NDA Inter-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	203441 / Supplement-013 (S-013)
Priority or Standard	Priority with 3-Month Extension due to Major Amendment
Submit Date(s)	September 11, 2018
Received Date(s)	September 11, 2018 (eCTD SN0265)
PDUFA Goal Date	June 11, 2019 (3-Month Extension due to Major Amendment; originally March 11, 2019)
Action Goal Date	May 16, 2019
Action Date	May 16, 2019
Division/Office	Division of Gastroenterology and Inborn Errors Products (DGIEP) / Office of Drug Evaluation III (ODE III)
Review Completion Date	May 16, 2019
Established/Proper Name	Teduglutide
(Proposed) Trade Name	GATTEX
Pharmacologic Class	Glucagon-like peptide-2 (GLP-2) analog
Code name	SHP633
Applicant	Shire-NPS Pharmaceuticals, Inc.
Dosage Form	Reconstituted lyophilized powder for subcutaneous (SC) injection
Applicant proposed Dosing Regimen	0.05 mg/kg subcutaneous (SC) once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients 1 year of age and above with short bowel syndrome (SBS) who are dependent on parenteral support
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	26629001
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adults and pediatric patients 1 year of age and older with Short Bowel Syndrome (SBS) who are dependent on parenteral support
Recommended Dosing Regimen	0.05 mg/kg SC injection once daily; self-administration or caregiver administration in adult patients, and caregiver-only administration in pediatric patients

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Reviewers of Inter-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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OND: Office of New Drugs
ODE: Office of Drug Evaluation
DGIEP: Division of Gastroenterology and Inborn Errors Products
OTS: Office of Translational Sciences
OCP: Office of Clinical Pharmacology
DCP: Division of Clinical Pharmacology
DPM: Division of Pharmacometrics
OB: Office of Biostatistics
DB: Division of Biometrics
DPMH: Division of Pediatric and Maternal Health
OSE: Office of Surveillance and Epidemiology
OMEPRM: Office of Medication Error Prevention and Risk Management
DRISK: Division of Risk Management

Additional Review Disciplines

OFFICE/DIVISION	SUPERVISORY/TEAM LEADER(S) / REVIEWERS(S)	REVIEW LOCATION
OND/ODEIII/DGIEP – ADL	Joette Meyer	Review not Required
OPQ/OLDP/DPMAI/PMBII	David Lewis/Lyudmila Soldatova / Le Zhang	CDER Informatics Platform/Panorama
OPQ/OPF/DMA	Jesse Wells / Peggy Kriger	CDER Informatics Platform/Panorama
OPQ/OPF/DIA	Christina Capacci-Daniel / Wenzheng (Wendy) Zhang	CDER Informatics Platform/Panorama
OPQ/OBP/DBRRIII	Susan Kirshner	DARRTS (Reference ID: 4404246)
OTS/OB/DBVI	Yi Tsong/Meiyu Shen / Tianjiao Dai	DARRTS (Reference ID: 4362572)
OPQ/OPRO/DRBPMII/RBPMBIV	Grecia Edwards	Review not Required
OSE/OMEPRM/DRISK	Donella Fitzgerald / Anahita Tavakoli	Review not Required
OSE/OMEPRM/DMEPA	Quynh Nhu Nguyen/Mishale Mistry/Sarah Vee/Millie Shah / Sherly Abraham / Matt Barlow	DARRTS (Reference IDs: 4395612 and 4423782)
OSE/OPE/DEPII	Sukhminder Sandhu/Patrician Bright / Monisha Billings	DARRTS (Reference ID: 4384944)
OSE/OPE/DPVI	Eileen Wu/Lisa Harinstein / Michelle Hines	DARRTS (Reference ID: 4328260)
OSE/PMS	*Project Management* Shawnetta Jackson / Ameet Joshi	Review not Required
CDRH/ODE/DAGID/GHDB	Alan Stevens/Sarah Mollo / Florencia (Flo) Wilson	DARRTS (Reference ID: 4394986)
OMP/OPDP	Meeta Patel	DARRTS (Reference IDs: 4397692 and 4401634)
OMP/OMPI/DMPP	LaShawn Griffiths/Marcia Williams / Nyedra Booker	DARRTS (Reference ID: 4404233)
OSMP/OCP	Patricia Love / Maryam Mokhtarzadeh	Review not Required
DPMH	*Project Management* Gettie Audain	Review not Required
OC/OSI	Susan Thompson / Susan Leibenhaut	Review not Required

ADL: Associate Director for Labeling
OPQ: Office of Pharmaceutical Quality
OLDP: Office of Lifecycle Drug Products
DPMA: Division of Post-Marketing Activities
PMB: Post-Marketing Branch
OPF: Office of Process and Facilities
DMA: Division of Microbiology Assessment
DIA: Division of Inspectional Assessment
OBP: Office of Biotechnology Products

DBRR: Division of Biotechnology Review and Research
OPRO: Office of Program and Regulatory Operations
DRBPM: Division of Regulatory and Business Process Management
RBPMB: Regulatory and Business Process Management Branch
DMEPA: Division of Medication Error Prevention and Analysis
OPE: Office of Pharmacovigilance and Epidemiology
DEPI: Division of Epidemiology
DPV: Division of Pharmacovigilance
PMS: Project Management Staff
CDRH: Center for Devices and Radiological Health
ODE: Office of Device Evaluation
DAGID: Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices
GHDB: General Hospital Devices Branch
OMP: Office of Medical Policy
OPDP: Office of Prescription Drug Promotion
OMPI: Office of Medical Policy Initiatives
DMPP: Division of Medical Policy Programs
OSMP: Office of Special Medical Programs
OCP: Office of Combination Products
OC: Office of Compliance
OSI: Office of Scientific Investigations

Glossary

ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
AET	analytical evaluation threshold
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BLA	biologics license application
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CSR	clinical study report
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DB	direct bilirubin
DILI	drug-induced liver injury
DMEPA	Division of Medication Error Prevention and Analysis
ECG	electrocardiogram
eCTD	electronic common technical document
EN	enteral nutrition
ER	exposure-response
FDA	Food and Drug Administration
GI	gastrointestinal
GLP-2	glucagon-like peptide-2
HF	human factors
ICH	International Conference on Harmonisation
IF	intestinal failure
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
NCA	noncompartmental analysis
NDA	new drug application
NTT	no-teduglutide treatment
PD	pharmacodynamics
PDE	permitted daily exposure
PK	pharmacokinetics
PN	parenteral nutrition
PT	preferred terms
PWR	pediatric written request
QC	quality control
REMS	risk evaluation and mitigation strategy

SAE	serious adverse event
SB	subcutaneous
SBS	short bowel syndrome
SOC	standard of care
TB	total bilirubin
TEAE	treatment emergent adverse event
TED	teduglutide
TESAE	treatment emergent serious adverse event
TPN	total parenteral nutrition
U/L	unit per liter
ULN	upper limit of normal
URI	upper respiratory tract infection

1. Executive Summary

1.1. Product Introduction

Teduglutide (Gattex, TED) is a glucagon-like peptide-2 (GLP-2) analog administered by daily subcutaneous (SC) administration. It is a 33-amino acid peptide that differs from the native peptide in a single substitution of glycine for alanine at the second position of the N-terminus, designed to confer resistance to degradation and enhance half-life.

Native GLP-2 is a peptide hormone, which is released from enterocytes in the terminal ileum and colon in response to nutrient ingestion. GLP-2 has trophic effects on the small and large bowel epithelium, via simulation of cell proliferation and inhibition of apoptosis (Lovshin and Drucker, 2000). Patients with short bowel syndrome (SBS) become GLP-2 deficient, particularly when resection includes the terminal ileum (as is common in patients with SBS). Provision of a GLP-2 analog may therefore be expected to improve intestinal adaptation and fluid/nutrient absorption by action to promote an increase of villus height and crypt depth.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Expansion of the indication for teduglutide from adults to include pediatric patients 1 to 17 years of age is supported by adequate and well controlled studies in adults, and relies upon partial extrapolation of efficacy, given similarity in disease progression and anticipated response to therapy between adults and pediatric patients with SBS.

The clinical program for pediatrics included a phase 2, open-label dose ranging study (TED-C13-003, hereafter "study 003") and a phase 3 study with an open-label standard of care (SOC)/ natural history arm, and two blinded doses of treatment (TED-C13-006, hereafter "study 006").

Study 006 assessed the same primary endpoint as the adult program, the proportion of responders, where a responder was defined as a patient achieving at least a 20% reduction in the volume of parenteral support[1] after 24 weeks of treatment. Results from this small pediatric study population were consistent with those of the adult phase 3 program. Eighteen of 26 (69%) subjects achieved at least 20% reduction in PN volume after 24 weeks of treatment with the proposed dose (0.05 mg/kg given once daily) and three of 26 (12%) receiving the same dose achieved complete enteral autonomy (i.e., weaned completely from PN). Although those who achieved complete enteral autonomy represent a small minority of trial participants, the results suggest that a subset of patients with SBS may be highly responsive to teduglutide, and thus have an opportunity to derive major clinical benefit. Further, interviews with families and

[1] In this review, the terms "parenteral support" and "PS/IV support" will be referred to as parenteral nutrition (PN) or PN/IV.

patients suggest that even a small incremental reduction in time spent on PN administration (such as 1 day/week) has value in improving the quality of life in pediatric patients with SBS who are PN dependent. The mean reduction in PN volume following treatment with 0.05 mg/kg/day was 23 mL/kg/day (from baseline of 60 mL/kg/day) and resulted in a mean decrease in daily infusion time of 3 hours per day (from baseline of 11 hours per day). Ten of 26 (38%) of patients achieved a reduction of at least 1 day per week in PN administration. By comparison, minimal changes in PN volume or infusion time were noted in patients treated with SOC.

The totality of evidence from adult and pediatric trials support expanding the indication to include pediatric patients 1 year of age and older.

1.3. Summary of Key Issues

1.3.1. Age-Appropriate Formulation

One review issue centered around the availability of an age-appropriate formulation suitable for use across the full age and weight spectrum targeted by the pediatric written request (PWR).[2] (b) (4) Due to manufacturing site issues, this presentation is not available currently.

The Applicant is therefore proposing use of the currently marketed 5-mg vial (which is co-packaged with 1-mL (b) (4) syringe and 26G 5/8" needle) for pediatric patients 1 year of age and older with a minimum body weight of 10 kg. While this needle size is acceptable for subcutaneous administration in pediatric patients (see Section 9.), patients with the lowest body weight (10 kg) could potentially be exposed to increased dosing variability due to tolerance and device-related issues (nominal syringe capacity and expelled volume). The maximal anticipated variability decreases with increasing body weight. The Applicant has thus proposed 10 kg as the lowest body weight for which this presentation and kit can safely be used; below this cutoff, the variability in dosing would exceed 32% and was considered unacceptable (details in section 6.3.2.9.

From an efficacy perspective (see section 6.3.2.1.) FDA's exposure response analysis incorporating pediatric data suggests that efficacy is expected to be comparable across a 2-fold range of doses (0.025mg/kg vs 0.05mg/kg), which supports the assertion that even with the potential dosing variability as described above, there is unlikely to be major negative impact on efficacy.

[2] Refer to section 3.2 (Regulatory Background) for full details of the studies required under the Pediatric Written Request, issued by the Agency on June 12, 2015.

Further, from a safety standpoint, the clinical trial data from study 006 included a comparison of patient safety data from those randomized to 0.025 mg/kg versus 0.05 mg/kg and did not show any major differences in safety between the two doses, taking into consideration rates and types of common and serious treatment emergent adverse events (TEAEs). These data are limited in that they do not provide direct evidence of safety specific to pediatric patients at doses greater than 0.05 mg/kg.

To supplement the available pediatric safety data, the adult data (which included a dose higher than 0.05 mg/kg) were also reviewed. In adults, no major difference in safety between the 0.05 mg/kg and 0.1 mg/kg doses was identified at the time of initial approval. While there was a nominal increase in "all TEAE" reported with the highest dose (97% in 0.1 mg/kg, 88% in 0.05 mg/kg, and 83% in placebo), the rates of serious adverse events were lower in the highest dose group (34% in 0.1 mg/kg, 36% in 0.05 mg/kg, 28% in placebo). The common adverse events were similar between pediatric and adult populations.

Per the Agency's request, the Applicant conducted additional ER analyses for safety. Three of the most common treatment emergent AEs from the pediatric studies (abdominal pain, vomiting, upper respiratory tract infection) were evaluated, and the analysis demonstrated that the probability of experiencing these events did not differ by the level of exposure. The review team concluded that these AEs were reasonable choices as they were among the most common TEAEs that were seen with greater frequency on treatment than placebo in the adult controlled clinical trial population and were also commonly experienced by pediatric patients in the core pediatric studies. Results are described in section 6.3.2.1.

Thus, the use of adult presentation for patients down to 10kg of body weight appears reasonable from both the efficacy and safety perspective.

1.3.2. Self-Administration

The Applicant has not provided adequate human factors (HF) data (b) (4) The Applicant submitted the HF validation study results; however, the Division of Medication Error Prevention and Analysis (DMEPA) identified multiple deficiencies. The HF validation study included only a trained group of pediatric patients, despite the Applicant being unable to guarantee all patients would receive training. Further, the study included some participants who were >18 years of age, and others who had previously participated in trial(s) for this product and thus had prior experience with the user interface. These limitations led to the conclusion that the results were not adequate (b) (4) Refer to finalized consult review (dated February 27, 2019, in DARRTS) for additional details.

The team evaluated whether caregiver administration for pediatric patients was an acceptable (b) (4) The DMEPA team reviewed all available HF data, which can be used to support caregiver administration to pediatric patients, considering that the safety concerns from dosing variability/potential overdose are considered acceptable (as discussed above). More

specifically, DMEPA reviewed the Applicant's justification, kit user interface, and use-related risk analysis, and determined that no additional data are necessary to support caregiver administration for pediatric patients, as the concerns regarding safe use would be similar between adults administering to another adult or to a pediatric patient.

The prescribing information will limit the indication to caregiver administration for pediatric patients. (b) (4)

Given the high-level complexity (i.e., multiple steps) involved to ensure appropriate use of this product, the team believes that limiting administration to adult self-administration and caregiver administration for the pediatric patients is reasonable at this time. DMEPA recommends that the language below be added to the product label:

"This product is for adult self-administration or caregiver administration only. Self-administration in pediatric patients has not been tested."

1.4. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Short bowel syndrome (SBS) that results in intestinal failure (IF) and dependence on parenteral nutrition (PN) is a rare condition in pediatrics and is associated with substantial morbidity and mortality. There are no treatments approved to treat pediatric patients with IF who are PN dependent. An unmet medical need exists for therapies that will improve the function of remaining bowel in these patients, promote increased absorption of fluids and nutrients, and reduce the requirement for PN.

There are limited options available for the treatment of short bowel syndrome and resultant intestinal failure. The only other FDA-approved therapies available (in adults) are Zorbtive (somatropin, recombinant growth hormone) and NutreStore (L-glutamine, which is approved only for use in conjunction with somatropin for this indication). These products are not approved for use in pediatric patients. Gattex (teduglutide) offers a different mechanism of action than these other therapies; it is a glucagon-like-peptide 2 (GLP-2) analog intended to promote intestinal adaptation and absorptive capacity in patients with SBS.

The benefits of teduglutide treatment in adults with SBS were demonstrated in adequate and well-controlled trials, which supported the approval of the 0.05 mg/kg dose for use in adults with SBS who are PN dependent. The primary efficacy measure in the adult program was based on the proportion of responders, where response was defined as at least 20% reduction from baseline in the PN volume prescribed. The pediatric program was designed based on partial extrapolation of efficacy from the adult program, based on the similar pathophysiology, progression of disease, and anticipated response to treatment, between adult and pediatric patients with SBS.

Benefits of teduglutide in pediatric patients were demonstrated in studies 003 (dose finding study for 12 weeks duration) and 006 (efficacy and safety study for 24 weeks duration). In both of these studies, more than 50% of subjects achieved at least a 20% reduction from baseline in PN volume. Secondary endpoints supported that clinical benefit was derived, including a proportionate decrease in PN calories from baseline (suggesting that both fluid and nutrient absorption are positively influenced by teduglutide) and a reduction in PN administration time per day and per week (which is an important determination of quality of life in pediatric SBS patients).

The pediatric program includes data from 87 patients dosed with teduglutide, 41 of whom received the to-be-marketed dose of 0.05mg/kg. The most common adverse reactions in adults were abdominal pain, nausea, upper respiratory tract infection, abdominal distention, injection site reaction, vomiting, fluid overload, and hypersensitivity. Primary pediatric safety data were compared with the risks identified within the adult program for teduglutide, which included data from 136 adults with SBS and PN dependence. The types and frequencies of common adverse

events in the pediatric population were generally comparable, or less severe than those seen in adults. The approved prescribing information also contains warnings and precautions for the following serious safety concerns: possible acceleration of neoplastic growth (including colonic polyps), intestinal obstruction, biliary and pancreatic disease, fluid overload including congestive heart failure, and potential for increased absorption of oral concomitant medications. All of these risks were carefully evaluated within the pediatric program. There was one case of intestinal obstruction, which resolved with treatment interruption and one possible case of colonic polyp (which was not identified on follow-up). No new serious safety concerns were identified in the pediatric population. Uncertainty exists as to whether the safety profile is well characterized and generalizable due to the small size of both the adult and pediatric programs. However, in the context of a rare disease, the size of the two programs is deemed generally acceptable as the conduct of a much larger program would be operationally infeasible.

A risk evaluation and mitigation strategy (REMS) program was implemented at the time of initial approval and continues to operate. It consists of training for prescribers as well as informational materials for patients and their caregivers to ensure understanding of the known and potential risks associated with teduglutide. Minor modifications to the REMS materials to account for the addition of the pediatric indication were made during the review cycle; these did not contain any major revisions to the content.

In conclusion, though the data are limited due to the low prevalence of this condition, available safety and efficacy data in pediatric patients, supported by the larger database available from the adult program, suggest that the benefit-risk profile of teduglutide for the treatment of pediatric SBS patients who are PN dependent is favorable and supports approval.

1.5. Patient Experience Data

Patient Experience Data Submitted or Considered		
Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) – survey-based study of caregivers of SBS patients	Section 1.5 below
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data was submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: (please specify) CDER initiated discussion with external subject matter experts	Description below in section 1.5

The Applicant provided limited patient experience data within this submission.

Healthcare-related quality of life (HRQOL) measures are being collected in both extension studies; however, the Applicant plans to analyze these once the extension studies are complete.

