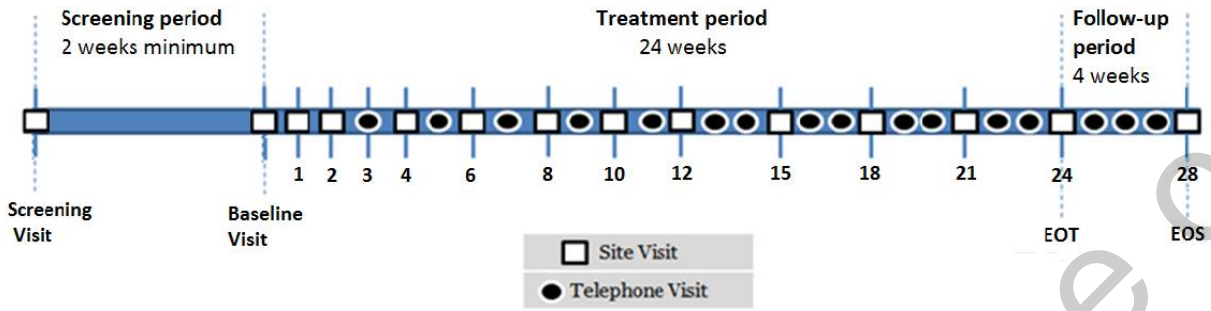
At the conclusion of the follow-up period (week 28), if subjects are determined to have positive/specific antibodies, they will be asked to return for a follow-up visit 3 months post EOT for another antibody sample. If the subjects continue to have positive/specific antibodies at 3 months post EOT, they will be asked to return for follow-up visit(s) up to 6 months post-treatment in order to determine their antibody status.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) which will convene approximately every 3 months during the active study period, based on subject enrollment.

All subjects who complete the study may participate in a long term extension study in which eligible subjects could receive teduglutide.

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

Figure 1 Study Diagram



EOS=end of study; EOT=end of treatment

3.2 Study Duration

There will be, at a minimum, a 2-week screening period from the time of the screening visit to the baseline visit, followed by 24 weeks of treatment. Attempts should be made to limit the screening period to 4 weeks. The EOS visit will be scheduled at week 28, 4 weeks after the EOT visit (week 24).

The start of the clinical phase is defined as first subject consented. The end of the clinical phase is defined as the last visit of the last subject.

3.3 Sites and Regions

This study will be conducted at approximately 5 investigational sites in Japan.

4 STUDY POPULATION

Planned enrollment is a minimum of 5 subjects aged 1 through 15 years and a minimum of 2 subjects of 4 to <12 months corrected gestational age.

4.1 Inclusion Criteria

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

1. Informed consent by a parent or guardian prior to any study-related procedures
2. When applicable, informed assent (as deemed appropriate by the Institutional Review Board) by the subject prior to any study-related procedures
3. Male or female infant 4 to <12 months corrected gestational age or child or adolescent aged 1 year through 15 years
4. Current history of SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)
5. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
6. Stable PN/IV support, defined as:

   For infants 4 to <12 months corrected gestational age:

   Inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 1 month prior to and during screening, as assessed by the investigator.

   For children 1 to 15 years of age:

   Inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator.

   Transient instability for events such as interruption of central access or treatment of sepsis is allowed if the PN/IV support returns to within 10% of baseline prior to the event.
7. Sexually active female subjects of childbearing potential must use medically acceptable methods of birth control during and for 4 weeks following the last dose of investigational product.

4.2 Exclusion Criteria

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

1. Subjects who are not expected to be able to advance oral or tube feeding regimens
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support

4. Unstable absorption due to cystic fibrosis or other known DNA abnormalities (eg, Familial Adenomatous Polyposis, Fanconi-Bickel syndrome)
5. Severe, known dysmotility syndrome such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility; that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
6. Evidence of clinically significant obstruction on the most recent upper GI series done within 6 months prior to screening.
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease or 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 nonaggressive and surgically resected cancer. Subjects with known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of GI cancer (including hepatobiliary and pancreatic cancer) will also be excluded.
10. Pregnant or lactating female subjects
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening and for the duration of the study
12. Previous use of teduglutide or native/synthetic GLP-2
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening
15. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit
16. Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than 3 serious complications of SBS (eg, documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit
18. A serious complication that affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject
19. Body weight <5 kg at screening and baseline visits

20. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period:

    For infants 4 to <12 months corrected gestational age at least 2 of any of the following parameters:

    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
    e. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period

    For children 1 to 15 years of age:

    a. Total bilirubin ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

21. Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate below 50 mL/min/1.73 m^2
22. Parent(s)/guardian(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Unstable, clinically significant, active, untreated pancreatic or biliary disease
24. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results. Examples of potential disease states/illnesses that may be excluded are listed in Table 3.

Table 3 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	• Active IBD which requires chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months • Tufting or autoimmune enteropathy or microvillus inclusion disease • Untreated pre-malignant or malignant change in the GI tract identified by upper GI series, biopsy or polypectomy • Known polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome) • Intestinal or other major surgery scheduled within the time frame of the study • Chronic active pancreatitis • Cholecystitis
Immune	• Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency)
Psychiatric	• Alcohol or drug abuse 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)

GI=gastrointestinal; IBD=inflammatory bowel disease

4.3 Reproductive Potential

Sexually active females of childbearing potential must be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 4 weeks following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception if they become sexually active during the period of the study and 4 weeks following the last dose of investigational product.

Female children and adolescent subjects should be either:

Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or

Females of childbearing potential with a negative serum β-HCG pregnancy test at the screening visit (visit 1) and a negative urine β-HCG pregnancy test prior to enrollment. Females of childbearing potential must agree to abstain from sexual activity (ie, true abstinence) that could result in pregnancy or agree to use medically acceptable methods of contraception at all times during the study and 4 weeks following the last dose of investigational product.