An information request was sent to the Applicant on January 23, 2019, and the Applicant submitted a response on January 29, 2019, with summary reports of 2 previously conducted surveys designed to assess impacts of PN on caregivers, one of which (study 0238-0368) was specific to caregivers of pediatric patients with SBS. This study was an online cross-sectional survey of caregivers of pediatric patients with SBS ages 1 to 17 who were recruited through a patient advocate group and two National Health Service (NHS) sites in the United Kingdom. The surveys were comprised of study-specific and standardized questions to collect caregiver and caregiver-reported patient demographics, patient clinical information, and multiple health-related quality of life measures, and they were aimed at collecting information on both the

quality of life and general impact of having a child with SBS on caregivers, as well as proxy data for the patients themselves.

Data were obtained from 45 caregivers who completed the study, and the patients they cared for appeared to span the range of disease severity (from those requiring 7 days per week PN and almost around the clock care, to those requiring only smaller amounts of PN support (1-3 days), and those who previously were PN dependent but had since weaned completely from PN). The results were variable, and it was not possible to identify clear conclusions from this study of small sample size involving caregivers of patients who varied in their disease severity at the time of participation. However, one message noted was that "most caregivers rated a reduction in PN (from a 1-day reduction to weaning off completely) as better for their child's life." Another point noted was that caregivers of patients in the "high PN" group (those with greater PN requirements) rated their happiness and care situation the lowest. However, the trend was not linear from greatest to least PN, suggesting that other factors besides the volume or days of PN administration are important in caregiver quality of life.

Other patient experience data that was considered by FDA but not submitted specifically by the Applicant included:

1) Summary documents from prior Advisory Committee (convened during the review cycle for the initial Gattex application submission, 2012), which discussed the clinical relevance of the 20% reduction in PN endpoint.
2) Informal interactions that FDA review staff had with outside experts (not specific to this application), to better understand the expectations that physicians who are experts in pediatric intestinal failure have of drugs aimed at treatment of pediatric SBS, including the minimal degree of improvement they would consider acceptable in order to utilize a drug for SBS in their patients.

2. Therapeutic Context

2.1. Analysis of Condition

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). The majority of SBS cases in pediatric patients are due to congenital anomalies or catastrophic events that occur during infancy, such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006).

SBS may result in intestinal failure (IF), characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet, such that PN is required to maintain health and/or growth (Pironi et al., 2016). The true incidence and prevalence of SBS in adults are unknown; however, it is estimated at 2 to 4

million worldwide, with the incidence of neonatal SBS estimated at 24.5 per 100,000 live births (Wales et al., 2004). An estimated 83% of pediatric cases of SBS begin during infancy (Spencer et al., 2005).

In general, all patients with SBS are prone to malnutrition, diarrhea, dehydration, electrolyte disturbances, malabsorption of nutrients, gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhea, small bowel bacterial overgrowth, and an inability to maintain weight due to reduced intestinal capacity to absorb macronutrients, water, and electrolytes (Dudrick et al., 1991; Nightingale et al., 2006; Nightingale, 1999). The small intestine is capable of adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on PN (O'Keefe et al., 2006). Some patients with intestinal insufficiency are able to metabolically adapt and compensate for their malabsorption of fluids, electrolytes, trace elements, vitamins or nutrients by increasing oral/enteral intake (Messing et al., 1999), and re-attain enteral autonomy (i.e., complete weaning off of PN).

Although PN is life-sustaining in IF, it is associated with serious complications including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (O'Keefe et al., 2006). There is also a higher mortality rate among patients who do not attain enteral autonomy than among those who do (Amiot et al., 2013). Dependence on PN is associated with a high cost of care and reduced quality of life for both patients and caregivers (Huisman-de Waal et al., 2007).

About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS can become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012b). Some children remain dependent on PN for many years, despite optimal medical management. Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (Wales et al., 2004).

Accelerating the adaptive process and achieving enteral autonomy is the goal for all patients with SBS who are dependent on PN (Gonzalez-Hernandez et al., 2017; Huisman-de Waal et al., 2007). The adaptive process is in part controlled by GLP-2, secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids. The adaptive process usually occurs within 1 to 2 years and further adaptation is not expected after 2 years (Brubaker, 2018). Therefore, patients with SBS who are unable to adapt further after 2 years are likely to develop chronic IF.

2.2. Analysis of Current Treatment Options

The current therapeutic goals in patients with SBS are to optimize enteral nutrition (EN), maximize the adaptive process, minimize PN requirements, manage symptoms related to the disease, limit PN-associated morbidity, and transition to enteral autonomy when possible

(Avitzur and Courtney-Martin, 2016; Carroll et al., 2016; Gosselin and Duggan, 2014). Zorbtive, a somatropin human growth hormone for subcutaneous administration, is approved for treatment of SBS in patients receiving specialized nutritional support; and Nutrestore, L-glutamine powder for oral suspension, is approved for treatment of SBS in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for the indication. Neither somatropin nor L-glutamine is approved for use pediatric SBS patients. There are currently no approved therapies that promote intestinal adaptation in children with SBS. Despite improvements in patient care, serious risks for patients with SBS remain, including IF-associated liver disease, catheter-related blood stream infections, central line-associated venous thrombosis, loss of central venous access, and the high impact on patients' and caregivers' quality of life (Bines, 2009; Brubaker, 2018; Duggan and Jaksic, 2017). Thus, there is an unmet medical need for treatments designed to help pediatric patients with IF achieve enteral autonomy.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NPS pharmaceuticals received orphan designation for teduglutide for the treatment of short bowel syndrome on June 29, 2000. The drug was first approved in the European Union under trade name Revestive on August 30, 2012 and was subsequently approved in the United States under trade name Gattex for treatment of adult patients with SBS on December 21, 2012 (Reference ID: 3253828). On February 21, 2015, Shire Pharmaceuticals, Inc. acquired NPS Pharmaceuticals Inc. and the above market authorizations for teduglutide. On June 29, 2016, the European Union granted an extension of marketing authorization to teduglutide for the treatment of patients aged ≥1 year with SBS.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following is a regulatory history of teduglutide with respect to its use in pediatric populations:

May 31, 2013: Proposed Pediatric Study Request submitted

May 2, 2014: Inadequate Proposed Pediatric Study Request letter issued; key disagreements in the proposed protocol included:

- Inadequate length of proposed trial (12 weeks versus 24 weeks for adult studies)
- Lack of standardized method for weaning off PN across multiple centers
- Lack of defined stopping rules for individuals and for the overall study
- Poorly defined enrollment criteria (i.e., need to clearly define "stable PN/IV support for at least 3 months," and allow enrollment of participants <5% body weight for age but stable on growth curve)

- November 24, 2014: Inadequate Proposed Pediatric Study Request letter issued, Division recommended:
  - Blinded instead of open-label design
  - Enrollment of teduglutide-naïve patients in the proposed 24-week trial

June 12, 2015: Agency issued pediatric written request (PWR)

July 13, 2015: Amendment 1 to PWR issued to remove lower year age limit of 1 year (Applicant confirmed agreement on September 30, 2015).

January 5, 2017: Amendment 2 to PWR: changes to required submission timelines

- Timeframe for submitting reports of studies extended from June 21, 2018, to September 21, 2018, if the Applicant wishes to extend the expiration of both the Orphan Drug Exclusivity (ODE) (expires on December 21, 2019) for Gattex as well as the U.S. composition of matter patent (expires April 14, 2020)
- Timeframe for submitting reports of studies extended to January 14, 2019, if the Applicant wishes to extend only the U.S. composition matter patent.

The final PWR including all amendments (dated January 5, 2017) is the subject of this review, and it outlined the following requirements:

- Nonclinical studies: Based on review of the available nonclinical toxicology, no additional animal studies were required to support the clinical studies described in this PWR.
- Clinical studies:
  - Study 1: A 12-week, multicenter, open-label, dose-finding, parallel group study evaluating pharmacokinetics (PK), pharmacodynamics (PD), and safety of at least three doses of teduglutide in teduglutide-naïve pediatric patients less than 17 years of age with SBS who have not been able to decrease PN requirement for at least 3 months before study enrollment.
  - Study 2: A 24-week, multicenter, randomized, double-blind, parallel group study evaluating PD and safety of at least two doses of teduglutide, compared to standard-of care, in teduglutide-naïve pediatric patients less than 17 years of age with SBS who have not been able to decrease PN requirement for at least 3 months before study enrollment.
  - Patients enrolled in studies 1 and 2 will continue to be followed in a long-term extension safety study or registry that captures known and/or unexpected adverse reactions and evaluates for the persistence of efficacy for at least one year. This extension study would not need to be completed to fulfill the PWR, but the study would need to be initiated and an interim clinical study report (CSR) with datasets containing at least 6 months of evaluable safety data must be submitted to fulfill the PWR.
  - Efficacy in patients with SBS less than 17 years will be supported by partial extrapolation of efficacy from adequate and well-controlled studies in adults. Dose selection must be supported by the ER relationship based on the PD measurement of decreased PN requirement in children. Additionally, adequate safety data will be collected for all doses that are identified and for all ages for which the drug will be labeled, including affected children up to and including 12 years and adolescents ages 13 to less than 17 years.
  - There must be multiple dose arms over an adequate dose range. The number of patients in each dose group and age group must be reviewed and agreed upon with the Agency.
  - Study 1 must be conducted prior to study 2. In addition, population PK modeling must be performed using all available adult and pediatric data upon completion of study 1.

November 14, 2017: Type B pre-sNDA meeting to discuss and obtain input and concurrence on proposed presentation and content of the sNDA that will formally respond to the PWR letter.

- Timing of submission was discussed. Agency strongly recommended delaying submission until the required 6 months of data from the extension study were available, rather than submitting earlier with subsequent data update.
- Agency agreed that an integrated summary of effectiveness was not required, but that an integrated summary of safety (ISS) should be submitted and should include both a summary of each individual trial's safety data, as well as a pooled integrated analysis where appropriate.

September 11, 2018: Efficacy supplement submitted (subject of this review).

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

To assess the need for site inspection, the proportions of patients who met the primary endpoint were analyzed by site, and results revealed that enrollment was distributed fairly evenly across multiple sites. There was no particular site that appeared to have outlying results or that would drive the overall study efficacy result. Given this and the low numbers of patients in each site (highest enrolling site had seven patients), the conclusion was made that site inspection was not required for this efficacy supplement.

4.2. Product Quality

From the product quality standpoint, this efficacy supplement provided for the addition of an elemental impurities risk assessment for teduglutide to demonstrate that the teduglutide drug product (DP) meets the ICH Q3D and USP <232> requirements for elemental impurities and to support non-testing of elemental impurities for the teduglutide DP. This supplement also provided (b) (4) reference standard for the teduglutide DP. These changes and this supplement were deemed as approvable by the product quality review team. In addition, revised labeling to expand the current indication to include pediatric patients 1 year of age and older with SBS who are dependent on parenteral support is acceptable from the product quality standpoint.

Within the original supplement submission, the Applicant proposed (b) (4) manufactured by (b) (4) which is a contract manufacturing facility located in, (b) (4) Due to ongoing compliance issues with Good Manufacturing Practice, and based on the amendment submitted and received on March 4, 2019, the Applicant is no longer pursuing the manufacturing (b) (4) for this efficacy supplement. Consequently, for this efficacy supplement, the Applicant has withdrawn from the eCTD all sections from Module 1, Module 2, and Module 3 that are related (b) (4) presentation from (b) (4) The Applicant has also (b) (4) Module 1, Module 2, and Module 3 (b) (4) The Applicant confirmed that the 5 mg/vial kit would continue to be manufactured and be sourced only from the primary supplier, (b) (4) which is a contract manufacturing facility located in (b) (4) The Applicant proposed to keep the 5 mg/vial sections of the NDA linked to (b) (4) as a backup and would only use this facility under extenuating circumstances and with prior written consent from FDA. Hence, OPF/DIA's recommendation for this efficacy supplement's facilities was 'No Evaluation Necessary'. On May 1, 2019, all other originally proposed product quality related changes (i.e., those that are not described as approvable from the paragraph above) were also

withdrawn from consideration from this efficacy supplement.

Based on the microbiology review, this supplement is adequate from the sterile assurance standpoint. Based on the statistical consult review for stability, (b) (4)

An Elemental Impurities Risk Assessment for teduglutide was submitted and received on March 21, 2019. The permissible daily exposure (PDE) calculations comply with the ICH Q3D guideline. A general risk assessment of teduglutide drug substance (DS), manufacturing equipment, process components, excipients, and diluent and container closure systems was performed, suggesting a low probability of exceeding PDEs of elemental impurities as described in the ICH Q3D guideline. In combination with 22 lots of DS and 3 lots of final DP testing as part of this elemental impurity assessment, demonstrating that all concentrations are below the control threshold of (b) (4)% of PDEs, no further controls on the levels of elemental impurities in teduglutide are required at this time.

Up to 60 months of accelerated stability data (25°C ±2°C/60% ±5% relative humidity) and up to 6 months of stability data (stress condition at 40°C ±2°C/75% ±5% relative humidity) are available for three teduglutide DP validation batches manufactured at (b) (4) The teduglutide DS used for these batches was produced by (b) (4) (b) (4) The additional accelerated stability data and stability data for stress condition still support the approved expiration date along with the storage time period and condition after dispending by the pharmacist (i.e., 3 months at room temperature) for the 5 mg/vial DP.

Teduglutide meets the criteria under 21 CFR 25.31(b) for a categorical exclusion from the requirement to conduct an environmental assessment and is in full compliance with FDA's requirement for categorical exclusion without extraordinary circumstances. Thus, an exemption of an environmental assessment was deemed acceptable. The set of vial and carton labels, Prescribing Information (PI) and Medication Guide for the 5 mg/vial DP produced at the (b) (4) remain acceptable from the product quality standpoint. Sections 3, 11, and 16 of the PI were also deemed as acceptable from the product quality standpoint.

For further details, see the three finalized Product Quality DS-DP reviews in Panorama, the finalized Product Quality Microbiology review in Panorama, and the finalized statistical consult review for stability dated December 13, 2018 (Reference ID: 4362572).

4.3. Devices and Companion Diagnostic Issues

Device

The approved 5 mg/vial administration kit consists of the 5-mg dose drug vial, sterile water for injection (sWFI), 1 mL (b) (4) syringe with 26G x 5/8" hypodermic

needle (b) (4) a reconstitution hypodermic needle (22G x 1 ½"), and alcohol prep pad. (b) (4)

The device review focused on evaluating Module 3.2.R.2 (b) (4) of the Applicant's eCTD efficacy supplement submission, with the goal of assessing the approvability of the device constituent parts of the combination product. The device review covered the essential device performance requirements (dose accuracy, break loose/glide force), biocompatibility of the patient contacting components, release specifications for the device constituent, and addressed whether a preapproval inspection (PAI) was needed for the device (b) (6) During the review cycle, it was identified that the originally approved 5 mg/vial administration kit had not been reviewed by CDRH. The Applicant (b) (4) provided data to support that (b) (4) administration kit (b) (4) i.e., 5-mg vial (b) (4) met the essential performance requirements based on its intended use. In addition, teduglutide is indicated to be administered daily, and due to this repeated or cumulative exposure, the subacute/sub-chronic systemic toxicity endpoint(s) was evaluated. (b) (4) is the supplier for the device constituents of the combination product, and they provided additional documentation that adequately addressed the repeated or cumulative exposure. (b) (4) also provided the subacute/sub-chronic toxicity systemic toxicity biocompatibility evaluation for the syringes (b) (4). Lastly, the device review team conducted a risk-based assessment for the administration kits and determined that the device facilities do not need a PAI. The administration kits consist of 510(k) cleared device products and the device constituent parts are packaged as they would be for independent distribution as a device-only product. The efficacy supplement did not introduce a change to the 510(k) cleared labeling or indications for use.

CDRH recommended that the device constituent of the combination product (i.e., (b) (4) administration kits) is approvable for the proposed indication (b) (4) In addition, as indicated in Section 6. below and the Human Factors section immediately below, the 5-mg/vial kit is approvable with caregiver-only administration for pediatric patients down to 1 year of age weighing at least 10 kg. For further details, see the finalized CDRH-ODE review dated February 22, 2019 (Reference ID: 4394986).

Human Factors (HF)

The Applicant submitted HF validation study (b) (4) using the 5 mg/vial packaging configuration/kit; however, several deficiencies were found with the HF validation study methodology, which necessitated the Applicant to submit an additional HF validation study (b) (4) These deficiencies were communicated to the Applicant via the midcycle deficiency information request (IR) sent on December 21, 2018, and then again during a January 28, 2019,

informal teleconference between the Applicant and the Agency. The Applicant responded by stating that their patient support program addresses FDA concerns regarding training; however, without regulatory oversight of such programs, the Agency does not have assurance that the program will ensure that every user will consistently and routinely receive training and whether such program will continue to exist when the product is marketed. As such, these deficiencies were found to be outstanding.

During the review cycle, (b) (4) MEPA reviewed the currently available data to assess whether the data supports caregiver only administration of the 5-mg/vial kit for pediatric patients.

DMEPA notes that the product is currently marketed as a 5-mg/vial kit for adult self-administration and caregiver administration to adult patients. A FAERS search found no relevant medication error cases, and DMEPA's review of the Use-Related Risk Analysis (URRA) for caregiver only administration concluded that use-tasks for a caregiver to administer the product to both pediatrics and adults are the same with the consideration that the doses for pediatrics would be less compared to the adult doses. As such, the clinical review team was consulted to determine whether there are any clinical concerns related to underdosing and overdosing for the pediatric doses. In addition, DMEPA was concerned with the variability of small doses using the 5-mg/vial kit for the smallest of the pediatric patients, and if that variability would translate to concerns regarding the safety and/or efficacy of the product. Discussions with the clinical team confirmed that underdosing, overdosing, and dosing variability is unlikely to have a meaningful impact on the efficacy and safety of teduglutide in pediatric patients.

Considering all available data in totality, DMEPA agreed that caregiver only administration of the teduglutide 5-mg/vial kit to pediatric patients is acceptable from a medication error perspective. However, DMEPA recommends that the following statement be added to Section 2 of the PI: "GATTEX is for adult self-administration or caregiver administration only. Self-administration in pediatric patients has not been tested." For further details, see the finalized DMEPA reviews dated February 27, 2019 (Reference ID: 4395612) and April 24, 2019 (Reference ID: 4423782).

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical studies were reviewed under the original NDA submission (pharmacology review of NDA 203441 dated August 3, 2012, by Tamal Chakraborti, PhD). As stated in Section 3.2, it was determined during negotiation of the PWR that no additional nonclinical studies would be required. Per the current label, Gattex for injection is supplied in a sterile, single-dose glass vial containing 5 mg of teduglutide as a white, lyophilized powder to be reconstituted with 0.5 mL Sterile Water for Injection. The Applicant did not submit a nonclinical CSR with this supplement. From a nonclinical perspective, there are no approvability issues.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

No pharmacology studies were submitted in this supplement. Pharmacology studies were reviewed under the original NDA.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Pharmacokinetic Study in Juvenile Minipigs (Study No. 51170*)*	The C_{max} and AUC_{0-t} were generally similar after single and multiple dosing. The increases in C_{max} or AUC were dose proportional. T_{max} ranged from 0.667 to 1.63 hours. There were no apparent gender differences in C_{max} or AUC. Bioavailability was 85% after subcutaneous administration.
Distribution	
Lacteal Excretion and Placental Transfer of ALX-0600 Following Administration of Subcutaneous Doses to Lactating Rats and Pregnant Rabbits (Study # 7203-104)	Teduglutide showed the potential to cross the placental barrier in rabbits and was excreted through breast milk in rats. In a milk excretion study in the rat, a single subcutaneous dose of 25 mg/kg of teduglutide (81 times the recommended daily human dose of 0.05 mg/kg based on body surface area) was administered to lactating female rats at day 12 postpartum. The maximum concentration of teduglutide in the milk corresponded to 0.9% and 2.9% of the plasma concentration at 1.5 and 4 hours after dosing, respectively.
Metabolism	
N/A	N/A
Excretion	
N/A	N/A

Type of Study	Major Findings
TK data from general toxicology studies 90-day Subcutaneous Toxicity Study in Juvenile Minipigs with 28-day Recovery Period (Study No. 66585)	Juvenile Minipigs *(examples)* $T_{1/2}$: Ranged from 0.7 to 1.2 hours Accumulation: No apparent accumulation Dose proportionality: Less than dose proportional
TK data from reproductive toxicology studies Subcutaneous Embryofetal Development Study in Rats (Study No. 7203-117) Subcutaneous Embryofetal Development Study in Rabbits (Study No. WIL-487001)	Rat $AUC_{0\text{-}8h}$: At gestation day 17: 1644, 5863 and 39228 ng.hr/mL at 2, 10 and 50 mg/kg/day, respectively. Rabbit $AUC_{0\text{-}8h}$: At gestation day 20: 2401, 8478, and 49306 ng.hr/mL at 2, 10 and 50 mg/kg/day, respectively.
TK data from Carcinogenicity studies 104-Week Subcutaneous Carcinogenicity Study in Wistar Han Rats (Study No. 800070) 2-Year Subcutaneous Carcinogenicity Study in CD-1 Mice (Study No. 8214171)	$AUC_{0\text{-}tlast}$: At Week 52: 2261, 6184 and 29684 ng.hr/mL at 3, 10 and 35 mg/kg/day, respectively. $AUC_{0\text{-}24h}$: At Week 52: 4800, 9900 and 36500 ng.hr/mL at 1, 3.5 and 12.5 mg/kg/day, respectively.

5.5. Toxicology

5.5.1. General Toxicology

No general toxicology studies were submitted in the current supplement. General toxicology studies were reviewed under the original NDA.

5.5.2. Genetic Toxicology

No genetic toxicology studies were submitted in this supplement. Genetic toxicology studies were reviewed under the original NDA.

5.5.3. Carcinogenicity

No carcinogenicity studies were submitted in this supplement. Carcinogenicity studies were reviewed under the original NDA.

5.5.4. Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted in this supplement. Reproductive and developmental toxicology studies were reviewed under the original NDA.

5.5.5. Other Toxicology Studies

No special toxicology studies were submitted in this supplement. Special toxicology studies were reviewed under the original NDA.

Container Closure System

Extractables/Leachables

The container closure system for teduglutide for injection is comprised of 3 mL, (b) (4) glass vials with 13 mm finish, 13 mm (b) (4) stoppers, and 13 mm crimped aluminum seals fitted with (b) (4) flip-off buttons.

Two studies (extractable and leachable studies) were performed that confirmed the compatibility of the teduglutide for injection formulation with the selected packaging components. The packaging components used in the two studies support the 5-mg strength drug product. The first study (P9715.00) consisted of an extractables study, examining the compounds that could be extracted from the packaging components under exaggerated conditions. The second study (P10454.00) consisted of a leachables study, examining those materials that may be leached into the drug product.

A standard extractable study was performed on two components (b) (4) rubber stopper and glass vial) of the packaging system under exaggerated (70°C for 24 hours) and aggressive extraction conditions in order to identify potential target leachables (volatile, semi-volatile, non-volatile, (b) (4) extractable materials) using different extraction solvents (water, isopropanol, hexane, toluene, and dilute nitric acid). The extracts were analyzed for volatile extractables by headspace gas chromatography/mass spectrometry, semi-volatile extractables by gas chromatography/mass spectrometry, non-volatile extractables by liquid chromatography/ultraviolet detection/mass spectrometry, for (b) (4) by (b) (4) plasma/mass spectrometry, and for (b) (4) by (b) (4) spectrophotometry.

The analytical evaluation threshold (AET) was used (AET (b) (4) for organic extracts as organic extracts are not representative of actual patient contact) in this study as the practical quantitation limit for volatile, semi-volatile, and non-volatile organic extractables. Typically, the AET is the threshold at or above which a particular extractable should be identified and reported. For aqueous extracts the AET was calculated using the safety concern threshold of (b) (4) µg/day for an individual organic leachable and a maximum dose of one vial per day (5-mg vial/day).

The safety concern threshold represents the absolute exposure threshold below which a leachable would have negligible safety concerns. For organic extracts ((b) (4) the AET was calculated based on threshold of toxicological concern of (b) (4) µg/day for mutagenic/carcinogenic impurities per the International Conference on Harmonisation M7

guidance. Nine elemental [redacted] and 10 non-elemental extractables [redacted] were observed in the extractables study. Safety assessment of the extractables was not conducted as the objective of the extractable study, performed under extreme conditions, was to identify potential leachables. Safety assessment was conducted only of the leachables.

The leachable study was conducted with the 5 mg/vial strength drug product to mimic the use conditions. In the leachables study (P10454.00), vials of reconstituted teduglutide for injection were prepared by reconstituting the drug product with 0.5 mL of purified water and stored in the inverted position for up to 24 hours at ambient temperature. After exposure, the samples were then tested for volatile, semi-volatile, non-volatile, [redacted] leachable materials using the methods described under the extractables study. Control samples were also tested, including a placebo, a teduglutide drug substance solution and a purified water sample. Final values were evaluated using baseline subtraction of the controls from the treated samples, using the AET of [redacted] µg/vial. [redacted] was the only leachable material that could be quantified in the drug product above the AET of [redacted] µg/vial. However, the levels of [redacted] contributed by the container closure [redacted] µg/vial and [redacted] µg/vial for the upright and inverted vials, respectively) were well below the permitted daily exposure (PDE) of less than or equal to [redacted] mg/day per the International Conference on Harmonisation Q3C guidance and do not raise a safety concern. No reportable semi-volatile and non-volatile leachables or [redacted] were detected in the leachables study. The amount of any leachable compound detected were below the AET of [redacted] µg/via [redacted] ng/vial, PDE has not been established due to low inherent toxicity) and [redacted] ng/vial, PDE = [redacted] µg/day) were found at very low levels. Additionally, [redacted] ng/vial, PDE = [redacted] µg/day) and [redacted] ng/vial, PDE has not been established due to low inherent toxicity) were detected in non-inverted sample, while [redacted] ng/vial, PDE has not been established due to low inherent toxicity) and [redacted] ng/vial, PDE = [redacted] µg/day) were detected in the inverted sample in trace amounts. The levels of elemental substances do not raise any safety concern as the daily exposure to the above elemental substances would be well below the respective PDEs. Overall, the leachable profile associated with the 5 mg/vial strength drug product container closure system appears to be acceptable. Based on the assessment of [redacted] as the single probable leachable, the 5 mg/vial strength drug product container closure system does not appear to raise a safety concern.

6. Clinical Pharmacology

6.1. Executive Summary

The key review questions for clinical pharmacology focus on appropriateness of the Applicant's recommended dose of 0.05 mg/kg/day by evaluating dose/exposure-response (D/E-R) analyses for both efficacy and safety and characterization of PK in pediatric patients with SBS via population PK analysis. The submitted justification overall supports the selection of the 0.05mg/kg for pediatric patients 1 year and older and at least 10 kg in body weight.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology
Teduglutide is a 33-amino acid recombinant analog of the human glucagon-like peptide-2 (GLP-2); native GLP-2 is a peptide secreted primarily from the lower gastrointestinal tract that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract.

Clinical Pharmacokinetics

Adult patients with SBS
PK characteristics of teduglutide in adults are detailed in the currently approved product label. Briefly, in adult patients with SBS, following 0.05 mg/kg subcutaneous dose, the median peak teduglutide concentration (C_{max}) was 36 ng/mL and the median area under the curve at steady state (AUC_{tau}) was 150 ng·hr/mL. No accumulation of teduglutide was observed following repeated subcutaneous administrations. The C_{max} and AUC of teduglutide was dose proportional over the dose range of 0.05 to 0.4 mg/kg. The mean terminal half-life ($t_{1/2}$) of teduglutide was approximately 1.3 hours in adult patients with SBS. Refer to the Clinical Pharmacology Review by Dr. Lanyan Fang dated September 19, 2012, for more details.

Pediatric patients with SBS
In the current submission, the PK of teduglutide in pediatric patients ages 1 year and older was characterized using a population PK approach. Following subcutaneous administration of 0.05 mg/kg, mean C_{max} at steady state ($C_{max,ss}$) of teduglutide ranged from 31.7 to 37.4 ng/mL and AUC_{tau} ranged from 98.6 to 114 ng·hr/mL. Mean $t_{1/2}$ of teduglutide ranged from 0.22 to 0.95 hours in pediatric patients following a dose of 0.05 mg/kg. The C_{max} and AUC of teduglutide increased approximately dose proportionally over the dose range of 0.0125 to 0.05 mg/kg in pediatric patients. Across age groups, $C_{max,ss}$ was similar to that in adults. However, AUC was lower in pediatric patients 1 to 17 years of age as compared with adults and increased with increasing age.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing
The proposed dose is 0.05 mg/kg SC once daily for pediatric patients with SBS from 1 to 17 years of age.

Therapeutic Individualization
The recommended dosage in pediatric patients with moderate and severe renal impairment and end stage renal disease (estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2) is 0.025 mg/kg once daily, consistent with the recommendation for adult patients.

Outstanding Issues
None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The PK characteristics in pediatric patients with SBS were evaluated in studies 003 and 006 and are summarized below.

Study 003
Sparse PK samples for teduglutide were collected from all patients (n=37) who received active treatment at Visit 2 (baseline) predose and 1 and 6 hours postdose, and at Visit 6 (Week 4) predose and at 2 and 4 hours postdose. A population PK approach was used to describe the data for study 003; results are shown in Table 1.

Table 1. Summary Pharmacokinetic Results of Teduglutide for Study TED-C13-003 (Population PK Analysis; 1 to 17 Years of Age)

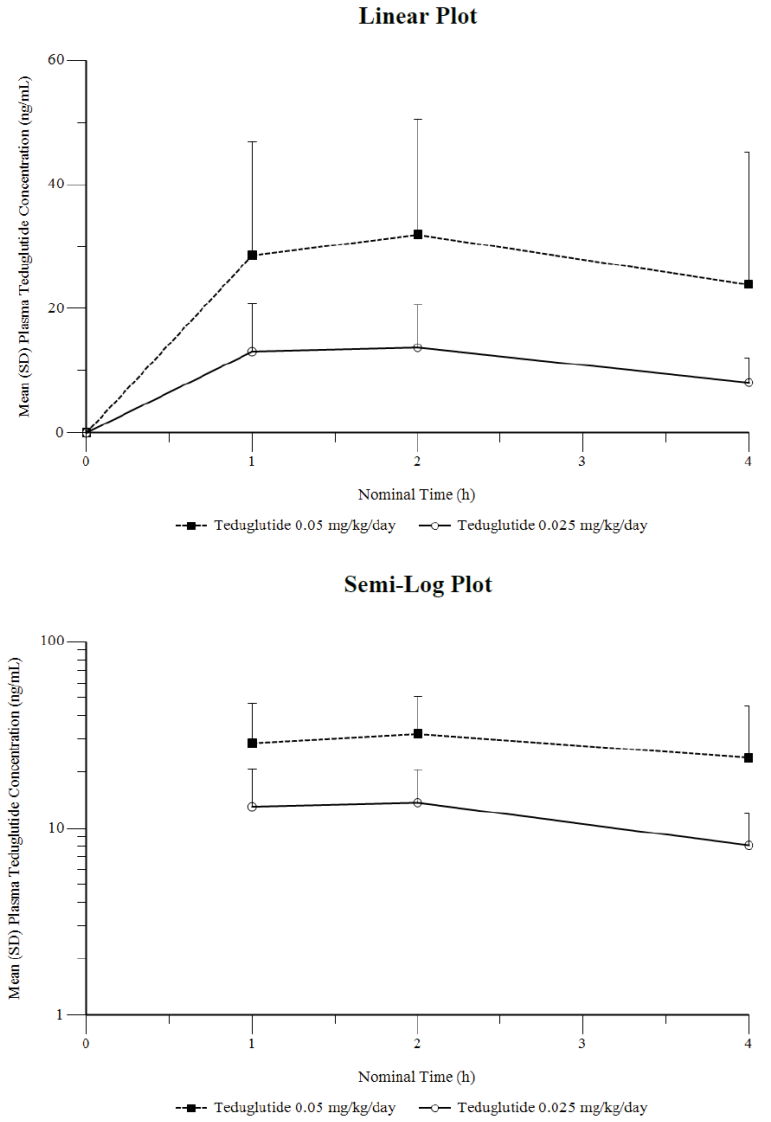
Dose	Statistic	V_c/F (L)	CL/F	K_a (1/h)	$t_{1/2}$ (h)	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$ (h)	$AUC_{0-\tau,ss}$ (ng h/mL)
0.0125 mg/kg (n=9)	Mean	3.35	6.59	0.442	0.273	10.2	0.934	32.9
	SD	5.11	2.01	0.0599	0.299	2.21	0.555	11.4
	Min	0.742	4.71	0.305	0.0891	8.11	0.565	22.5
	Median	1.02	5.77	0.441	0.127	9.29	0.67	27.4
	Max	16.4	11.3	0.516	1.01	14.2	2.29	53.2
	CV%	152.7	30.5	13.5	109.4	21.7	59.4	34.7
0.025 mg/kg (n=13)	Mean	3.56	7.16	0.383	0.301	17.9	1.09	65.7
	SD	3.81	1.98	0.0958	0.214	5.04	0.441	13.5
	Min	0.961	4.23	0.276	0.14	12.3	0.687	46.3
	Median	2.61	7.37	0.346	0.245	15.8	1.03	62.6
	Max	15.2	11.4	0.529	0.922	25.7	2.27	96.4
	CV%	106.9	27.6	25	71.1	28.1	40.6	20.6
0.05 mg/kg (n=15)	Mean	2.42	7.28	0.363	0.218	31.7	0.913	114
	SD	2.37	1.85	0.0905	0.14	11.8	0.293	30.4
	Min	0.829	4.49	0.247	0.0998	18.8	0.638	79.3
	Median	1.86	7.21	0.339	0.18	30.8	0.833	106
	Max	10.7	11.2	0.594	0.664	58.8	1.85	170
	CV%	97.8	25.4	25	64.2	37.3	32.1	26.6

$AUC_{0-\tau,ss}$ = area under the plasma concentration–time curve from zero to the last measurable concentration at steady state; CL/F = apparent clearance; $C_{max,ss}$ = maximum (peak) concentration at steady state; K_a = absorption rate constant; $t_{1/2}$=terminal half-life; T_{max} = time to maximum plasma concentration; V_c/F = apparent central volume of distribution; SD = standard deviation
Source: Reviewer's table, adapted from Applicant's Table 11-12 in Study TED-C13-003 CSR

Study 006

Blood samples for PK analysis were collected at baseline (the first dose), predose and 1, 2, and 4 hours postdose. The PK set included all enrolled subjects who received at least one SC injection of teduglutide and had evaluable and interpretable PK data. The mean plasma concentration-time profile of teduglutide following a single SC administration is presented in Figure 1. The PK parameters were estimated using non-compartmental analysis and summarized in Table 2.

Figure 1. Mean (+SD) Plasma Concentrations Versus Time Profile for Teduglutide Following a Single SC Administration of 0.025 mg/kg/day or 0.05 mg/kg/day (Study 006)



Source: TED-C14-006 CSR - PK Tables, Figures, and Listings, Figure 14.1.1

Table 2. Estimated Pharmacokinetic Parameters of Teduglutide for Study TED-C14-006 (NCA Analysis; Less Than 17 Years of Age)

	0.025 mg/kg/day (n=23)		0.05 mg/kg/day (n=23)	
	Mean	**SD**	**Mean**	**SD**
AUC_{last} (ng h/mL)	39.2	14.51	98.6	54.06
C_{max} (ng/mL)	15.5	7.07	37.4	22.87
T_{max} (h)	2.06	0.922	2.12	1.017

AUC_{last} = area under the plasma concentration-time curve from zero to the last measurable concentration; C_{max} = maximum plasma concentration; SD = standard deviation
Source: Reviewer's table, adapted from Table 2 in Applicant's summary of clinical pharmacology

Population PK Modeling and Simulation

To support dosing of teduglutide in pediatric patients with SBS, the Applicant also conducted population PK analysis of teduglutide using pooled datasets from pediatric studies 003 and 006, as well as data from adult trials. A one-compartment disposition model with first-order absorption and lag time and allometric exponents for parameters Ka, apparent clearance (CL/F), and apparent central volume of distribution (Vc/F) developed previously for adult population was used as a starting point for the current analysis (see Appendix 14.3.1. for details).