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

4.4 Discontinuation of Subjects

4.4.1 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified without prejudice to further treatment. However, a discussion should be held by the investigator and the Shire medical monitor or designee prior to the subject discontinuing or withdrawing.

4.4.2 Reasons for Discontinuation

- Reasons for discontinuation may include but are not limited to:
- Adverse event
- Death
- Failure to meet enrollment criteria
- Lost to follow-up
- Non-compliance with investigational product
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problems
- Withdrawal by parent/guardian
- Withdrawal by subject

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 8.1.

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

4.4.3 Subjects "Lost to follow-up" Prior to Last Scheduled Visit

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

5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including non-prescription herbal treatments, vitamins, invasive and diagnostic procedures) received within 14 days prior to the screening visit (visit 1) and through the end of study (ie, including the protocol-defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Treatment

Prior treatment includes all treatment received within 14 days of the first dose of investigational product, but discontinued before the first dose of investigational product.

5.2 Concomitant Treatment

Concomitant medications are those that continue after the start of investigational product or are newly introduced after the start of treatment through the end of study. In all instances the start date of prior and concomitant therapies must be recorded to the extent possible.

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, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

Changes in any medication and/or dosage will be recorded on the eCRF. See also nutritional support in Section 7.2.15.2.

5.3 Prohibited Treatment

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 following prior therapies are excluded within the timeframes noted (see Section 4.2).

Prior Therapy	Time Restriction Prior to Screening
Native/synthetic glucagon-like peptide-2	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy used to treat inflammatory bowel disease (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

Teduglutide for subcutaneous (SC) injection is provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide as a lyophilized powder that must be reconstituted using 0.5 mL of sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the investigator's brochure.

6.1.1 Blinding of the Treatment Assignment

Not applicable.

6.1.2 Administration of Investigational Product

A dose of 0.05 mg/kg/day of teduglutide will be administered once daily to the subjects for 24 weeks. The dose calculation will be based on body weight measured at the baseline visit (visit 2) and may be adjusted at week 12 (visit 14). No other adjustments to dose will be made during the study period, unless discussed with the Shire medical monitor or designee.

Following reconstitution, teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Each day, the injection site should be rotated. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later. Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

The subject should be dosed at approximately the same time each day. If a dose is delayed, that day's dose should be administered as soon as possible, but consecutive doses should be separated by at least 12 hours.

6.1.2.1 Administration by Parent/Guardian

The first dose of teduglutide will be administered by a study physician and the subject is observed for possible hypersensitivity reactions for at least 4 hours during their initial dosing visit.

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

After the study physician certifies that the parent/guardian can safely administer the study drug, subsequent doses may be administered by the parent/guardian at home without direct supervision by the physician. However, at selected study visits during the dosing period (refer to Table 1), administration of the study drug must be performed under direct supervision by the study physician, and the teduglutide administration checklist must be completed again. This ensures that the parent/guardian continues to administer the study drug correctly and safely throughout the dosing period.

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

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

Criteria to Initiate Teduglutide Administration by the Parent/Guardian:

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

Criteria to Discontinue Teduglutide Administration by the Parent/Guardian:

- The parent/guardian is unable to administer teduglutide in compliance with the checklist.
- The subject's condition has deteriorated such that the study physician assesses it is inappropriate for the subject to have teduglutide administered by their parent/guardian. In addition to discontinuing administration of teduglutide by the parent/guardian, if a subject sustains an adverse drug reaction where the symptoms are considered intolerable, dose interruption or study drug discontinuation should be considered (see Section 8.4).

- In the study physician's judgment, it is inappropriate for the parent/guardian to continue administration of the study drug for any other reason.

6.1.3 Allocation of Subjects to Treatment

This is an open-label study; all subjects will receive teduglutide 0.05 mg/kg/day as described in Section 6.1.2. Subject numbers are assigned to all subjects as consent/assent to take part in the study is provided. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. These numbers will be used to identify the subjects throughout the study period. Once a number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

6.2 Labeling, Packaging, and Storage

6.2.1 Labeling and Packaging

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

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

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

6.2.2 Storage

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2 and 8°C until dispensed to a subject. The pre-filled sterile water for injection syringes will be stored at a temperature between 2 and 25°C. Once dispensed/supplied to a subject, the investigational product can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25°C). Parent/guardian will be instructed to keep the subject's investigational product and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the investigational product may be refrigerated.

6.3 Drug Accountability

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

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

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

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

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

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

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

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

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

See the Pharmacy Manual for additional information.

6.4 Treatment Compliance

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

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

Compliance is considered to be achieved if the subject has 80% of the planned doses administered. Subjects falling outside of these parameters will not be included in the per-protocol efficacy analyses (see Section 9.6).

7 STUDY PROCEDURES

7.1 Study Schedule

Subject evaluations will be performed during the indicated days and weeks of the study as provided in the Study Schedules (Table 1 and Table 2).

All data collected are to be recorded on the appropriate eCRF.

Details for study procedures including sample collection are described in the Operations Manual for this study.

7.1.1 Screening

All subjects' parents/guardians must sign an informed consent form and, if applicable, subjects must sign an informed assent form prior to initiation of any study-related procedure. All subjects will be screened for a minimum of 2 weeks. Attempts should be made to limit the screening period to 4 weeks.

Subjects will be designated as a screen failure if they fail to meet all inclusion criteria and/or meet any of the exclusion criteria. Screen failures will not be administered investigation product.

At the discretion of the investigator, subjects who fail screening may be rescreened one time with prior sponsor approval. In the event of rescreening, a new subject number will be assigned to the subject and the subject will also be reconsented.

7.1.2 Treatment Period

Subjects who meet all eligibility criteria at screening, and eligibility criteria are confirmed at visit 2/baseline, will be enrolled in the study and will receive the first dose of investigational product at the baseline visit (visit 2). Subjects will enter a 24-week treatment period consisting of either visits or scheduled weekly telephone contacts as outlined in the Section 3.1.