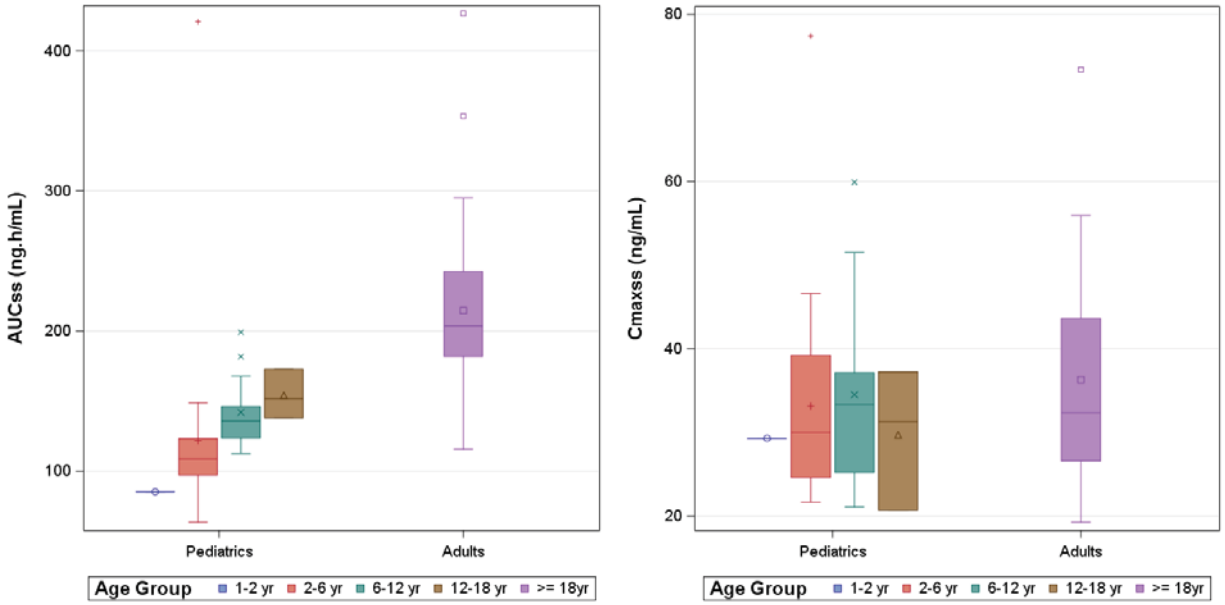
Rich concentration-time profiles were simulated with the final population PK model to derive exposure metrics, such as the area under the curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$), following repeated doses of 0.05 mg/kg in patients with SBS. The derived exposure parameters were then summarized by age group (Table 3). The predicted C_{max} and AUC at steady state following 0.05 mg/kg/day of teduglutide were plotted for pediatric patients (studies 003 and 006) and adult patients with SBS (studies ALX-0600-92001 and CL0600-004) in Figure 2.

Table 3. Summary of PK Parameters of Teduglutide by Age Group for the 0.05 mg/kg Teduglutide Dose Based on Pooled Analysis

Statistics	Age Categories	$C_{max,ss}$ (ng/mL)	AUC_{ss} (ng·h/mL)	CL/F (L/h)	$t_{1/2}$ (h)
Mean (SD) Median [Min, Max]	Adults ≥18 years (n=33)	36.3 (12.5) 32.3 [19.3, 73.4]	215 (64.1) 204 [115, 427]	14.6 (3.48) 14.8 [6.56, 22.6]	1.12 (0.386) 1.01 [0.520, 2.17]
	Adolescents 12 to 17 years (n=3)	29.7 (8.37) 31.3 [20.7, 37.2]	154 (17.6) 152 [138, 173]	13.0 (2.34) 12.5 [11.0, 15.6]	0.953 (0.00574) 0.952 [0.948, 0.959]
	Pediatrics 1 to 11 years (n=37)	33.5 (11.5) 30.7 [21.1, 77.4]	128 (56.7) 116 [63.5, 421]	7.45 (2.07) 7.42 [1.64, 11.8]	0.703 (0.247) 0.665 [0.316, 1.64]

Source: Reviewer's table, adapted from Applicant's Table 5 from SHIR-CSC-148

Figure 2. Predicted C_{max} and AUC at Steady State Following 0.05 mg/kg/day Dosing of Teduglutide for Pediatric Patients (Studies 003 and 006) and Adult Patients With SBS (Study ALX-0600-92001 and CL0600-004)



AUC = area under the curve, SBS = short bowel syndrome
Source: Reviewer's figure (derived from the population PK analysis)

Overall, the PK results indicated that the C_{max} values of teduglutide in pediatric subjects (1 to 17 years) were similar to adults, while the simulated AUC_{ss} were age-dependent and gradually increased from children between 1 and 2 years of age to adults.

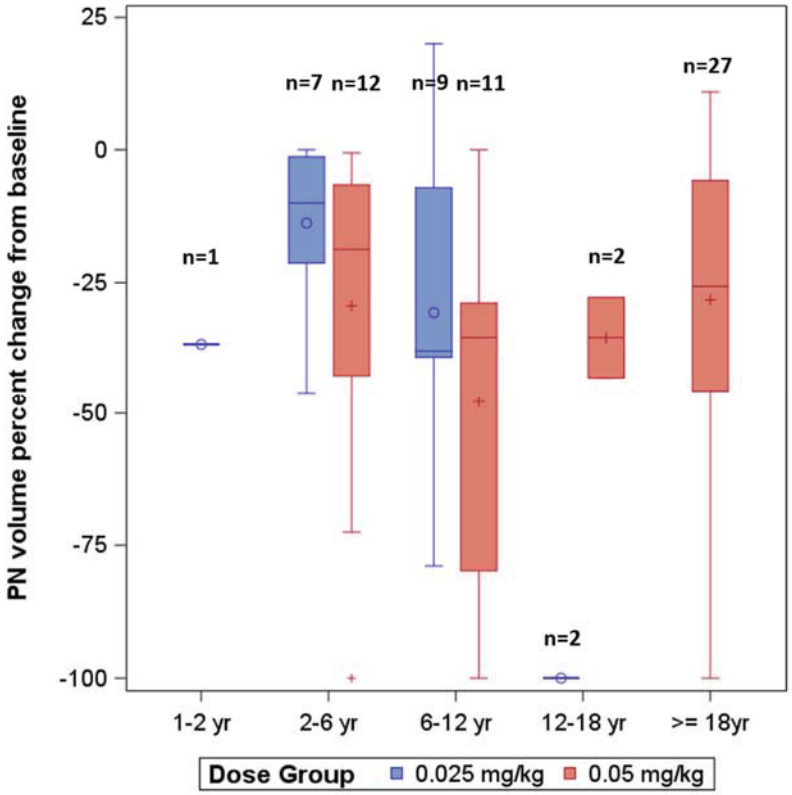
6.3.2. Clinical Pharmacology Questions

6.3.2.1. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 0.05 mg/kg once daily is generally supported by the observed PK, efficacy and safety data in pediatric patients with SBS.

Although the AUC is lower in pediatric patients as discussed in Section 6.3.1. , the change in PN volume across age groups at 0.05 mg/kg dose level (study 006) appears comparable to that observed in adult patients with SBS (study CL0600-004) (Figure 3). In addition, there is numerical difference favoring 0.05 mg/kg over 0.025 mg/kg for the group of 2 to 12-year-old patients, which represents majority (88%) of pediatric patients treated with teduglutide in study 006.

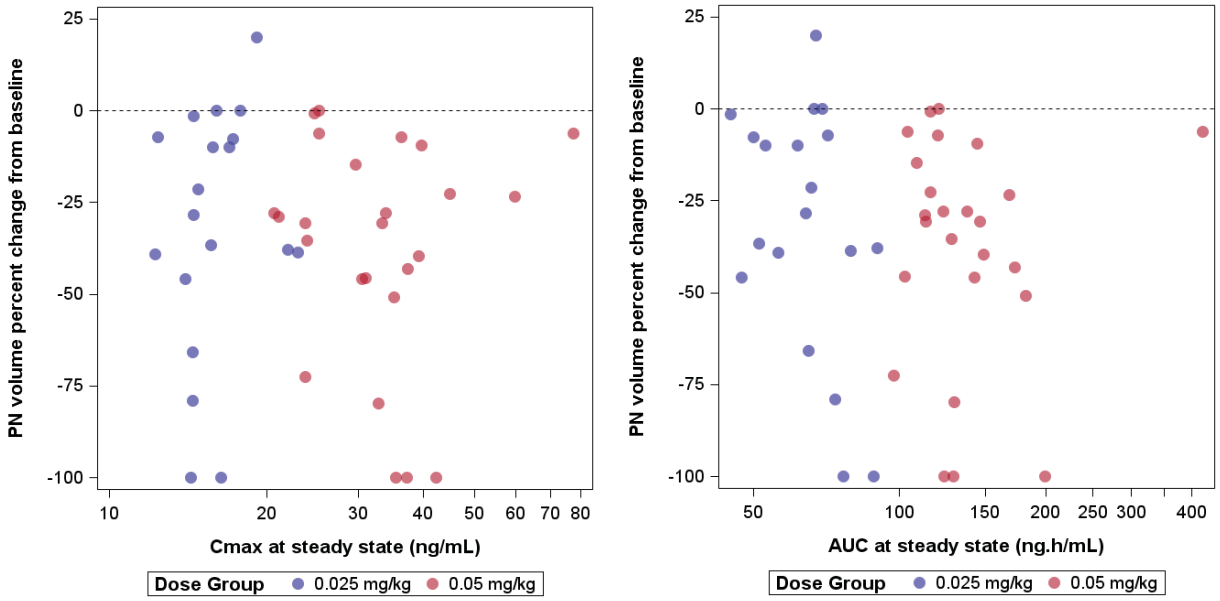
Figure 3. The PN Volume Change From Baseline in Adult (CL0600-004) and Pediatric Patients With SBS (Study 006) Following 24 Weeks of Treatment With Teduglutide by Age and Dose Groups



Source: Reviewer's figure (derived from the exposure-response analysis dataset)

The ER relationship between teduglutide exposure (AUC and C_{max}) and PN volume reduction was explored in Figure 4. Due the limited sample size and lack of control group (the SOC arm was not included as it was not blinded by design), the overall ER relationship in pediatric patients was inconclusive. However, among patients treated with a dose of 0.025 mg/kg, those with lower teduglutide exposure as measured by AUC appeared to have smaller changes in PN volume than patients with higher teduglutide exposure.

Figure 4. Exposure-Response Relationship Between Teduglutide Exposure (Left: C_{max}, Right: AUC) and the Percent Change in PN Volume Reduction at Week 24 in Study TED-C14-006



Source: Reviewer's figure (derived from the exposure-response analysis dataset)

The Applicant conducted exploratory ER analysis for safety using the most frequent treatment emergent adverse events (TEAEs) in studies 003 and 006 (i.e., vomiting, abdominal pain and upper respiratory tract infection (URI)). Logistic regression was used to characterize the relationship between the occurrence of these adverse events and exposure parameters at steady state ($C_{max,ss}$ and AUC_{ss}) in pediatric patients with SBS. The results suggest no significant ER relationship for any of these safety measures, supporting the proposed 0.05 mg/kg dose.

6.3.2.2. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. The recommended dosage in pediatric patients with moderate and severe renal impairment and end stage renal disease (estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2) is 0.025 mg/kg once daily, consistent with the recommendation for adult patients.

No pediatric patients with renal impairment were enrolled in studies 003 or 006. The recommended dose reduction is based on simulation using the updated population PK model with pooled data from adults and pediatrics (see Appendix 14.3.2. for details).

6.3.2.3. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No new drug-drug interaction studies were performed in this submission. Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant oral medications, which should be considered if these drugs require titration or

have a narrow therapeutic index. The currently approved label includes Warning and Precaution for Increased Absorption of Concomitant Oral Medication.

6.3.2.4. What is the incidence of the formation of the anti-product antibodies, including the rate of pre-existing antibodies, the rate of anti-product antibodies formation during and after the treatment, time profiles and adequacy of the sampling schedule if possible?

Among pediatric patients with SBS treated with teduglutide 0.05 mg/kg/day, the immunogenicity incidence was 19% (5/26), 36.6% (15/41) and 53.8% (14/26) following treatment cycles of 24, 36, and 48 weeks, respectively (extension study 304). Overall, the immunogenicity incidence rate increased with the duration of treatment, which was similar to the trend observed in adult patients with SBS. Immunogenicity incidence in pediatric patients was similar to that of adult patients after 24 weeks of treatment (19% versus 18%) but about twice as high in pediatric as adult patients after 48 weeks of treatment (53% versus 25%) (Table 4).

Table 4. Summary of Antibody to Teduglutide in Pediatric Patients with SBS Across Different Studies and Comparison With Adult Data

Study	Dose mg/kg/ day	Baseline	Week 12	Week 24	Week 36	Week 48	Month 24	Month 30
TED-C13-003 Pediatric	0.0125	0/8	0/7					
	0.025	0/14	0/13					
	0.05	0/15	0/14					
SHP633-303 Pediatric	0.05			6.3% (1/15)	38.5% (5/13)			
TED-C14-006 Pediatric	0.025	4.2% (1/24)		12.5% (3/24)				
	0.05	0/26		19.2% (5/26)				
SHP633-304 Pediatric	0.05				36.6% (15/41)	53.8% (14/26)		
Adults	0.05		3% (2/60)	18% (13/74)		25% (18/71)	31% (10/32)	48% (14/29)

Source: Reviewer's table based on CSR of studies TED-C13-003, SHP633-303, TED-C14-006, SHP633-304 and currently approved Gattex product label

Immunogenicity was assessed after 12 weeks of treatment with 0.0125, 0.025 and 0.05 mg/kg/day doses of teduglutide in study 003 and after 24 weeks of treatment with 0.025 and 0.05 mg/kg/day doses of teduglutide in study 006. Patients from studies 003 and 006 had the option of enrolling in open-label extension studies 303 and 304, respectively, where patients had the option to participate in multiple 28-week teduglutide treatment cycles and/or multiple periods of no teduglutide treatment (NTT) for up to 3 years. Each 28-week teduglutide treatment cycle consisted of 24 weeks of teduglutide treatment (0.05 mg/kg/day SC once daily) followed by a 4-week follow up period (no treatment). Immunogenicity was evaluated at

baseline and at weeks 12, 24, and 28. These two open-label extension studies 303 and 304 are ongoing and the Applicant's current submission includes an interim analysis of these studies.

In study 003 (n=37) with treatment groups of 0.125 mg/kg/day (n=8), 0.025 mg/kg/day (n=14) and 0.05 mg/kg/day (n=15), no patient developed anti-drug antibody (ADA) by the end of the 12-week treatment period. However, one of 14 patients in the 0.025 mg/kg/day group developed ADA at the 16-week follow-up visit, which was 4 weeks after the end of treatment (EOT). Antibody testing repeated 3 months later was negative. This patient did not have hypersensitivity or injection site reactions.

In extension study 303, which included patients who began teduglutide treatment in study 003, the numbers of patients who developed ADA were one of 16 (16.3%) at week 12 (24 weeks of total treatment) and five of 13 (38.5%) at week 24 (36 weeks of total treatment). None of these patients had neutralizing antibody, none experienced an injection-site reaction, and no hypersensitivity reactions were reported

Study 006 evaluated two dose levels of 0.025 mg/kg/day (n=24) and 0.05 mg/kg/day (n=26). After 24 weeks of treatment, three of 24 (12.5%) patients in the 0.025 mg/kg/day group developed ADA. Four weeks after the end of treatment (28 weeks or end of study), four patients had ADA. Of patients with ADA, one patient (subject (b) (6) had neutralizing antibody at EOT (week 24) and at 4 weeks after EOT. It is not clear whether there was any follow-up at 3 or 6 months for this patient based on the submitted study report. At the 0.05 mg/kg/day dose, five of 26 (19.2%) patients had ADA at 24 weeks and at 4 weeks after EOT. Of the five patients with ADA, two patients (subjects (b) (6)) had neutralizing antibody at week 24 but did not have neutralizing antibody 4 weeks after EOT. None of these subjects experienced an injection site reaction, and no hypersensitivity reactions were reported.

In open-label extension study 304, the number of patients who developed ADA were as follows: six of 44 patients (13.6%) at baseline (24 weeks of treatment), 15 of 26 (36.6%) at week 12 (36 weeks of total treatment), 14 of 26 (53.8%) at week 24 (48 weeks of total treatment) and one of six (16.7%) at week 28 (4 weeks after EOT). One subject had neutralizing antibody at week 24. One of the patients with ADA reported an injection site reaction, and no hypersensitivity reactions were reported.

6.3.2.5. Does the immunogenicity affect the PK of the therapeutic protein?

Overall, impact of immunogenicity on PK is unknown in the pediatric patients with SBS. PK samples were only collected in the core studies 003 and 006. In study 003, only one patient developed ADA at dose of 0.025 mg/kg/day 4 weeks after the end of 12 weeks of treatment, which is not enough to assess the effect of antibodies on PK. In study 006, although five patients developed ADA at the end of 24 weeks of treatment, PK samples were only collected

after the first dose. Therefore, effect of immunogenicity on PK cannot be assessed in this study of pediatric patients with SBS.

In an open-label extension study of adults with SBS, ADA appeared to have no impact on PK, as teduglutide concentrations in ADA positive patients were similar to those in ADA negative patients. (Details are available in the Clinical Pharmacology Review for NDA 203441 (SND 113) by Dr. Lin Zhao dated May 27, 2014). The pediatric extension studies 303 and 304 are on-going and the Applicant is not planning to collect additional PK blood samples to assess the effect of immunogenicity on PK. Based on no significant impact of ADA on PK in adult patients with SBS, additional PK sampling from the on-going study was not considered critical.

6.3.2.6. Do the anti-product antibodies have neutralizing activity?

In study 003, no pediatric patients with SBS developed neutralizing activity after 12 weeks of treatment. When patients in study 003 were enrolled in extension study 303, none developed neutralizing antibody after 24 weeks of additional treatment (total treatment of 36 weeks).

In study 006, two pediatric patients with SBS had neutralizing antibodies at the end of 24 weeks of treatment with 0.5 mg/kg/day dose. Four weeks after EOT, these two patients no longer had neutralizing antibodies. However, one patient treated with 0.025 mg/kg/day developed neutralizing antibody after 24 weeks of treatment and remained to have neutralizing antibody 4 weeks after EOT. It is not clear whether there was any follow-up in 3 or 6 months for this patient based on the submitted study report. Of the patients in study 006 who were enrolled in extension study 304, one patient developed neutralizing antibody with 24 weeks of additional treatment (total treatment of 48 weeks).

6.3.2.7. What is the impact of anti-product antibodies on clinical efficacy?

Because of the very low number of patients who developed neutralizing antibodies in the pediatric program, it is not possible to directly assess potential impact of anti-drug antibodies on efficacy.

For study 006, 44/55 (80%) patients received teduglutide in both core and extension studies as of the time of the data cut-off. Two patients discontinued the study early; one patient who did not receive teduglutide in the core or extension studies was lost to follow-up, and one patient discontinued from teduglutide early due to physician decision died from worsening SBS, not related to teduglutide (see death narrative in Section 8.3.). No patient discontinued treatment due to loss of efficacy.

In extension study 303, 24 patients enrolled following their participation in study 003. Of 16 patients who received teduglutide in both the core and extension studies, 13 completed at least 24 weeks of treatment in the extension study at the time of the cut-off date. There was no discontinuation from treatment among patients who enrolled in the extension study.

Taken together these results suggest that loss of efficacy (regardless of available data on ADA status) was not prominent over the available follow-up period.

6.3.2.8. What is the impact of anti-product antibodies on clinical safety (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

There were two cases of anaphylaxis in the pediatric teduglutide program, neither of which were related to teduglutide. One was due to vancomycin-related reaction (red man syndrome) of which there was a prior history, and which resolved with discontinuation of vancomycin. The second case of anaphylaxis was due to a double dose of fondaparinux and resolved with epinephrine, diphenhydramine and racepinephrine. Neither case was related to teduglutide administration. In the core studies, there were higher rates of reported injection site reactions and hypersensitivity in patients treated with teduglutide 0.05 mg/kg/day (12/41, 29%) than in patients treated 0.025mg/kg/day (8/38, 21%) or with SOC (none) (see Table 33). However, none of the cases of injection site reactions and hypersensitivity reactions were related to teduglutide. Therefore, based on the available patient narratives, there appears to be no evidence for the impact of ADA on clinical safety.

6.3.2.9. Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

In pediatric studies (studies 003, 006, 303 and 304), teduglutide was provided as a lyophilized powder in a sterile, single-use, 3 mL glass vial with different strengths (1.25 mg, 2.5 mg or 5 mg per vial) and was reconstituted with 0.5 mL Sterile Water for Injection provided in a prefilled syringe (Table 5). All three strength vials have the same formulation matrix but have different concentrations of teduglutide upon reconstitution with 0.5 mL sterile water in the prefilled syringe (Table 6). Intended doses/volumes were withdrawn with either 0.3 mL or 0.5 mL dosing syringe from the glass vials in the pediatric studies.

Table 5. Comparison of Formulation and Device Used in Phase 3 Pediatric Studies, (b) (4)

Study Reference	Doses (mg/kg/day)	Strength (mg teduglutide/vial)	Dosing Syringe/Needle Combination
TED-C13-003	0.0125, 0.025, 0.05	1.25, 2.5, and 5 mg	0.3 mL insulin syringe with 31Gx5/16" needle attached
TED-C14-006	0.025, 0.05	2.5 mg/vial for 0.025 mg/kg/day dose 5.0 mg/vial for 0.05 mg/kg/day dose	0.5 mL insulin syringe with 30Gx5/16" needle attached
SHP 633-303	0.05	5 mg	0.5 mL insulin syringe with 30Gx5/16" needle attached
SHP 633-304	0.05	1.25 mg and 5 mg	0.5 mL insulin syringe with 30Gx5/16" needle attached
[redacted]			(b) (4)

Study Reference	Doses (mg/kg/day)	Strength (mg teduglutide/vial)	Dosing Syringe/Needle Combination
Commercial 5-mg kit (approved for adults)	0.05	5 mg	(b) (4) syringe with 26G 5/8" needle attached

Source: Reviewer's table based on Applicant's response to IR, received February 7, 2019, CSR of studies TED-C13-003, SHP633-303, TED-C14-006, SHP633-304 and proposed product label

Table 6. Volume Needed for 0.05 mg/kg Dose for Different Body Weight and Different Vial Strength

Patient Weight (kg)	Dose Based on 0.05 mg/kg (mg)	Concentrations of Reconstituent/ Volume Needed for Prescribed Dose		
		1.25 mg/Vial (2.5 mg/mL)	2.5 mg/Vial 5 mg/mL	5 mg/Vial 10 mg/mL
10	0.5	0.2 mL	0.1 mL	0.05 mL
20	1.0	0.4 mL	0.2 mL	0.1 mL
30	1.5	0.6 mL	0.3 mL	0.15 mL
40	2.0	0.8 mL	0.4 mL	0.2 mL
50	2.5	1 mL	0.5 mL	0.25 mL

Source: Reviewer created table

(b) (4)

the Applicant is proposing to use the currently marketed 5-mg vial for adults, which is co-packaged with 1-mL (b) (4) dosing syringe attached with 26G 5/8" needle, in pediatric patients 1 year of age and older with a minimum body weight of 10 kg.

Dose withdrawal from 5-mg vial with 1-mL syringe increases the dosing variability for pediatric patients due to the smaller volume for the same dose compared to dosing from 1.25-mg vial (Table 6). In addition, use of a 1-mL syringe compared to 0.5 mL syringe used in clinical trials can also increase the variability due to a greater syringe graduation for a 1-mL syringe compared to a 0.5 mL syringe. The variability in dosing, which depends on the tolerance and expelled volume from the syringe, increases for pediatric patients with lower body weight (up to 32% dosing variability in patient with 10 kg body weight) compared to larger pediatric patients and decreases with increasing body weight (Table 7). The Applicant has thus proposed 10 kg as the lowest body weight for which this presentation and kit can be safely used. Refer to Office of Device Evaluation review for the variability due to the syringe size.

Table 7. Potential Highest Variability for Dosing with Various Syringes, by Body Weight

Patient Weight (kg)	Dose Prescribed with 0.05 mg/kg Posology (mg)	Intended Volume (mL) of Delivery with 5 mg/Vial (10 mg/mL)	Variability/ +/- Percent of Prescribed Dose		
			0.3-mL Syringe	0.5-mL Syringe	1-mL Syringe
10.0	0.50	0.050	11%	17%	32%
12.5	0.63	0.063	9%	14%	26%
15.0	0.75	0.075	8%	12%	22%
17.5	0.88	0.088	7%	11%	19%
20.0	1.00	0.100	7%	10%	17%
25.0	1.25	0.125	6%	8%	14%
30.0	1.50	0.150	5%	7%	12%
35.0	1.75	0.175	5%	6%	11%
40.0	2.00	0.200	5%	6%	10%
45.0	2.25	0.225	5%	5%	9%
50.0	2.50	0.250	5%	5%	8%

Source: Reviewer's table, based on Applicant's response to IR, received February 7, 2019

The potential impact of this potential dosing variability was assessed from both efficacy and safety perspectives. The conclusion is that this degree of dosing variability is acceptable for the following reasons:

1. A concern of receiving a lower dose due to dosing variability could potentially represent up to 32% lower dose than the prescribed dose of 0.05 mg/kg. This may result in a suboptimal efficacy. In study 006, 50% lower dose, 0.025 mg/kg, performed similarly to the proposed 0.05 mg/kg dose in the pediatric patients with SBS. In addition, ER relationship based on 0.025 and 0.05 mg/kg doses for efficacy assessed as percent change from baseline in PN volume, did not suggest any notable exposure-dependent change in the response. Taken together, if a 10-kg pediatric patient received up to 32% less than the prescribed 0.05 mg/kg dose due to dosing variability, efficacy is anticipated to be minimally affected.

2. A concern of receiving higher dose due to dosing variability could represent potentially up to 32% higher dose than the prescribed dose of 0.05 mg/kg. This could be an increased risk for adverse events. In study 006, no major differences in AE profiles were observed between 0.025 mg/kg versus 0.05 mg/kg doses for the rate and type of common and serious treatment emergent adverse events in pediatric patients with SBS. These data are limited in their ability to provide direct evidence of safety specific to pediatric patients at doses greater than 0.05 mg/kg. Nevertheless, a significant increase in AEs is not anticipated based on the experience in adult patients. In adults, no major difference in safety between the 0.05 mg/kg and 0.1 mg/kg doses was identified at the time of initial approval while the common adverse events were similar between pediatric and adult populations.

3. In pediatric studies, patients receiving the 0.05 mg/kg dose with 0.5 mL syringe were already exposed to some degree of dosing variability, but it was less than the maximum 32% estimated with use of the proposed 1-mL syringe with 26-gauge needle (Table 7). Specifically, for the lowest body weight (10 kg) a patient's anticipated variability was up to ±17% in the pediatric studies (when dosed with 0.5ml syringe). Thus, the difference between potential dosing variability that patients were exposed to in the pediatric studies (and is reflected in the safety data) and the theoretical "worst case" represents the difference between these two values, or 15%.

4. Based on population PK modeling, the systemic exposures (AUC) in pediatric patients appear to be lower compared to that of adults with the same mg/kg dose (Figure 2). The difference in exposure appears most pronounced in the youngest (lowest body weight) patients. Thus, it is also reasonable to consider that even in the "worst case" scenario, where a pediatric patient weighing 10 kg is exposed to the upper limit of 32% greater dose than prescribed, the systemic exposure associated with that dose will be comparable to that achieved in adults, and which demonstrated to be acceptable from a safety standpoint, in that population.

7. Sources of Clinical Data, Review Strategy, and Review of Efficacy

7.1. Table of Clinical Studies

Table 8 summarizes the phase 3 and extension studies of teduglutide for the treatment of SBS in pediatric patients greater than 1 year of age to 17 years of age.

Table 8. Clinical Studies/Trials Supporting Efficacy and Safety

Study ID	Study Design	Total Enrollment/ Enrollment Goal	Dose, Route, and Regimen	No. of Subjects by Arm Entered/ Completed	Treatment Duration	Study Objectives Study Population	Inclusion Criteria	Efficacy Endpoint
Core Studies								
TED-C13-003 17 sites in US, UK Completed: 11/2013–1/2015	Open-label, 4 cohorts: 3 teduglutide (TED) and 1 SOC	Enrolled: 42 Goal: 24–36	TED 0.0125, 0.025, 0.05 mg/kg/day SC qd	0.0125: 8/7 0.025:14/14 0.05: 15/14 SOC: 5/5	12 weeks	PD, safety, and PK Male:28 Female:14 Age (Years): Median: 3.0 Range: 1–14	Pediatric subjects with SBS aged 1 through 17 years	Change from baseline in parenteral support
TED-C14-006 27 sites in US, UK, Canada, Belgium, Finland, Germany, and Italy Completed: 11/2016–8/2017	Open-label, choice of TED or SOC arms. Double-blind TED dose groups	Enrolled: 59 Goal: 26	TED 0.025 and 0.05 mg/kg/day SC qd	0.025:24/24 0.05: 26/26 SOC: 9/9	24 weeks	Efficacy/ PD, safety, and PK Male:41 Female:18 Age (Years): Median: 6.0 Range: 1–17	Pediatric subjects with SBS through 17 years	Reduction in PS volume of at least 20% at end of treatment (EOT) from baseline.
Extension Studies								
SHP633-303[a] 11 sites in US, UK Ongoing Started: 12/2016 Interim Data Cutoff: 1/2018	Open-label extension study, includes retrospective and prospective data collection periods	Retrospective: Enrolled: 29 Prospective: Enrolled: 24 Goal: 40	TED 0.05 mg/kg/day SC qd	Retrospective: TED/NTT: 24 TED/TED: 5 Prospective: TED/NTT: 8 TED/TED: 16	Retrospective observation: App. 2.5- to 3-year gap Prospective: Pts in multiple NTT periods and/or 28-week treatment cycles	Retrospective: M/F: 20/9 Age (Years): Median: 4.0 Range: 1–17 Prospective: M/F: 17/7 Age (Years): Median: 4.0 Range: 1-14	Pediatric subjects who completed TED-C13-003	Reduction in PS volume of at least 20% at EOT from baseline.

Extension Studies								
Study ID	**Study Design**	**Total Enrollment/ Enrollment Goal**	**Dose, Route, and Regimen**	**No. of Subjects by Arm Entered/ Completed**	**Treatment Duration**	**Study Objectives Study Population**	**Inclusion Criteria**	**Efficacy Endpoint**
SHP633-304 Ongoing 23 sites in US, UK, Canada, Belgium, Finland, Germany, and Italy Ongoing: Started: 1/2017 Interim Data Cutoff: 2/2018	Open-label extension study	Enrolled: 55 Goal: 59	TED 0.05 mg/kg/day SC qd	TED/TED: 44 TED/NTT: 3 NTT/NTT: 6 NTT/TED: 2	Subjects could participate in multiple NTT periods and/or 28-week teduglutide treatment cycles	Male:37 Female:18 Age (Years): Median: 6.1 Range: 1–17	Pediatric subjects with SBS through 17 years	Reduction in PS volume of at least 20% at EOT from baseline.

Source: Reviewer's Table, adapted from the Applicant's Summary of Clinical Efficacy, submitted on September 11, 2018
NTT = no-teduglutide treatment; PD = pharmacodynamic; PK = pharmacokinetic; Prosp = prospective; qd = once daily; Retro = retrospective; SC = subcutaneous; TED = teduglutide; SOC = standard of care; PS = parenteral support; SBS = short bowel syndrome
[a] Study SHP633-303 includes retrospective (n=29) and prospective (n=24) data collection periods.
RETRO TED/NTT-Subjects who received teduglutide in TED-C13-003 who never received teduglutide in the retrospective portion of SHP633-303
RETRO TED/TED- Subjects who received teduglutide in TED-C13-003 and received teduglutide in the retrospective portion of SHP633-303
NTT/NTT-Subjects in the SOC arms of the core studies who never received teduglutide treatment in the prospective portions of the extension studies
NTT/TED-Subjects in the SOC arms of the core studies who then received teduglutide treatment in the prospective portions of the extension studies
TED/NTT-Subjects who received teduglutide treatment in the core studies but not in the prospective portions of the extension studies
TED/TED-Subjects who received teduglutide treatment in both the core and prospective portions of the extension studies.

7.2. Review Strategy

The sNDA application to support expansion of the indication from adults to include pediatric patients 1 year of age and older relied upon partial extrapolation of efficacy from adult data. The FDA considered the pathophysiology of the condition (SBS resulting in IF with resultant dependence upon parenteral nutrition) and anticipated response to treatment to be sufficiently similar between adults and pediatric patients to support partial extrapolation of efficacy. As a result, the pediatric program for teduglutide negotiated with the Applicant and contained within the PWR outlined a need for a dose-ranging study designed to obtain PK, PD, and safety information on a range of doses, and a single phase 3 trial to confirm that the selected dose is safe and efficacious in pediatric patients.

Short bowel syndrome severe enough to require parenteral nutrition dependence is rare, even within the adult population. The population of afflicted pediatric patients is further limited, because young children may have an increased opportunity for intestinal adaptation as compared with older pediatric patients and adults. Thus, when serious insult occurs in the infant or young child, the chances that they will remain PN dependent are lower than if a similar insult occurred in an older patient with a GI tract that is more mature/fully developed.

Since the overall patient population which stands to benefit from teduglutide is small, a large, formally powered, efficacy trial was not feasible. Given the unmet medical need in this small but severely affected population, this pediatric program was considered acceptable despite its limited size and scope.

The review strategy, thus, focused on three key elements. The first was understanding the available evidence in support of dose selection. This was analyzed by summarizing descriptive statistics on the efficacy data derived from study 003 and was supported by ER analyses conducted by clinical pharmacology/pharmacometrics review team. Second, the efficacy of the selected dose (0.05 mg/kg) was described descriptively based primarily on the efficacy results of study 006. While data from a small SOC arm were available, formal comparisons were underpowered and subject to significant bias, as participation in the SOC arm was open label and not randomized. It is noted that uncertainty exists regarding the minimal “clinically meaningful” reduction in PN volume, and that the defined “20% reduction in PN volume” which is analogous to the cutoff used to define a responder in the adult program may not be the most relevant or clinically important to pediatric patients. Thus, a number of additional supportive analyses were conducted to support that a meaningful clinical improvement was attained. While not multiplicity controlled, the results of such analyses are summarized below. Data on long-term effectiveness, need for chronic administration, and durability of benefit achieved off treatment were derived from the combined experience across two long-term extension studies (303 and 304) and these results were considered collectively when describing the long-term outcomes. Third, all available safety data were considered including those derived from the phase 2 and phase 3 studies, long-term extension studies, as well as registry data submitted by the Applicant from the interim approval study report (NDA 203441/S013; TED-R13-002 v.3.0,

data cut-off June 30, 2018; broad postmarketing registry, including both adult and children with SBS on PN).

7.3. Review of Relevant Individual Trials Used to Support Efficacy

Compliance with Good Clinical Practices
The Applicant attested that studies 003 and 006 were conducted in accordance with the current applicable International Conference on Harmonisation guidelines, good clinical practice, and World Medical Association Declaration of Helsinki and its amendments concerning medical research in humans.

According to the Applicant, informed consent/assent was documented by use of a written consent/assent approved by the Independent Ethics Committee/Institutional Review Board and signed by the patient and/or patient's parent or guardian before any screening and protocol-specific procedures were performed. A consent/assent form template was provided by the Applicant or designee and adapted by the investigator to meet study site, state, and country ethical guidelines, as appropriate.

Financial disclosure
For studies 003 and 006 and extension studies 303 and 304, the Applicant provided a signed copy of FDA Form 3454 with a list of investigator names from each trial, certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Refer to Section 14.2.

The Applicant also certified that each of the listed clinical investigators were required to disclose whether they had a proprietary interest in the study drug or a significant equity in the Applicant as defined in 21 CFR 54.2(b), and none disclosed any such interests. In addition, the Applicant certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Issues Regarding Data Integrity and Submission Quality
The submission was complete and well-organized. All required information was readily available electronically, except that some patient disposition information was not readily available in the submitted report. However, the Applicant responded adequately to questions and concerns raised during the review cycle.

7.3.1. 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

Trial Design

This was a four-cohort open-label PK/PD study in pediatric patients with SBS who were dependent on PN, and included three parallel cohorts that received teduglutide doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks, as well as an observational SOC cohort. The three teduglutide cohorts were investigated in a staggered approach starting with the lowest dose, with a planned approximate eight patients for each cohort. The first enrolled cohort was assigned to 0.0125 mg/kg/day dose, the second cohort to 0.025 mg/kg/day, and the third cohort to 0.05 mg/kg/day (Figure 5).