7.1.3 Follow-up Period

During the 4-week follow-up period, weekly telephone visits will be conducted on week 25 to week 27 followed by the EOS visit (week 28). Similar to assessments performed during the treatment period, phone visits during follow-up will include review of intake diaries, and adjustment of nutritional support as needed (see Section 3.1). Procedures to be performed at the EOS visit (week 28) are specified in the Study Schedules (Table 1 and Table 2); subjects will be queried on serious adverse events (SAEs), AEs, and concomitant treatments, and all AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

7.2 Study Evaluations and Procedures

7.2.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent (and, when applicable, informed assent) must be obtained from the subject's parent(s) or guardian(s) and from the subject (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject, the subject's parent(s), or the subject's guardian(s) by the investigator or designee in accordance with the guidelines described in Section 10.3.1. Documentation and filing of informed consent documents should be completed according to Section 10.2.

7.2.2 Study Entrance Criteria

At screening, each subject will be reviewed for eligibility against the study entrance criteria by the investigator or designee. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.2.3 Confirmation of Study Eligibility

Subject eligibility according to the study inclusion and exclusion criteria will be confirmed at baseline by the investigator or designee on the basis of review of the study entrance criteria.

7.2.4 Demographics and Other Baseline Characteristics

Demographic and/or other baseline variables obtained at the screening and/or baseline visits 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 (including surgical history)
- SBS history, including remnant anatomy
- GI-specific symptoms history (Section 7.2.15.1)
- Physical examination, including body weight, height (or length), and head circumference (up to 36 months of age), and trends on growth charts
- Vital signs including temperature, heart rate, and blood pressure
- Prior medications (medications used within 14 days prior to screening and discontinued prior to the first dose of investigational product), including drug name, dose, route, reason for use, and therapy dates. Medications used during the treatment period (after the first dose of investigational product) will be recorded as concomitant medications.
- Electrocardiogram (ECG) (12-lead) variables include general findings (normal/ abnormal, not clinically significant/ abnormal, clinically significant). The cause of any clinically significant ECG will be specified.

- Laboratory test results: biochemistry, hematology, coagulation, and urinalysis
- Plasma citrulline levels will be obtained in subjects over 12 months of age
- Presence of antibodies to teduglutide and titer level, if present
- Gastrointestinal imaging/testing (Section 7.2.14)

  For children 1 to 15 years of age: GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through.

  For infants 4 to <12 months corrected gestational age: upper GI series with small bowel follow-through.
- Pregnancy testing for females of childbearing potential
- Nutritional support prescriptions (eg, PN/IV and enteral nutrition [EN] volume and calories, PN/IV hours per day and days per week) (Section 7.2.15.2)
- Nutritional support diary data (Section 7.2.15.3)

7.2.5 Pharmacokinetic Assessments

Pharmacokinetic assessments are listed in Section 9.10.1.

Blood samples for teduglutide concentrations will be collected at the baseline and week 4 visits. If blood samples are not/cannot be collected at Week 4, the uncollected samples can be collected during any future site visit while the subject is still on investigational product. In smaller children for whom blood sampling may impose unacceptable phlebotomy volume, the number of PK samples may be reduced. A schedule of PK sample collection is provided in Table 4. Instructions for sample collection and handling are included in the Laboratory Manual.

Table 4 Blood Sample Collection Schedule for Pharmacokinetic Testing

Study week	Baseline			Week 4		
Visit Number	2			6		
Hour	0[a]	1	6	0[a]	2	4

[a] Prior to investigational product administration

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

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose (at the week 4 draw).
- 1-hour postdose draw: ±10 minutes
- 2-hour postdose draw: ±10 minutes
- 4-hour postdose draw: ±30 minutes
- 6-hour postdose draw: ±30 minutes

At PK timepoints, the date and time of investigational product administration and blood collection must be recorded on the eCRF.

7.2.6 Physical Examination (Including Height and Weight)

Physical examinations will be performed, and body weight, height (or length), and head circumference (up to 36 months of age) measured according to the Study Schedules (Table 1 and Table 2).

Physical examinations will be performed by the investigator during the study to assess the subject's physical status. New clinically significant abnormalities that are detected or diagnosed after study evaluations have begun (after signing of the informed consent) should be recorded on the appropriate AE page of the eCRF.

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

Body mass index (BMI) and z-scores for weight, height (or length), head circumference, and BMI will be calculated by the sponsor.

7.2.7 Vital Signs

Vital signs will be measured according to the Study Schedules (Table 1 and Table 2). Measurements will include body temperature (°C), heart rate (beats per minute), and systolic and diastolic blood pressure (mmHg). Blood pressure should be determined by cuff (using the same method, the same extremity, and in the same position throughout the study).

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

7.2.8 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing according to the Study Schedules (Table 1 and Table 2). Subjects should be in a seated or supine position during blood collection.

Laboratory collections required at intervals that do not coincide with site visits (safety laboratory assessments eg, biochemistry and urinalysis following PN/IV adjustments) will be performed at the investigational site. For infants, safety labs at phone visits are at the discretion of the investigator.