Figure 5. Design of 12-Week Safety Study in Three Cohorts of Pediatric Patients With Short Bowel Syndrome

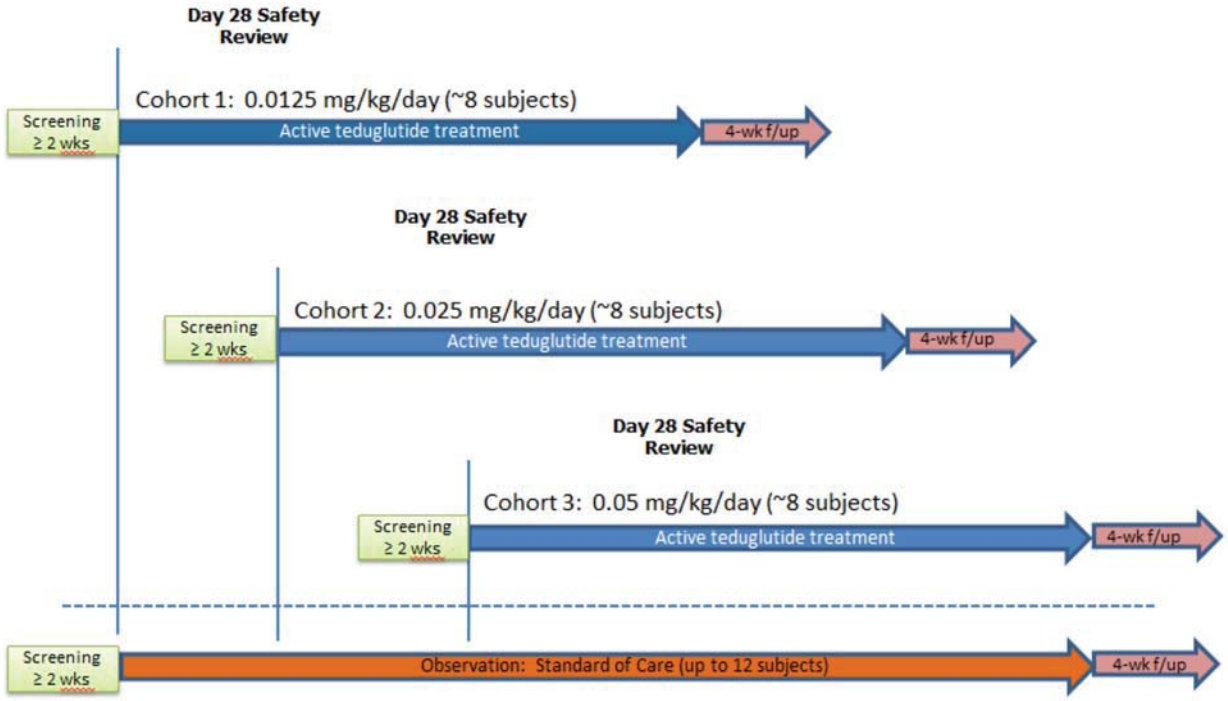


Figure 1: General Study Overview for Study 003
Source: Study 003 CSR p. 39

In study 003, patients or their parents/guardians were required to keep diaries of oral/enteral dietary intake, PN/IV support, and urine output throughout the screening period, the 12-week study period (or if early terminated, at EOT), and 4 weeks after EOT. Diaries were to be completed daily to the extent possible to provide the most accurate clinical representation. The most pertinent recordings were those 48 to 72 hours prior to scheduled visits, which were reviewed by the investigator or their designee to assess clinical status and opportunity for PN/IV changes and advance in feeds. Investigator prescribed data were captured in the PN/EN

history, and adjustments were recorded on the electronic case report forms.

Key Inclusion Criteria:

1. Age 1 to 17 years inclusive
2. History of SBS as a result of a major intestinal resection, (e.g., due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis) for at least 12 months prior to screening
3. Requiring PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs prior to screening
4. Stable PN/IV support for at least 3 months (defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds [i.e., 10% or less change in PN or advance in feeds]) prior to baseline, based upon the opinion of the investigator.

Key Exclusion Criteria

1. Any major gastrointestinal (GI) surgical intervention (including but not limited to serial transverse enteroplasty or any other bowel lengthening procedure) performed within 3 months of screening (enteral feeding tube insertion and/or endoscopy are were permissible)
2. Evidence of clinically significant untreated intestinal obstruction or active stenosis, or evidence of clinically significant obstruction noted on upper GI series within 6 months of screening
3. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease, or known DNA abnormalities (i.e., familial adenomatous polyposis, Fanconi syndrome)
4. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome, including persistent, severe gastroschisis-related motility disorders
5. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of patients who had undergone ventricular or atrial septal defect repair
6. 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
7. Pregnant or lactating female patients
8. Participation in a clinical study using an experimental drug 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
9. Previous use of native GLP-2 and glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening or any prior use of teduglutide
10. Previous use of oral or IV glutamine, octreotide, or dipeptidyl peptidase IV (DPP-IV) inhibitors within 3 months prior to screening
11. Patients with active Crohn's disease who had been treated with biological therapy (e.g., antitumor necrosis factor [anti-TNF] or natalizumab) within the 6 months prior to screening

12. Patients with inflammatory bowel disease who required chronic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
13. More than three SBS-related or PN-related hospital admissions (e.g., catheter sepsis, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to screening
    a. Any scheduled hospital admission within 1 month prior to screening (24-hour observations or central line replacement/repair, in an otherwise stable patient, are allowed)
14. Body weight <5 percentile for age or <10 kg
15. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the following laboratory test results at screening:
    a. Total bilirubin (TB) ≥2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥5x ULN
    c. Alanine aminotransferase (ALT) ≥5x ULN

    For patients with Gilbert's disease:
    d. Indirect (unconjugated) bilirubin ≥2x ULN
16. Signs of known continuous, active or unstable, clinically significant renal dysfunction shown by any of the following laboratory test results at screening:
    a. Serum creatinine ≥2x ULN
    b. Creatinine clearance <50 mL/min*
       *Only applied to patients with a history of creatinine clearance <50mL/min who then will be required to have >50mL/min to participate in the study
17. Unstable, clinically significant pancreatic or biliary disease
18. Presence of any of the excluded disease states described in Table 9.

Table 9. Excluded Disease States

Body system	Known conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis Celiac disease Refractory or tropical sprue Pseudo-obstruction
Gastrointestinal	Active IBD which required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months IBD that required chronic systemic immunosuppressant therapy for symptom control Tufting or autoimmune enteropathy or microvillous inclusion disease Untreated pre-malignant or malignant change in upper GI, biopsy or polypectomy Known, untreated, polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome, Eversmeyerous polypius) Intestinal or other major surgery scheduled within the time frame of the study Chronic active pancreatitis Cholecystitis
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
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)

Source: TED-C13-003 Protocol Amendment 3, July 11, 2014, page 11, page 30/68. Overall protocol submission 228/266, and TED-C14-006 Protocol Amendment 4; March 15, 2016, pages 29–31/77. Overall protocol submission 334-337/384

Study Endpoints

Study 003 did not have a pre-specified primary efficacy endpoint. PK/PD endpoints for evaluation were as follows:

PK parameters

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})

Maximum plasma concentration (C_{max})
Time to C_{max} (t_{max})
Terminal-phase half-life ($t_{1/2}\lambda z$)

PD/Efficacy parameters
≥10% reduction in PN/IV support. According to the Applicant, this PD endpoint was considered clinically meaningful to PN/IV-dependent children who plateaued in their ability to wean PN/IV and advance their oral/enteral feeds.
≥20% reduction in PN/IV support
An increase in EN tolerance (calories and volume)
A decrease in PN (calories and volume)
Ostomy output/stool balance testing (at selected sites)
Urine output (mL/day).

Statistical Analysis Plan
The sample size for the study was not determined based on a formal power calculation. The Applicant pre-specified descriptive statistics to evaluate efficacy endpoints. The Applicant did not plan to conduct any formal hypothesis testing.

For analyses of PN/IV support and EN support, two sets of results were reported based on two data sources: patient diary data and investigator prescribed data. Since the patient diary data were considered as a more representative measure of efficacy than the investigator prescribed data, efficacy summaries focused on the patient diary data. This approach is consistent with that taken in the adult program.

The intent-to-treat (ITT) population consisted of all subjects who enrolled into the trial. The ITT population was the primary analysis population analyzed for PK/PD endpoints.

Protocol Amendments
As this study did not have pre-specified efficacy endpoints, none of the protocol amendments impacted the integrity of the study design or conduct. Amendment 1 dated January 2014 (UK only), Amendment 2 dated February 2014 (Sweden only) and Amendment 3 dated July 2014 (all sites) did not make changes to sample size or statistical method sections.

7.3.2. TED-C13-003: Study Results

Patient Demographics
Seventeen sites in two countries enrolled patients for this study (16 sites in USA; and one site in United Kingdom).

For the ITT population, the majority of patients enrolled in this study were white (33/42, 78.6%) and male (28/42, 66.7%); the mean age was 4.4 years (range: 1 to 14 years). The baseline demographics were not balanced across treatment arms in this non-randomized study. For example, the proportion of female patients was 21% in the 0.025 mg/kg/day arm but 47% in

the 0.05 mg/kg/day arm; the mean age in the 0.05 mg/kg/day arm was 4.5 years but was 2.2 years in the SOC arm; and patients in 0.025 and 0.05 mg/kg/day arms were aged 1-18 years old, whereas 100% (5/5) of the patients in the SOC arm were 2 to 6 years of age.

Table 10. Patient Demographics of Study 003

	TED-C13-003				
Parameter	0.0125 mg/kg/day (N=8)	0.025 mg/kg/day (N=14)	0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Standard of Care (N=5)
Age (years), Mean (SD)	5.1 (4.55)	4.6 (3.43)	4.5 (3.16)	4.7 (3.50)	2.2 (0.45)
Age distribution, n (%)					
1 to <12 years	7 (87.5)	13 (92.9)	14 (93.3)	34 (91.9)	5 (100.0)
<2 years	1 (12.5)	2 (14.3)	1 (6.7)	4 (10.8)	0
2 to <6 years	4 (50.0)	8 (57.1)	11 (73.3)	23 (62.2)	5 (100.0)
6 to <12years	2 (25.0)	3 (21.4)	2 (13.3)	7 (18.9)	0
12 to 18 years	1 (12.5)	1 (7.1)	1 (6.7)	3 (8.1)	0
Gender n (%)					
Male	6 (75.0)	11 (78.6)	8 (53.3)	25 (67.6)	3 (60.0)
Female	2 (25.0)	3 (21.4)	7 (46.7)	12 (32.4)	2 (40.0)
Race, n (%)					
White	6 (75.0)	11 (78.6)	13 (86.7)	30 (81.1)	3 (60.0)
Black or African American	2 (25.0)	1 (7.1)	1 (6.7)	4 (10.8)	1 (20.0)
Asian	0	0	1 (6.7)	1 (2.7)	1 (20.0)
Other	0	1 (7.1)	0	1 (2.7)	0
Not allowed based on local regulations	0	1 (7.1)	0	1 (2.7)	0
Ethnicity n (%)					
Hispanic or Latino	1 (12.5)	6 (42.9)	3 (20.0)	10 (27.0)	0
Not Hispanic or Latino	7 (87.5)	7 (50.0)	11 (73.3)	25 (67.6)	4 (80.0)
Not reported	0	1 (7.1)	1 (6.7)	2 (5.4)	1 (20.0)
Weight Z-Score at Baseline, Mean (SD)	-1.29 (0.95)	-0.50 (1.00)	-0.74 (0.89)	-0.77 (0.96)	-0.41 (1.34)
Height Z-Score at Baseline, Mean (SD)	-1.07 (0.83)	-1.03 (1.11)	-1.10 (1.44)	-1.07 (1.18)	-0.52 (1.67)
BMI Z-Score at Baseline, Mean (SD)	-0.56 (0.64)	0.35 (0.96)	-0.01 (0.93)	0.01 (0.93)	0.00 (1.15)
BMI Percentile for Age, Mean (SD)	0.32 (0.19)	0.59 (0.28)	0.50 (0.30)	0.49 (0.28)	0.51 (0.34)

Source: Applicant's IR Response, dated January 29, 2019
[1] Data on race and/or ethnicity were not collected when prohibited by in XX country because of local regulations.

Other Baseline Characteristics

Baseline disease characteristics in study 003 were generally representative of the pediatric SBS population. Some of the baseline characteristics were not comparable across treatment arms, which may be attributed to the fact that the study was not a randomized study. The mean total remaining small intestine lengths were 28, 66, 33 and 37 cm in patients treated with

teduglutide 0.0125, 0.025 and 0.05 mg/kg/day and SOC, respectively. The baseline PS volumes were 55, 74, 66 and 80 mL/kg/day in patients treated with teduglutide 0.0125, 0.025 and 0.05 mg/kg/day and SOC, correspondingly.

Table 11. Short Bowel Syndrome History in Study 003

	Treatment Group				
Parameter	**0.0125 mg/kg/day (N=8)**	**0.025 mg/kg/day (N=14)**	**0.05 mg/kg/day (N=15)**	**Total Teduglutide (N=37)**	**Standard of Care (N=5)**
Primary reason for the diagnosis of SBS, n (%)					
Necrotizing enterocolitis	1 (12.5)	2 (14.3)	3 (20.0)	6 (16.2)	2 (40.0)
Midgut volvulus	2 (25.0)	4 (28.6)	7 (46.7)	13 (35.1)	2 (40.0)
Intestinal atresia	1 (12.5)	4 (28.6)	2 (13.3)	7 (18.9)	1 (20.0)
Gastroschisis	2 (25.0)	7 (50.0)	3 (20.0)	12 (32.4)	0
Long-segment Hirschsprung disease	NA	NA	NA	NA	NA
Other	2 (25.0)	0	1 (6.7)	3 (8.1)	0
Subjects with a stoma, n (%)	1 (12.5)	1 (7.1)	1 (6.7)	3 (8.1)	0
Type of stoma[a], n (%)					
Jejunostomy	0	0	0	0	0
Ileostomy	1 (100)	1 (100)	1 (100)	3 (100)	0
Colostomy	0	0	0	0	0
Subject with any remaining colon, n (%)	7 (87.5)	14 (100)	14 (93.3)	35 (94.6)	5 (100.0)
Estimated percentage of colon remaining, mean (SD)	75.0 (30.17)	67.1 (34.64)	75.4 (29.77)	72.2 (30.91)	66.6 (31.27)
Colon in continuity[b], n (%)	7 (100)	12 (85.7)	14 (100)	33 (94.3)	5 (100.0)
Total estimated remaining small intestinal length (cm), mean (SD)	28.1 (25.89)	66.3 (37.19)	32.8 (21.74)	45.0 (33.60)	37.4 (25.89)
Distal/terminal Ileum present, n (%)	2 (25.0)	1 (7.1)	4 (26.7)	7 (18.9)	1 (20.0)
Ileocecal valve present[c], n (%)	2 (100)	1 (100)	4 (100)	7 (100)	1 (100.0)
Baseline PS volume (mL/kg/day), mean (SD)	55.31(23.98)	74.23(29.73)	66.45(27.41)	67.33(27.9)	79.62(15.22)

[a] Percentages are based on the number of subjects with a stoma in each treatment group.
[b] Percentages are based on the number of subjects who have remaining colon in each treatment group.
[c] Percentages are based on the number of subjects with distal/terminal ileum present in each treatment group.
Source: Applicant's Summary of Clinical Efficacy Table 4, page 33
SD = standard deviation; SBS = short bowel syndrome

Overall imbalances in demographics and baseline disease characteristics are important to consider when interpreting results and suggest that a direct comparison between arms (particularly between treatment group and SOC) may be confounded.

Treatment Compliance, Concomitant Medications

Overall, the majority of patients who enrolled in the core studies completed treatment and completed the studies. Table 12 shows the disposition of patients in study 003.

Table 12. Disposition for Patients in Study 003

	Treatment Group				
Parameter	**0.0125 mg/kg/day n (%)**	**0.025 mg/kg/day n (%)**	**0.05 mg/kg/day n (%)**	**Total Teduglutide n (%)**	**Standard of Care n (%)**
Enrolled	8	14	15	37	5
Treated	8 (100)	14 (100)	15 (100)	37 (100)	-
Completed treatment[a]	7 (87.5)	14 (100)	14 (93.3)	35 (94.6)	5 (100)
Early treatment discontinuation	1 (12.5)	0	1 (6.7))	2 (4.8)	0
Withdrawal of consent	0	0	1 (6.7)	1 (2.7)	0
Protocol non-compliance	1 (12.5)	0	0	1 (2.7)	0
Completed study[b]	7 (87.5)	14 (100)	14 (93.3)	35 (94.6)	5 (100)

Source: Applicant's Study 003 CSR, Table 10-1, page 79/172
[a] Completion of treatment based on whether subject completed 12 weeks of study drug or standard of care
[b] For TED-C13-003, completion of study based on the End of Study page of the electronic case report form at Visit 15 (Week 16).

In study 003, 37 patients were treated with teduglutide, 15 of whom received 0.05 mg/kg/day. Two patients did not complete treatment and were withdrawn from the study: one patient (treated with 0.0125 mg/kg/day) was withdrawn due to protocol non-compliance, and one patient (treated with 0.05 mg/kg/day) withdrew consent. Five patients were enrolled in the SOC arm and all of them completed the 12-week study.

Concomitant Medications

All patients took at least one concomitant medication as shown in Table 13.

Table 13. Concomitant Medications Used in ≥15% of Patients in the Total Teduglutide Cohort - Safety Population

	Treatment Group				
Medication	0.0125 mg/kg/day N=8 n (%)	0.025 mg/kg/day N=14 n (%)	0.05 mg/kg/day N=15 n (%)	Total Teduglutide N=37 n (%)	SOC N=5 n (%)
Any concomitant medication					
No	0	0	0	0	0
Yes	8 (100)	14 (100)	15 (100)	37 (100)	5 (100)
Paracetamol	4 (50)	6 (42.9)	9 (60.0)	19 (51.4)	3 (60.0)
Nystatin	2 (25.0)	3 (21.4)	4 (26.7)	9 (24.3)	3 (60.0)
Loperamide	1 (12.5)	4 (28.6)	5 (33.3)	10 (27.0)	1 (20.0)
Cholestyramine	3 (37.5)	1 (7.1)	2 (13.3)	6 (16.2)	2 (40.0)
Piperacillin/tazobactam	0	5 (35.7)	3 (20.0)	8 (21.6)	0
Bactrim	0	5 (35.7)	3 (20.0)	8 (21.6)	1 (20.0)
Electrolyte solutions	2 (25.0)	2 (14.3)	2 (13.3)	6 (16.2)	1 (20.0)
Enzymes	2 (25.0)	2 (14.3)	2 (13.3)	6 (16.2)	2 (40.0)
Glucocorticoids	1 (12.5)	3 (21.4)	2 (13.3)	6 (16.2)	0
Vancomycin	3 (37.5)	6 (42.9)	4 (26.7)	13 (35.1)	1 (20.0)
H-2 receptor antagonists	0	3 (21.4)	3 (20.0)	6 (16.2)	4 (80.0)
Heparin group	2 (25.0)	5 (35.7)	5 (33.3)	12 (32.4)	1 (20.0)
Metronidazole	3 (37.5)	7 (50.0)	6 (40.0)	16 (43.2)	2 (40.0)
Ferrous sulfate	2 (25.0)	6 (42.9)	4 (26.7)	12 (32.4)	1 (20.0)
Ethanol	1 (12.5)	6 (42.9)	3 (20.0)	10 (27.0)	1 (20.0

	Treatment Group				
Medication	0.0125 mg/kg/day N=8 n (%)	0.025 mg/kg/day N=14 n (%)	0.05 mg/kg/day N=15 n (%)	Total Teduglutide N=37 n (%)	SOC N=5 n (%)
Ibuprofen	4 (50.0)	4 (28.6)	2 (13.3)	10 (27.0)	2 (40.0)
Lansoprazole	0	4 (28.6)	4 (26.7)	8 (21.6)	0
Cholecalciferol	3 (37.5)	5 (35.7)	4 (26.7)	12 (32.4)	0

Source: Adapted from Applicant's TED-C13-003 Study Report Body, Table 11-4, page 92-95/2333 and Section 14, Table 14.1.10.2; Appendix 16.2, Listing 16.2.4.7
N = total number of subjects in a dosing cohort; n = number of subjects for category specified
Percentages are based on the Safety population in each treatment arm.
Concomitant medications are defined as medications taken during the treatment period. For the standard of care cohort, the treatment period is between the baseline visit and the Week 12/end-of-treatment visit.
Patients are counted no more than once for incidence.