Clinical laboratory tests will include the following (see Table 5):

Table 5 List of Laboratory Tests

Hematology:	Biochemistry:
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Platelet count	Alanine aminotransferase
Red blood cell (RBC) count	Amylase
RBC morphology, if needed	Aspartate aminotransferase
White blood cell count with differential	Bicarbonate
Coagulation:	Bilirubin (total, direct, and indirect)
Prothrombin time/International normalized ratio will be measured in all subjects at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected (Section 8.4.2)	Blood urea nitrogen
	Calcium (total)
	Chloride
	Cholesterol
Urinalysis:	Citrulline (plasma)
Blood	C-reactive protein
Glucose	Creatinine
Leucocytes	Estimated glomerular filtration rate (Schwartz formula)
Microscopic analysis	Gamma-glutamyl transferase
pH	Glucose
Protein	Lipase
Specific gravity	Magnesium
Pregnancy tests (females of childbearing potential):	Phosphorus
Serum β-HCG (screening)	Potassium
Urine β-HCG (all other visits)	Sodium
	Triglycerides
	Uric acid

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

7.2.9 Plasma Citrulline

Plasma citrulline levels will be measured as a biomarker of enterocyte mass. Blood samples will be collected 2 to 4 hours postprandial, whenever possible, at the timepoints specified in the Study Schedules (Table 1 and Table 2). Plasma citrulline will not be collected from infant subjects. Samples may be drawn from a central line or peripheral access and processed according to instructions in the Laboratory Manual.

7.2.10 Antibody Assessments

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the baseline visit (day 0) and at least 14 hours after the previous dose at the EOT visit (week 24 or early termination); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, week 28 or EOS).

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

7.2.11 Pregnancy Testing

Any female subject of childbearing potential (Section 4.3) must have negative pregnancy tests to enroll or continue in the study. Pregnancy tests will be performed at screening (serum β-HCG testing) and at all site visits (urine β-HCG testing).

7.2.12 Volume of Blood

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

The amount of blood to be drawn may vary according to instructions provided by the manufacturer or laboratory for an individual assessment. When more than one blood assessment is to be done at the same timepoint, the assessments should be combined if they require the same type of tube.

7.2.13 Electrocardiogram

Twelve-lead ECGs will be performed in accordance with the clinical site's standard practice(s) as indicated in the Study Schedules (Table 1 and Table 2). Electrocardiogram recordings will be read locally by an experienced physician. Results (normal; abnormal, not clinically significant; and abnormal, clinically significant with a description of the abnormality) will be recorded on the eCRF.

7.2.14 Gastrointestinal-specific Testing

Gastrointestinal testing will be performed as needed for all subjects during the screening period, as indicated in Sections 7.2.14.1 to 7.2.14.4. Follow-up testing will be performed as needed according to the guidelines noted in Sections 7.2.14.1 to 7.2.14.4 and the Study Schedules (Table 1 and Table 2).

7.2.14.1 Upper Gastrointestinal Series with Contrast

An upper GI series with small bowel follow-through (UGI/SBFT) will be performed following the ingestion of barium contrast material during the screening period. Results from procedures performed within 6 months prior to visit 1 will also be acceptable if the most recent results show no evidence of obstruction. If there is evidence of obstruction on the most recent UGI/SBFT prior to the study, this test should be performed during the screening period.

7.2.14.2 Abdominal Ultrasound

An abdominal ultrasound will be performed in subjects over 12 months of age. Results from procedures performed within 6 months prior to visit 1 will also be acceptable.

7.2.14.3 Fecal Occult Blood Testing

In subjects over 12 months of age, FOBT will be performed at screening, week 12, and week 24 (EOT). Fecal occult blood testing will not be performed in infants (age 4 months through 12 months corrected gestational age).

Subjects with positive fecal occult blood testing results at screening or at week 24 for whom a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy. Subjects with positive fecal occult blood testing results at week 12 for which a cause is not identified by a physical examination will be discussed with the medical monitor or designee. If clinically indicated, upper endoscopy may also be performed with any colonoscopy or sigmoidoscopy at the discretion of the investigator.

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

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

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

7.2.14.4 Colonoscopy/Sigmoidoscopy

Subjects who are 12 years and older will undergo a colonoscopy or sigmoidoscopy at screening. If the fecal occult blood testing is negative at screening and the procedure was performed within 1 year before the screening visit (visit 1), then those prior results are acceptable for the screening assessment.

Children over 12 months will undergo the procedure if they test positive for FOBT at screening and the cause is not identified by physical examination (see Section 7.2.14.3). Colonoscopy/sigmoidoscopy is not to be performed for infant subjects.

Requirements for colonoscopy or sigmoidoscopy in response to positive fecal occult blood testing at weeks 12 or 24 are presented in Section 7.2.14.3.

7.2.15 Other Study Procedures

7.2.15.1 GI-specific Symptoms History

GI symptoms during the screening period will be recorded by the subject/parent/guardian representative in a GI-specific symptoms history diary on a daily basis. At the baseline visit, the investigator will review the GI-symptoms diary and summarize the findings.

7.2.15.2 Nutritional Support

Nutritional support includes PN/IV and EN. Advances in enteral nutrition and/or reductions to PN/IV support will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2 and Appendix 3 respectively.

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

7.2.15.3 Diaries

The subject/parent/guardian/study site staff will complete the appropriate fields of the PN/IV and EN (formula) sections of the intake diary.

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

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

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

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

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

    At the discretion of the investigator, the parent may be asked to collect the first void after the daily PN/IV infusion to measure specific gravity.
- Stool data (includes diapers with mixed urine and stool)
  - *Toilet-trained subjects (who do not wear diapers)*
    Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see output diary)
  - *Nontoilet-trained subjects (who wear diapers)*
    Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (see output diary). Stool volume will be calculated using the formula: 1 g (scale weight) = 1 mL or 1 cc

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

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

8 ADVERSE AND SERIOUS ADVERSE EVENT ASSESSMENTS

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

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

All AEs are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

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

8.1.1 Severity Categorization

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

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

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

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

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

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy

data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

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

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

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

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent/assent is signed until the defined follow-up period stated in Section 3.2.

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

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

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

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

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Administration of a dose greater than the allocated dose of investigational product or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

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

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

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

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

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol and verify the

accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). The investigator must fax or e-mail the completed form to IQVIA Services Japan K.K. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover).

8.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent/assent is signed until the defined follow-up period stated in Section 3.2 and must be reported to IQVIA Services Japan K.K. within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the

event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

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

8.2.6 Fatal Outcome

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

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

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

IQVIA Services Japan K.K. is responsible for notifying the relevant regulatory authorities/central institutional review boards (IRBs)/ethics committees (ECs) of related, unexpected SAEs. In addition the sponsor and/or designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the teduglutide program.

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

8.3 Adverse Events of Special Interest

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

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

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

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

8.4 Dose Interruption of Individual Subjects

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

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

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to the investigational product. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE listed in Table 6 that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to the investigational product administration (see Section 8.4.1)
- Confirmed drug-induced liver injury (DILI) related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Known Risks of Teduglutide

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

Investigators and the DMC should be guided by the descriptions of Grade 3 and 4 events, as they relate to identified risks associated with the administration of teduglutide (see Table 6).

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	>5.0 to 20.0x ULN	>20.0x ULN
Blood bilirubin increased	>3.0 to 10.0x ULN	>10.0x ULN
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Lipase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN

Table 6 Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

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

8.4.2 Dose Interruption Criteria Based on Drug-induced Liver Injury

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

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

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. INR should be measured with this set of verification laboratory assessments and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin M [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

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

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

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

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

or

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

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

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

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

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

9.3 Statistical Analysis Process

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

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. Accordingly, no claims of significance will be made for any of the data.

Continuous variables 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.

Data will be analyzed and presented by subject cohorts. The infant cohort will be analyzed in a manner analogous to the pediatric cohort unless specified otherwise.

All statistical analyses will be performed using SAS®.

9.4 Planned Interim Analysis and Data Monitoring Committee

9.4.1 Planned Interim Analysis

An interim analysis of subjects 1-15 years of age will be performed at the completion of their participation.

9.4.2 Data Monitoring Committee

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

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

Safety and tolerability results will be evaluated by a DMC which will convene approximately 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), based on subject enrollment. The DMC review will include all cumulative safety data from study assessment through the end of each review period.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility of this orphan population in children in Japan, rather than power calculation.

9.6 Study Population

Subjects are considered enrolled in the study when they meet all eligibility criteria at screening and eligibility criteria are confirmed at visit 2/baseline.

The ITT population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least 1 administration of investigational product with any safety follow-up. The primary population analyzed for efficacy/PD will be the ITT population.

An additional per-protocol population analysis will also be performed as secondary/sensitivity analysis. The per-protocol population is defined as the subset of subjects in the ITT population without a major protocol deviation. Details will be prospectively defined in the final SAP prior to database lock.

The PK analysis population is defined as all subjects in the safety analysis population for whom the primary PK data are considered sufficient and interpretable.

9.7 Demographics and Baseline Characteristics

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

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

Medical history (including surgical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

9.8 Efficacy/Pharmacodynamic Analyses

The efficacy/PD endpoints include:

- Change (absolute and percent change) from baseline in PN/IV support (volume and calories), citrulline, and enteral nutritional support (volume and calories), separately, at each visit
- Reduction in PN/IV volume of at least 20% at week 24 (or EOT) compared to baseline
- 100% reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 (or EOT) compared to baseline
- ≥20% reduction in PN/IV volume at each visit
- Change (absolute and percent change) from week 24 (or EOT) in PN/IV support (volume and calories), citrulline, and enteral nutritional support (volume and calories), separately, to week 28 (or EOS)

- Change in hours per day and days per week of PN/IV support

No formal statistical test will be performed due the limited sample size.

Continuous variables 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.

9.9 Safety Analyses

The safety and tolerability variables include:

- Adverse events, including those pertaining to GI symptoms
- Body weight, height (or length), head circumference (up to 36 months of age), and trends on growth charts
- Vital signs, including temperature, heart rate, blood pressure
- Electrocardiograms
- Laboratory safety data (ie, biochemistry, hematology, coagulation, urinalysis) including the following lab tests at all site visits and interim safety labs to detect hepatotoxicity signals: AST, ALT, alkaline phosphatase (ALP), and bilirubin
- Urine output (measured volume)
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, UGI/SBFT

Adverse events will be coded using MedDRA. Treatment-emergent AEs will be summarized by system organ class and preferred term. The number and percentage of subjects with AEs, SAEs, AEs that lead to discontinuation, investigational product-related AEs (determined by the investigator), and AEs that resulted in a fatal outcome will be summarized. AEs will also be summarized with regard to intensity and relationship to investigational product. For AEs of special interest, the CTCAE grading system will be used as described in Section 8.4.1.

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

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

9.10 Other Analyses

9.10.1 Pharmacokinetic Analyses

The following PK parameters will be estimated based on measured teduglutide plasma concentrations using a population PK modeling approach and reported separately:

- Area under the concentration-time curve at steady state ($AUC_{tau,ss}$)
- Maximum plasma concentration at steady state ($C_{max,ss}$)
- Minimum plasma concentration at steady state ($C_{min,ss}$)
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{\lambda z}/F$)

Descriptive statistics for PK parameters (mean, median, standard deviation, minimum and maximum values, geometric mean) will be calculated.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Public Posting of Study Information

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

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

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

Original source data to be reviewed during this study will include, but are not limited to subject's medical file, subject diaries, and original clinical laboratory reports, and imaging reports. All key data must be recorded in the subject's medical records.

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

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

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the Pharmaceuticals and Medical Devices Agency) or an auditor.