Paracetamol, antibiotics, and proton-pump inhibitors were the most common concomitant medications in study 003. This appears to be consistent with some of the common TEAEs (pyrexia, catheter associated infections) in this clinical program where the use of concomitant medications such as paracetamol will be needed for pyrexia and different antibiotics will be needed for catheter-associated infections. Nevertheless, these concomitant medications are not expected to confound the efficacy results (i.e., none have direct impact on absorptive capacity).

Data Quality and Integrity
The submitted data followed FDA guidance and were analysis ready.

Efficacy Results – Primary Endpoint
There was no pre-specified primary endpoint for study 003. A reduction in PN/IV volume from baseline of at least 20% at week 12 (or EOT) was evaluated post hoc in the CSR to support this submission. The results are shown in Table 14. Of 15 patients who received teduglutide 0.05 mg/kg/day, 53% (8/15) achieved the responder status for this efficacy endpoint. The response rates in the treatment arms 0.0125 mg/kg/day, 0.025 mg/kg/day and SOC were 13% (1/8), 71% (10/14) and 0% (0/5), respectively.

Table 14 also summarizes distribution of patients who obtained different levels of reduction in PS/IV volume at EOT from baseline, including ≥50% reduction, ≥75% reduction, and 100% complete weaning (i.e., enteral autonomy). The 0.0125 mg/kg dose did not appear to be effective. Of eight patients in 0.0125 mg/kg arm, there was only one patient who achieved 20% and 50% improvement.

The two higher doses (0.025 and 0.05 mg/kg) showed higher response rates compared to the 0.0125 mg/kg/day, regardless of the threshold used for reduction in PN. More than 60% (18/29) of patients in both arms combined had ≥20% reduction, and more than 25% (8/29) had ≥50% reduction. There were two patients who were able to achieve full enteral autonomy, one from each dose arm.

Table 14. Distribution of Reduction in PN/IV Volume at End of Treatment Based on Subject Diary Data, Study 003

	Treatment Group				
	0.0125 mg/kg/day (N=8) n (%)	0.025 mg/kg/day (N=14) n (%)	0.05 mg/kg/day (N=15) n (%)	Total Teduglutide (N=37) n (%)	Standard of Care (N=5) n (%)
≥20% Reduction (primary endpoint)	1 (12.5)	10 (71.4)	8 (53.3)	19 (51.4)	0
≥50% Reduction	1 (12.5)	3 (21.4)	5 (33.3)	9 (24.3)	0
≥75% Reduction	0	1 (7.1)	3 (20.0)	4 (10.8)	0
100% Reduction (complete weaning or enteral autonomy)	0	1 (7.1)	1 (6.7)	2 (5.4)	0

Source: Applicant's Summary of Clinical Efficacy, Tables 5 and 6, pages 36 and 38, verified by FDA.

Efficacy Results – Secondary and other relevant endpoints

This sub-section summarizes secondary efficacy endpoints that are of clinical interest. The secondary endpoint results appeared consistent with the primary efficacy findings summarized above and supported the dose selection for study 006.

Complete Weaning

Two patients (one in 0.025 mg/kg group and one in 0.05 mg/kg) achieved enteral autonomy, which was maintained to end of study visit (4 weeks after treatment discontinuation), representing a clinically important benefit (Table 15). These patients were severely affected and had no reasonable expectation of achieving enteral autonomy over a period of weeks, given their longstanding history of PN dependence, baseline disease characteristics, and remaining bowel length. Both patients had disease onset in infancy and had required PN for at least the four preceding years, but they were able to wean completely from PN by week 12, and remained off PN at week 16 (end of study). Characteristics of these patients are summarized below.

Table 15. Patients Who Weaned Completely From PN in Study 003 (ITT)

Teduglutide Dosage (mg/kg/day)	Subject Number	Gender/ Age	Reason for Major Intestinal Resection	Presence of Stoma/Colon in Continuity (Yes/No)	Percent Colon Remaining/ Small Intestinal Length	Baseline PN/IV Volume (L/week)	PN/IV Days/Week at Screening	Study Week PN/IV Stopped	PN/IV Resumed at Week 16 (Yes/No)	Baseline PN/IV volume prescribed in ml/kg/day
0.025	(b) (6)	M/14	Gastroschisis	No/Yes	100% / 145 cm	6.94	7	11	No	22.38
0.05		F/8	Intestinal atresia	No/Yes	100% / 23 cm	4.00	4	4	No	30.89

Source: Adapted from Applicant's table 11-7 in CSR for TED-C13-003 (page 106/2333) (revised table received in response to IR, dated February 12, 2019)

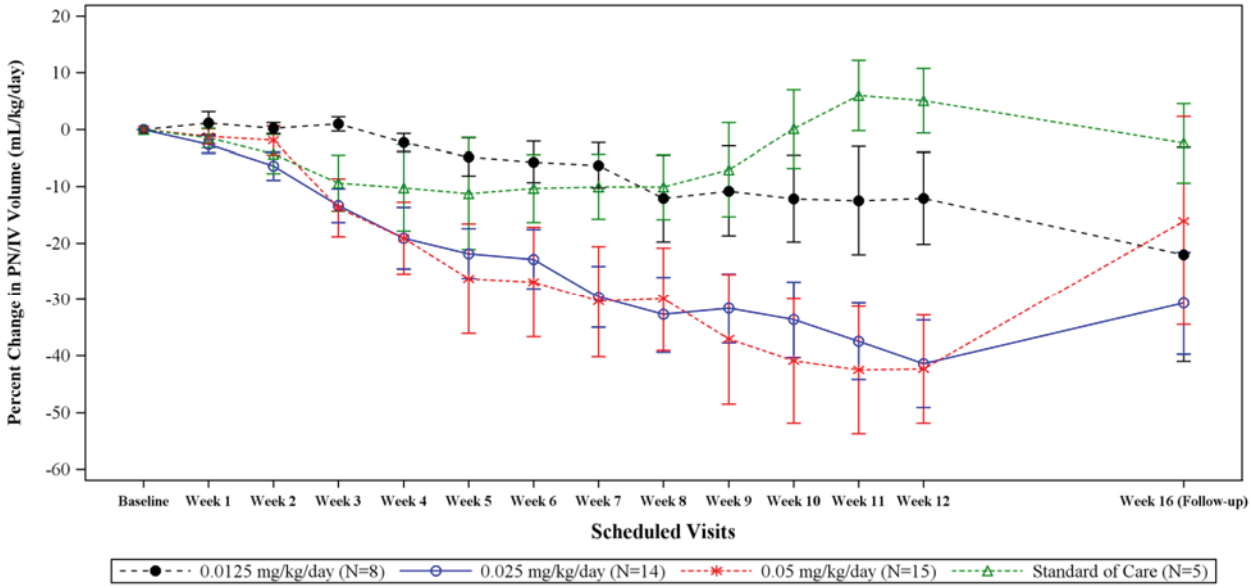
Although they represent a minority of teduglutide-treated patients, those who were able to achieve this milestone in this small study derived unequivocal benefit from treatment. No similar successes were observed in the SOC or 0.0125 mg/kg arms.

Percent Change in PN volume

The Applicant provided supportive analyses to explore the effect of the three studied doses of teduglutide on required PN volume. The following figure demonstrates that 0.025 mg/kg (blue)

and 0.05 mg/kg (red) appeared to perform better than 0.0125 mg/kg dose (black) or SOC (green) on mean percent change from baseline in PN volume over time by Week 12. Although this was an open-label, non-randomized study, this assessment supports the selection of the two doses that were carried forward to study 006.

Figure 6. Mean Percent Change From Baseline in PN/IV Volume by Visit (ITT, Diary Data) in Study 003



PN/IV = parenteral nutrition/intravenous, SE = standard error
Average daily value is calculated as [(sum of non-missing daily values in the diary / number of days with non-missing values)] / last available body weight prior to the visit.
Figure illustrated mean percent change accompanied by small bars representing ± SE.
Source: CSR for TED-C13-003, Applicant's Figure 14.2.1.8.1, (1/157) Post hoc analysis outputs (intention to treat set, based on subject diary data)

Patients continued to make progress in reducing necessary PN volume as time progressed, to the last timepoint on treatment in this study (12 weeks). This indicated a potential need to study a longer treatment duration in the subsequent study, to evaluate if the benefit plateaus after a given treatment duration, or if patients will continue to improve and have greater chance of weaning from PN with longer treatment. Longer durations of treatment were assessed in study 006 as well as in the long-term extension studies (discussed later in this review).

Percent Change in PN/IV Calories

Study 003 only collected investigator-prescribed PN calories, and the actual intake based on diary data was not available. The percent change in the total weight normalized calories (kcal/kg/day) provided by PN/IV was assessed and showed similar trend to the percent change in PN volume over the 12 weeks. Patients who received 0.025 mg/kg and 0.05 mg/kg doses appear to have similar pattern of reduction, and illustrate more reduction in PN calories than those treated with 0.0125 mg/kg or SOC.

Infusion Administration Time

One of the most clinically important benefits that a pediatric patient may attain from a treatment for SBS (outside of complete weaning from PN and ability to remove central line) is a reduction in the amount of time the child must be connected to a PN delivery device. Even a small decrease may be considered important to patients and families, as it permits increased mobility (such as opportunity to take young child out for appointments, playdates, participate in physical therapy without hinderance of being attached to infusion pole or backpack, etc.) Similarly, for older children and adolescents, an extra hour not connected to medical equipment may permit increased opportunities for socialization, recreation, extracurricular activities, etc., that are often invaluable to patients with chronic illness who spend much of their time on their own medical care and administration of treatments.

Mean percent change from baseline in the number of days per week at Week 12 that PN was administered was reported at +1.32% (±2.63), -4.08% (±6.97), -15.24% (±29.90), -23.57% (±38.28) for the SOC, 0.0125, 0.025, 0.05 mg/kg groups respectively (see Table 14.2.3.4.1 on page 477 of study 003 CSR). It appeared that, as dose increased, the number of days/weeks on PN decreased.

Analogously, the Applicant also assessed the change in time on PN administration by an alternative scale, number of hours per day. Particularly in younger patients, who may not tolerate big changes in PN support from one day to the next or long (more than 24 hours) periods off all PN, this measure is of clinical interest. The mean reduction in hours per day of PN administration at Week 12 from baseline was -3.94 (±3.75) and -4.18 (±4.08) hours/day in the 0.025 mg/kg and 0.05 mg/kg groups, respectively, while there was nearly no change in the 0.0125 mg/kg and SOC groups (see Table 14.2.3.6.1 on page 544 of study 003 CSR). Taken together, these results support further investigation of the 0.025 mg/kg and 0.05 mg/kg doses in study 006.

Durability of Response

There was limited ability to assess durability of response (and some suggestion of deterioration after discontinuing treatment at week 12) in this study of limited size and short duration of follow-up. This is better assessed in the context of the 24-week study 006 and from extension study data and will be discussed further in this review.

7.3.3. 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"

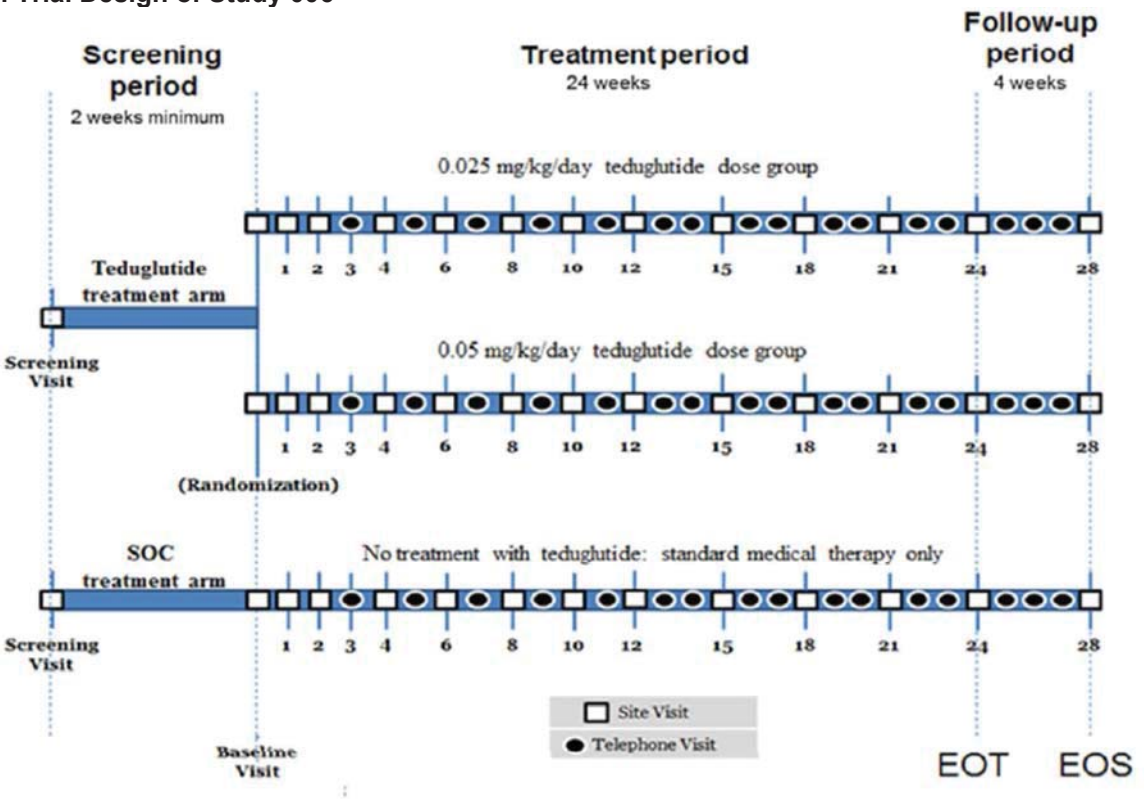
Trial Design

Study 006 was a 24-week, open-label, safety, efficacy, and PD study in pediatric patients 1 through 17 years of age. Patients in study 006 had the treatment options of two teduglutide treatment arms and an SOC treatment arm. During the study's screening period, patients chose between SOC and active treatment (randomization to one of two blinded doses). During the 24-

week treatment period, patients in the SOC treatment arm received standard medical therapy for SBS that included a PN weaning algorithm, and patients in the teduglutide treatment arm received daily SC injections of teduglutide in addition to standard medical therapy. In the teduglutide treatment arm, patients were randomized 1:1 in a double-blinded manner into two parallel teduglutide dose groups: 0.025 mg/kg/day and 0.05 mg/kg/day. Randomization across dose groups was stratified by age: <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years.

In study 006, intake diaries were used to collect and evaluate each patient's nutritional support. The patient/parent/guardian completed the appropriate fields of the PN/IV and EN (formula) sections of the intake diary. The PN/IV volume and infusion duration and EN (formula) volume were provided in the intake diaries, which were completed every day of the study from screening through week 28/EOS. Site personnel determined the actual PN/IV and EN daily calories based on diary entries.

Figure 7. Trial Design of Study 006



EOS=end of study; EOT=End of treatment; SOC=standard of care
Figure 2: General Study Overview for Study 006
Source: Study 006 CSR p. 26

Key Inclusion Criteria

1. Age 1 to 17 years inclusive
2. History of SBS as a result of a major intestinal resection (e.g., due to necrotizing enterocolitis, midgut volvulus, intestinal atresia or gastroschisis) for at least 12 months prior to screening

3. Requiring PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs prior to screening
4. Stable PN/IV support for at least 3 months (defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds [i.e., 10% or less change in PN or advance in feeds]) prior to baseline, based upon the opinion of the investigator.

Key Exclusion Criteria

1. Patients not expected to be able to advance oral or tube feeding regimens (i.e., patients with oral aversion)
2. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months screening
3. Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce PN
4. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (i.e., familial adenomatous polyposis, Fanconi syndrome)
5. Severe, known dysmotility syndrome, such as pseudo-obstruction and persistent, severe, active gastroschisis-related motility disorders that are the primary contributing factors to feeding intolerance and inability to reduce PN, prior to screening
6. Evidence of clinically significant obstruction on upper GI series done within 6 months of screening
7. Major GI surgical intervention including significant intestinal resection within 3 months prior to the screening visit (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, or endoscopic procedure is allowed)
8. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of patients who had undergone ventricular or atrial septal defect repair and patent ductus arteriosus 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 patients
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegavan) within 1 month or an experimental antibody treatment within 3 months prior to screening, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide
12. Previous use of teduglutide or native GLP-2
13. Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
14. Previous use of octreotide, or dipeptidyl peptidase IV (DPP-IV) inhibitors within 3 months prior to screening
15. Patients with active Crohn's disease who had been treated with biological therapy (e.g., antitumor necrosis factor [anti-TNF] or natalizumab) within the 6 months prior to screening

16. Patients with inflammatory bowel disease who required chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
17. More than three SBS-related or PN-related hospital admissions (e.g., 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 may affect PN requirements within 1 month prior to screening visit or during screening, excluding complicated or uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable patient.
19. Body weight <10 kg at screening and baseline visits
20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the following laboratory test results at screening:
    a. Total bilirubin (TB) ≥2x ULN
    b. Aspartate aminotransferase (AST) ≥7x ULN
    c. Alanine aminotransferase (ALT) ≥7x ULN

    For patients 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. Unstable, clinically significant pancreatic or biliary disease
23. Presence of any of the excluded disease states described in Table 9.

Parenteral Nutrition Adjustments:
Investigators assessed patients for the ability to adjust PN at each planned visit. The protocol provided guidance to investigators on how to make a determination regarding ability to wean, or worsening in clinical status, to standardize care across sites. While compliance with specified weaning algorithms was strongly encouraged, deviations from these algorithms were not considered protocol violations.

Prior to weaning of PN support, investigators were instructed to consider clinical factors such as maintained weight/growth parameters, normal electrolytes, stable BUN/creatinine level, and increase in the volume intake/output ratio, accounting for mixed (stool/urine) output. Two weaning algorithms were provided, one for patients who are not toilet trained, and one for toilet trained patients (Refer to Clinical Appendices, Sections 14.4.5. and 14.4.6.). During the 48 hours prior to planned visits, strict intake/output values were measured, and investigators were instructed not to adjust PN prescription.

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

Additional PD endpoints were as follows:

- 100% reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 (or EOT) compared to baseline
- Changes (absolute and percent change) from baseline in PN/IV support (volume and calories), citrulline, and EN (volume and calories), separately, at each clinic visit
- Changes (absolute and percent change) from week 24 (or EOT) in PN/IV support (volume and calories), citrulline, and EN (volume and calories), separately, to week 28 or end of study
- Change in hours per day and days per week of PN/IV support
- ≥20% reduction in PN/IV volume at each clinic visit.