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

10.2.3.3 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator or designee to obtain written informed consent from all subjects or parents/guardians, and assent from subjects where applicable, prior to any study-

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

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

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

10.3.2 Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent/assent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation. Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

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

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

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

10.4 Privacy and Confidentiality

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

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

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

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

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

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

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

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

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

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12 APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	18 Dec 2015	Global
Amendment 1	27 Apr 2016	Global
Amendment 2	06 Jun 2017	Global
Amendment 3	24 Jan 2018	Global
Amendment 4	12 Jun 2018	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date 24 Jan 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Updated the emergency contact information for the study.		Emergency Contact Information
Updated the product quality complaint section to address the drug delivery device.		Product Quality Complaints
Revised study drug administration language for clarity.		Section 6.1.2
As requested by PMDA, updated text to specify the process for training parent/guardian and measures to be taken to provide oversight on study drug administration.		Synopsis, Table 1, Section 6.1.2.1
Clarified that the study drug administration diary can be completed by study site staff.		Table 1, Section 6.4, Section 7.2.15.3
Added direct bilirubin to the list of laboratory tests.		Table 5
Replaced the term “legally authorized representative” with guardian.		Throughout protocol
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date 06 Jun 2017**	**Global**
Description of Change		**Section(s) Affected by Change**
The Pharmacovigilance SAE Reporting fax number and email address have been updated. A sentence has been removed from the emergency contact information to eliminate a redundancy with the information provided under the Pharmacovigilance SAE Reporting heading (Protocol Administrative Change Memo #2, dated 24 Aug 2016). The title of Andrew Grimm MD PhD is now Medical Director and his email address has been changed.		Protocol Signature Page Emergency Contact Information
Urine osmolality (Protocol Administrative Change Memo #1, dated 10 Aug 2016) and urine sodium have been removed from the list of urinalysis parameters to be tested. Neither parameters are needed as safety parameters nor required for the decision to adjust a subject’s nutritional support.		Table 5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** **06 Jun 2017**	**Global**
Description of Change		**Section(s) Affected by Change**
Clarification that biological therapy prohibited during teduglutide treatment and within 6 months prior to the pretreatment visit refers to biological therapy used to treat inflammatory bowel disease.		Section 5.3
Clarification that subjects, and/or any designated person who will be administering the investigational product, will be trained on investigational product preparation and administration before the first dose of teduglutide or the implementation of any change in ancillary kit components.		Section 6.1.2
Language on contents of ancillary kits has been revised.		Section 6.2.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Age range for subjects has been specified. Subjects will be 1 year through 15 years of age.		Title page Protocol signature page Synopsis Sections 4 and 4.1
Emergency contact information has been updated.		Emergency Contact Information Sections 8.1.6, 8.2.2, 8.2.4
Clarification that departing from the nutritional support adjustment guidelines and weaning algorithms in Appendix 2 and Appendix 3, respectively, will not constitute a protocol deviation.		Synopsis Section 3.1
Statement added that subjects who complete the study may participate in a long-term extension study in which eligible subjects could receive teduglutide.		Synopsis Section 3.1
Inclusion and Exclusion criteria have been refined and clarified; there were no criteria added with the exception of the age of subject population which has been added as an inclusion criterion (was previously in introductory sentence).		Synopsis Sections 4.1 and 4.2
Exclusion Criterion #11 has been updated to indicate that a subject would be excluded from the study if the subject had participated in a clinical study of experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.		Synopsis Section 4.2
Efficacy/PD endpoints have been lumped together and clarified. The small population does not warrant primary versus secondary endpoints. The statistical method has been clarified.		Synopsis Section 9.8
Safety assessments and statistical methods have been clarified.		Synopsis Section 9.9
Study schedule of events tables have been revised to reflect the changes to		Table 1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
the protocol and for clarity.		Table 2
Any phone contacts may be replaced with unscheduled site visits if necessary.		Table 1 Table 2 Section 3.1
Requirement added that female subjects of child-bearing potential undergo a serum-based pregnancy test at screening.		Table 1 Table 2 Sections 4.3, 7.2.8, 7.2.11
Definition of prior and concomitant medications has been expanded to include invasive and diagnostic procedures.		Table 1 Table 2 Section 5
Additional information on selection of teduglutide dosing regimen and duration in the study has been inserted.		Section 2.1
Frequency of Data Monitoring Committee meetings has been specified.		Sections 3.1 and 9.4.1
Definition of screening period has been clarified.		Section 3.2
Inflammatory bowel disease that requires chronic systemic immunosuppressant therapy for symptom control has been removed from the list of excluded disease and illness in Exclusion Criterion #24.		Section 4.2 (Table 3)
Definition of acceptable methods of contraception has been revised to reflect available methods in Japan.		Section 4.3
List of prohibited prior therapy has been revised to remove experimental antibody treatment, as it is now included in the revised exclusion criterion #11.		Section 5.3
Requirement that teduglutide should be administered in the morning has been removed.		Section 6.2
Language on labeling, packaging, and drug accountability has been clarified.		Sections 6.3 and 6.4
Reviewing subject diaries has been included in the subject compliance with dosing check. Clarification that attempts should be made by the investigator to contact the sponsor or designee prior to dose interruption has been added.		Section 6.5
Requirement has been added that subjects who are re-screened must be re-consented.		Section 7.1.1
Timeframe for a subject to be considered enrolled in the study has been clarified.		Sections 7.1.2 and 9.6
Demographics and other baseline characteristics have been clarified.		Section 7.2.4
Windows for PK blood collection have been extended; possibility to collect week 4 timepoint at any future visit if needed has been added.		Section 7.2.5
PT/INR testing has been added at screening and subsequently if confirmed drug-induced liver injury (DILI) is suspected thereafter.		Table 1 Table 2 Section 7.2.8
For children in diapers, urine specimen collection should be attempted as		Table 1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
part of the safety lab assessments, but lack of urinalysis will not constitute a protocol deviation.		Table 2 Section 7.2.8
Timeframe of follow-up for subjects with blood samples testing positive for anti-teduglutide antibodies at week 28 or EOS has been clarified.		Synopsis Table 1 Table 2 Section 7.2.10
Need for a subject with a positive fecal occult blood testing at week 12 without a readily identifiable cause by physical examination to undergo a colonoscopy or sigmoidoscopy is now open to discussion with the Shire medical monitor or designee.		Table 1 Table 2 Section 7.2.14.3
Need for children younger than 12 years to undergo a colonoscopy or sigmoidoscopy if they test positive for fecal occult blood at screening and the cause is not identified by physical examination has been specified.		Section 7.2.14.4
GI symptoms history worksheet has been renamed GI-specific symptoms history diary, and details on recording and reviewing symptoms have been added.		Table 1 Table 2 Section 7.2.15.1
"Other nutrition (regular diet and drink)" has been removed from the Intake diary.		Section 7.2.15.2
Output diary data collection will continue to occur over a 48-hour period of PN/IV and EN stability before every site visit. Between site visits, the output diary collection will only be required within 1 week of implementing a change in the PN/IV prescription.		Table 1 Table 2 Section 7.2.15.3
Severity categorization has been updated to specify that the severity of AEs listed in Table 6 that may lead to dose interruption based on known risks of teduglutide will also be evaluated using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria.		Section 8.1.1
Definition of an overdose to teduglutide has been revised.		Section 8.1.7
Adverse events of special interest have been redefined and procedures for reporting them have been added.		Section 8.3
More information has been provided on criteria for dose interruption of individual subjects. Dose discontinuation has been made absolute for an AE known to be a risk associated with teduglutide administration (Table 6) that is of NCI CTCAE severity ≥Grade 3 and considered to be related to investigational product; cases of severe hypersensitivity that are determined to be related to investigational product; DILI that is related to investigational product; and pregnancy. SAEs related to investigational product are potential but not absolute reasons for dose discontinuation.		Sections 8.4, 8.4.1, and 8.4.2
Criteria for DILI have been added.		Section 8.4.2
Criteria for early termination of the study have been clarified.		Section 8.5
Clarification that original diary data should be entered into the eCRF and take precedence over data collected over the phone.		Section 9.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **27 Apr 2016**	**Global**
Description of Change		**Section(s) Affected by Change**
Definition of PK analysis population has been added.		Section 9.6
Pharmacokinetic analyses methods and parameters have been clarified.		Synopsis Section 9.10.1
Protocol history has been added in Appendix 1.		Appendix 1
Guidelines for nutritional support management during the study have been clarified.		Appendix 2

Appendix 2 Guidelines for Nutritional Support Management During the Study (SHP633-302)

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

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

Appendix 3 Weaning Algorithms

Figure A-1 Weaning Algorithm for Subjects Who Are Not Toilet-trained and in Diapers

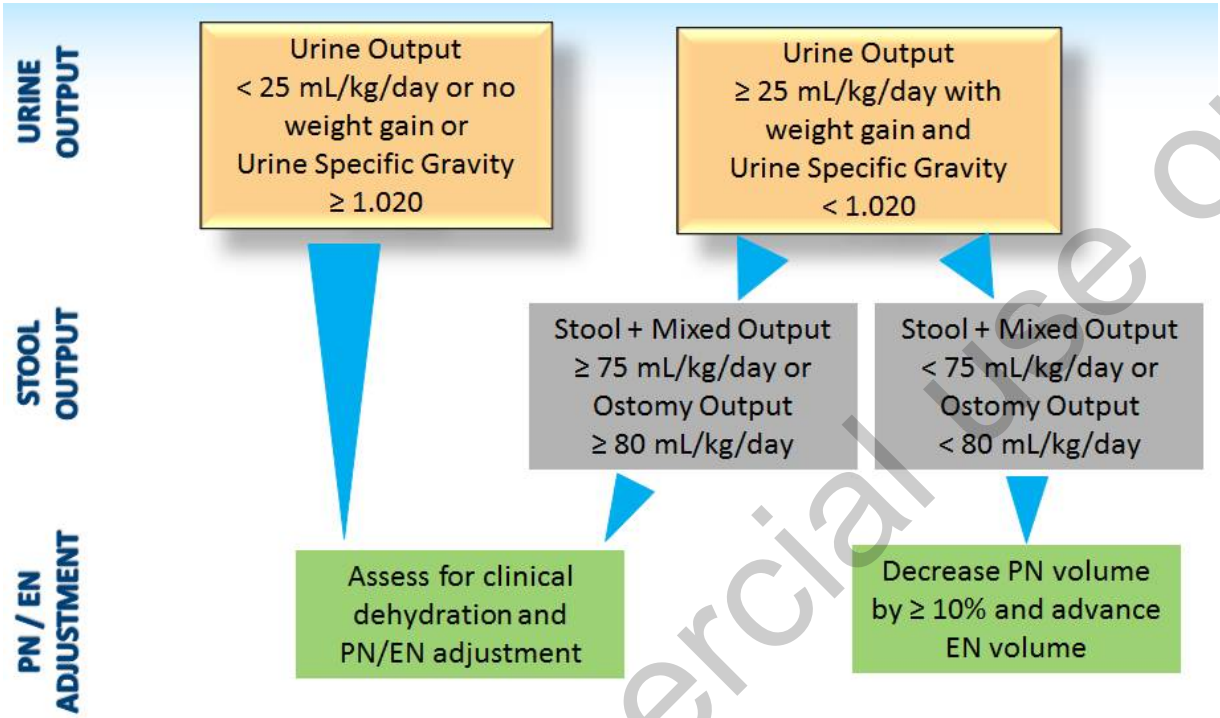


Figure A-2 Subjects Who Are Toilet-trained and Not in Diapers

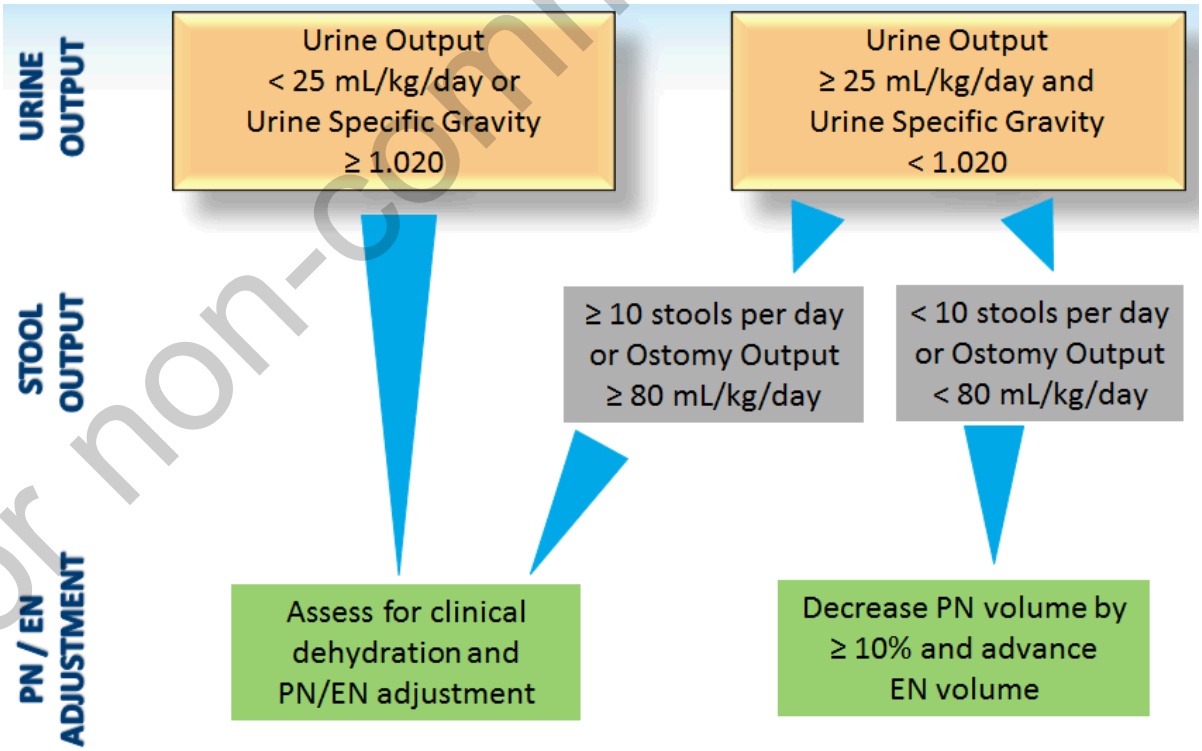
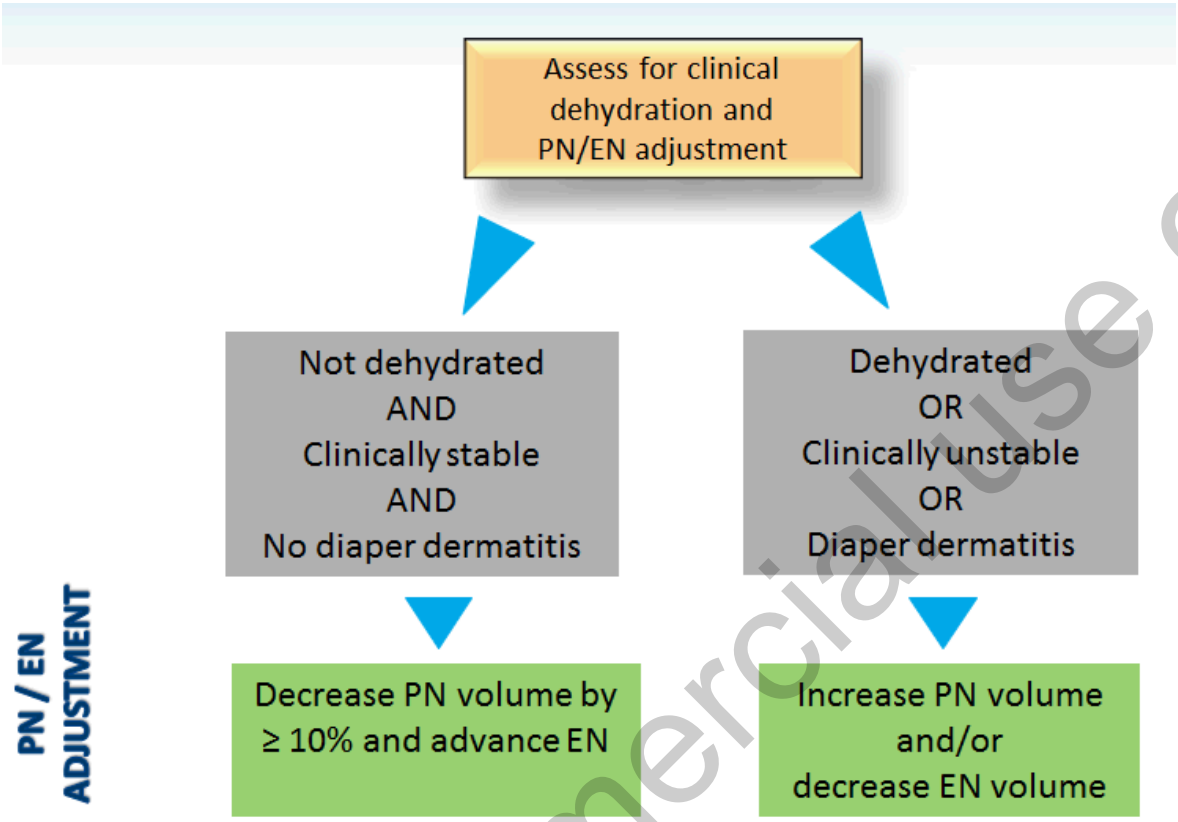


Figure A-3 Clinical Dehydration Assessment and PN/EN Adjustment



Appendix 4 Monitoring Personnel

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1-8-2 Marunouchi, Chiyoda-ku, Tokyo, 100-000, Japan

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