Statistical Analysis Plan

The sample size for the study was not determined based on a formal power calculation. The Applicant pre-specified descriptive statistics used to evaluate efficacy endpoints. The Applicant did not plan to conduct any formal hypothesis testing.

For analyses on PN/IV support and EN support, two sets of results were reported based on two data sources: patient diary data and investigator prescribed data. Since the patient diary data were considered as a more representative measure of efficacy than the investigator prescribed data, efficacy summaries focused on the patient diary data. This approach is consistent to that taken in the adult program.

The ITT population consisted of all patients who enrolled into the trial. The ITT population was the primary analysis population for efficacy analyses.

Protocol Amendments

The Applicant finalized study protocol Version 1 in March 2015. This section focuses on amendments related to primary efficacy endpoint (stated as PD parameter in the Applicant's protocol), randomization, sample size and statistical methods. In the original protocol, (1) subjects enrolled for teduglutide treatments would be randomized in a 1:1 ratio to receive either 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide for 24 weeks in this double-blind part of the study; (2) the primary efficacy endpoint was PN reduction of 20% to 100% at 24 weeks (or EOT) compared to baseline; (3) the study planned to enroll approximately 20 teduglutide-naïve subjects (at least 10 subjects per treatment arm) and up to eight teduglutide-naïve subjects in a SOC cohort; and (4) descriptive statistics would be used due to the limited size of the study population and no claims of significance would be made for any of the data.

1. Amendment 1 dated June 2015 and Amendment 2 dated October 2015: no changes made on primary efficacy endpoint, sample size and statistical method section.
2. Amendment 3 dated February 2016 included the following updates to the protocol:
   a. The primary efficacy/PD endpoint is a reduction in PN/IV volume of at least 20% at week 24 (or EOT) compared to baseline.

b. Randomization across dose groups will be stratified by age: <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years.
c. Increased the number of subjects who are teduglutide-naïve from 20 to 26 (a minimum of 10 subjects per teduglutide dose arm)
d. Attempts will be made to enroll into each teduglutide dose group at least one subject younger than 1 year and at least two subjects aged 12 to <17 years.

3. Amendment 4 dated March 2016 remained the same as Amendment 3 on the aspects of interest.

7.3.4. TED-C14-006: Study Results

Demographic Characteristics

For the ITT population, the baseline demographics were balanced between the two teduglutide arms with 70% male, 74% white and mean age of 6.4 years (ranging 1-17 years). Baseline characteristics in the SOC arm (n=9) appeared different from the two teduglutide arms (0.025 mg/kg/day: n=24; 0.05 mg/kg/day: n=26). This could be attributed to the fact that patients were not randomized to SOC arm but allocated based on patients' preference. For example, 1) 46% (23/50) of patients in combined teduglutide arm were in 6-12 years age group as opposed to 22% (2/9) in the SOC arm; 2) 74% subjects were white in combined teduglutide arm and only 22% were white in the SOC arm; 3) 78 % of patients in the SOC arm were Hispanic or Latino compared to 28% in combined teduglutide arm.

Table 16. Patient Demographics, Study 006

	TED-C14-006			
Parameter	0.025 mg/kg/day (N=24)	0.05 mg/kg/day (N=26)	Total Teduglutide (N=50)	Standard of Care (N=9)
Age (years), Mean (SD)	6.6 (3.61)	6.2 (3.67)	6.4 (3.61)	5.7 (4.72)
Age distribution, n (%)				
1 to <12 years	22 (91.7)	24 (92.3)	46 (92.0)	8 (88.9)
<2 years	1 (4.2)	0	1 (2.0)	0
2 to <6 years	9 (37.5)	13 (50.0)	22 (44.0)	6 (66.7)
6 to <12years	12 (50.0)	11 (42.3)	23 (46.0)	2 (22.2)
12 to 18 years	2 (8.3)	2 (7.7)	4 (8.0)	1 (11.1)
Gender n (%)				
Male	16 (66.7)	19 (73.1)	35 (70.0)	6 (66.7)
Female	8 (33.3)	7 (26.9)	15 (30.0)	3 (33.3)
Race, n (%)				
White	16 (66.7)	21 (80.8)	37 (74.0)	2 (22.2)
Black or African American	3 (12.5)	3 (11.5)	6 (12.0)	1 (11.1)
Asian	1 (4.2)	1 (3.8)	2 (4.0)	1 (11.1)
Other	1 (4.2)	0	1 (2.0)	2 (22.2)
Not allowed based on local regulations	3 (12.5)	1 (3.8)	4 (8.0)	3 (33.3)
Ethnicity n (%)				
Hispanic or Latino	5 (20.8)	5 (19.2)	10 (20.0)	4 (44.4)
Not Hispanic or Latino	16 (66.7)	20 (76.9)	36 (72.0)	2 (22.2)
Not reported	3 (12.5)	1 (3.8)	4 (8.0)	3 (33.3)
Weight Z-Score at Baseline, Mean (SD)	-0.85 (1.08)	-0.88 (1.11)	-0.86 (1.08)	-0.22 (0.81)
Height Z-Score at Baseline, Mean (SD)	-1.28 (1.22)	-1.31 (1.18)	-1.30 (1.19)	-0.39 (1.59)
BMI Z-Score at Baseline, Mean (SD)	-0.09 (1.05)	-0.03 (1.18)	-0.06 (1.11)	0.08 (0.56)
BMI Percentile for Age, Mean (SD)	0.46 (0.31)	0.52 (0.31)	0.49 (0.31)	0.53 (0.20)

Source: Applicant's IR Response, page 7/51, dated January 29, 2019

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
In study 006, baseline characteristics were similar between the two teduglutide arms, except for the reason for SBS diagnosis. SBS history differed between teduglutide-treated and SOC-treated patients; the percentages of patients with any remaining colon were 94% and 67%, for the teduglutide arms and SOC arm, respectively.

Table 17. Short Bowel Syndrome History, Study 006

	Treatment Group			
Parameter	**0.025 mg/kg/day Teduglutide (N=24)**	**0.05 mg/kg/day Teduglutide (N=26)**	**Total Teduglutide (N=50)**	**Standard of Care (N=9)**
Primary reason for the diagnosis of SBS, n (%)				
Necrotizing enterocolitis	5 (20.8)	3 (11.5)	8 (16.0)	2 (22.2)
Midgut volvulus	10 (41.7)	6 (23.1)	16 (32.0)	3 (33.3)
Intestinal atresia	2 (8.3)	1 (3.8)	3 (6.0)	0
Gastroschisis	6 (25.0)	14 (53.8)	20 (40.0)	2 (22.2)
Long-segment Hirschsprung's disease	1 (4.2)	1 (3.8)	2 (4.0)	2 (22.2)
Other	0	1 (3.8)	1 (2.0)	0
Subjects with a stoma, n (%)	5 (20.8)	5 (19.2)	10 (20.0)	3 (33.3)
Type of stoma[a], n (%)				
Jejunostomy	3 (60.0)	4 (80.0)	7 (70.0)	2 (66.7)
Ileostomy	0	1 (20.0)	1 (10.0)	1 (33.3)
Colostomy	2 (40.0)	0	2 (20.0)	0
Subject with any remaining colon, n (%)	22 (91.7)	25 (96.2)	47 (94.0)	6 (66.7)
Estimated percentage of colon remaining, mean (SD)	60.9 (36.1)	68.8 (30.7)	65.1 (33.1)	60.3 (33.5)
Colon in continuity[b], n (%)	22 (100)	22 (88.0)	44 (93.6)	6 (100)
Total estimated remaining small intestinal length (cm), mean (SD)	38.20 (38.76)	46.75 (27.90)	42.86 (33.15)	45.28 (31.05)
Distal/terminal ileum present, n (%)	9 (37.5)	9 (34.6)	18 (36.0)	3 (33.3)
Ileocecal valve present[c], n (%)	6 (66.7)	7 (77.8)	13 (72.2)	3 (100)
Baseline PS volume (mL/kg/day), mean (SD)	56.8 (25.2)	60.1(29.2)	58.6 (27.3)	79.6 (31.1)

[a] Percentages are based on the number of subjects with a stoma in each treatment group.
[b] Percentages are based on the number of subjects who have remaining colon in each treatment group.
[c] Percentages are based on the number of subjects with distal/terminal ileum present in each treatment group.
Source: Applicant's Summary of Clinical Efficacy Table 4, page 33
SD = standard deviation

Patient Disposition, Treatment Compliance, Concomitant Medications

Study 006 was conducted at 27 sites in the United States, Belgium, Canada, the United Kingdom, Finland, Germany, and Italy.

The following table summarizes patient disposition in study 006. The completion and compliance rates were excellent (i.e., 100% in all arms), likely related to high disease burden and frequent interaction with the healthcare system due to PN dependence.

Table 18. Patient Disposition, Study 006

	Treatment group			
Parameter	**0.025 mg/kg/day n (%)**	**0.05 mg/kg/day n (%)**	**Total Teduglutide n (%)**	**Standard of Care n (%)**
Enrolled[a]	24	26	50	9
Treated	24 (100)	26 (100)	50 (100)	-
Completed treatment[b]	24 (100)	26 (100)	50 (100)	9 (100)
Early treatment discontinuation	0	0	0	0
Withdrawal of consent	0	0	0	0
Protocol non-compliance	0	0	0	0
Completed study	24 (100)	26 (100)	50 (100)	9 (100)

Source: Applicant's Summary of Clinical Efficacy, page 29/88

[a] A subject was considered enrolled in TED-C14-006 at the baseline visit when the choice of treatment arm (i.e., teduglutide or standard of care) has been made.

[b] Completion of treatment based on whether subject completed 12 or 24 weeks of study drug or standard of care depending on study.

As shown in the table above, 50 patients were enrolled and treated with teduglutide in study 006; 26 of these patients were randomized to 0.05 mg/kg/day. Nine patients were in the SOC arm. None of the patients withdrew consent. All 59 patients completed 24 weeks of treatment in the group they were assigned.

Concomitant Medications

All (59 [100.0%]) patients reported a concomitant medication. In general, the concomitant medications of the patients were similar in both treatment arms (see Table 19).

Table 19. Concomitant Medication Used in Greater Than or Equal to 15% of Patients in the Total Teduglutide Cohort, Safety Population

	Teduglutide			
	0.025 mg/kg/day N=24 n (%)	**0.05 mg/kg/day N=26 n (%)**	**Total Teduglutide N=50 n (%)**	**SOC N=9 n (%)**
Any concomitant medication				
No	0	0	0	0
Yes	24 (100)	26 (100)	50 (100)	9 (100)
Paracetamol	9 (37.5)	12 (46.2)	21 (42.0)	6 (66.7)
Metronidazole	8 (33.3)	11 (42.3)	19 (38.0)	1 (11.1)
Cholecalciferol	6 (25.0)	9 (34.6)	15 (30.0)	2 (22.2)
Ibuprofen	5 (20.8)	8 (30.8)	13 (26.0)	4 (44.4)
Vancomycin	4 (16.7)	10 (38.5)	14 (28.0)	3 (33.3)
Ondansetron	7 (29.2)	4 (15.4)	11 (22.0)	5 (55.6)
Loperamide	6 (25.0)	6 (23.1)	12 (24.0)	3 (33.3)
Loperamide Hydrochloride	5 (20.8)	7 (26.9)	12 (24.0)	0
Ethanol	6 (25.0)	6 (23.1)	12 (24.0)	1 (11.1)
Sodium Chloride	5 (20.8)	5 (19.2)	10 (20.0)	3 (33.3)
Piperacillin tazobactam	4 (16.7)	7 (26.9)	11 (22.0)	1 (11.1)
Propofol	4 (16.7)	4 (15.4)	8 (16.0)	3 (33.3)
Fentanyl	4 (16.7)	2 (7.7)	6 (12.0)	4 (44.4)
Ferrous Sulfate	3 (12.5)	7 (26.9)	10 (20.0)	0
Ranitidine	6 (25.0)	4 (15.4)	10 (20.0)	0
Alteplase	3 (12.5)	5 (19.2)	8 (16.0)	1 (11.1)

	Teduglutide			
	0.025 mg/kg/day N=24 n (%)	0.05 mg/kg/day N=26 n (%)	Total Teduglutide N=50 n (%)	SOC N=9 n (%)
Heparin	3 (12.5)	3 (11.5)	6 (12.0)	3 (33.3)
Lansoprazole	3 (12.5)	6 (23.1)	9 (18.0)	0
Rifaximin	4 (16.7)	5 (19.2)	9 (18.0)	0
Ceftriaxone	3 (12.5)	3 (11.5)	6 (12.0)	2 (22.2)

Source: Reviewer's Table, Adapted from Applicants' TED-C14-006 Clinical Study Report, Table 14.1.6.2, page 177/1888
Concomitant medications are defined as medications taken on or after the first dose of study drug (or the baseline visit for the standard of care treatment group).
Percentages are based on the number of patients in the analysis set in each treatment group.
Patients who have more than one medication with the same preferred name will be counted only once in a category per preferred name.
Medications are coded to preferred name using WHO Drug Dictionary, September 1, 2016. Preferred Names are sorted by the descending order of the frequency of the Total treatment group.

The most common concomitant medications in patients who were exposed to teduglutide of any dose (>25% of patients overall) were paracetamol (21 [42.0%] patients), metronidazole (19 [38.0%] patients), cholecalciferol (15 [30.0%] patients), ibuprofen (13 [26.0%] patients), vancomycin (14 [28.0%] patients), ondansetron (11 [22.0%] patients), and loperamide (12 [24.0%] patients). None of these concomitant medications would be expected to have direct impact on the absorptive capacity of teduglutide and confound efficacy results.

Data Quality and Integrity

The submitted data followed FDA guidance and were analysis ready.

Efficacy Results – Primary Endpoint

The primary efficacy results based on the patient diary data indicated that 13 (54.2%) patients in the 0.025 mg/kg/day group, 18 (69.2%) patients in the 0.05 mg/kg/day group, and one (11.1%) patient in the SOC arm achieved greater than or equal to 20% reduction in PN volume (primary efficacy endpoint) (see Table 20).

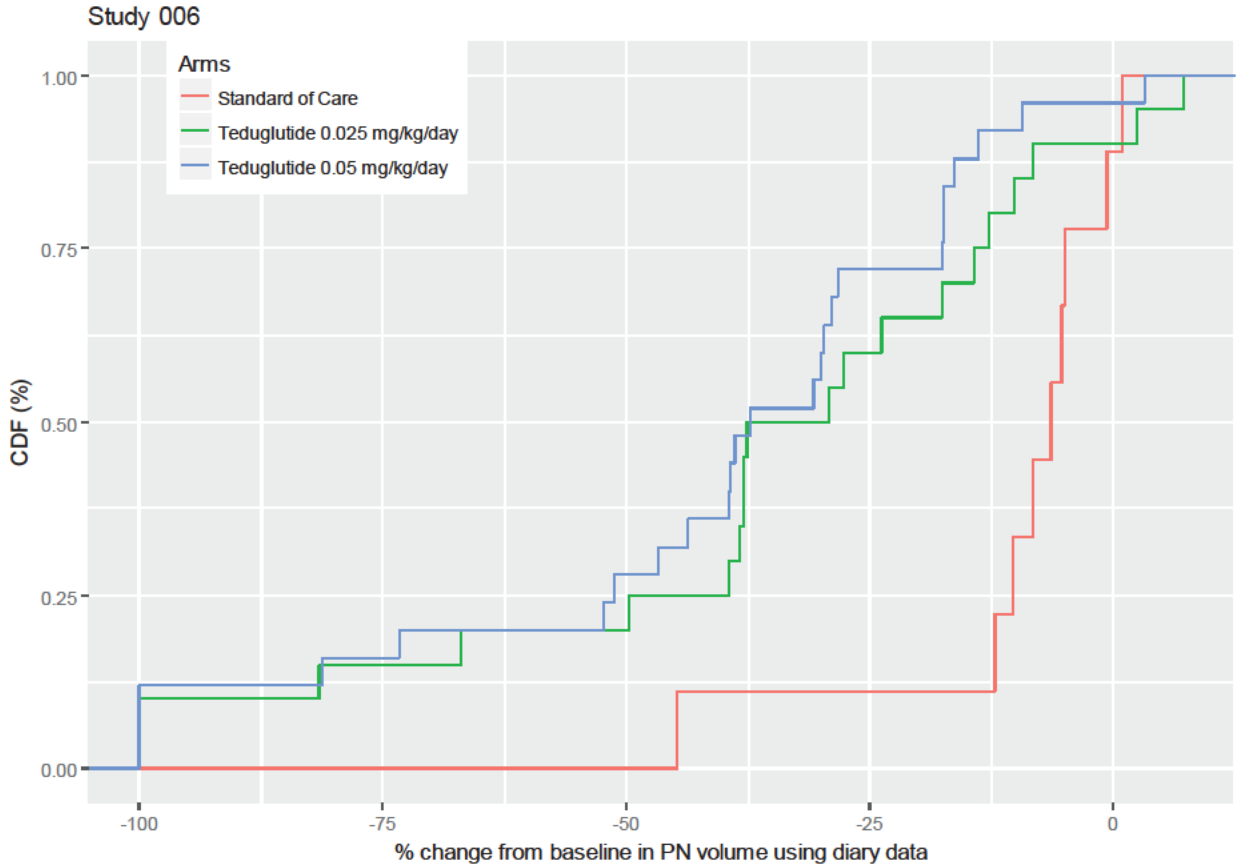
Figure 8 illustrates cumulative distribution functions (CDFs) of percent changes from baseline in the PN volume across treatment arms. The CDFs for the teduglutide 0.025 mg/kg/day and 0.05 mg/kg/day arms appear similar. Approximately 50% of patients receiving teduglutide (both, 0.025 and 0.05 mg/kg/day) achieved 35% or more reduction in the PN volume, and approximately 25% of patients had at least 50% reduction. Although there was no clear separation between the curves for the two dose arms, 0.05 mg/kg/day had slightly higher numerical response rates for almost all cutoff points.

Table 20. Summary of Percent Reduction in PN/IV Volume at EOT Based on Subject Diary Data, Study 006

	TED-C14-006			
	0.025 mg/kg/day (N=24) n (%)	0.05 mg/kg/day (N=26) n (%)	Total Teduglutide (N=50) n (%)	Standard of Care (N=9) n (%)
≥20% reduction (primary endpoint)	13 (54.2)	18 (69.2)	31 (62.0)	1 (11.1)
≥50% reduction	4 (16.7)	7 (26.9)	11 (22.0)	0
≥75% reduction	3 (12.5)	4 (15.4)	7 (14.0)	0
100% reduction (complete weaning or enteral autonomy)	2 (8.3)	3 (11.5)	5 (10)	0

Source: Applicant's Summary of Clinical Efficacy, Tables 5 and 6, pages 36 and 38, verified by FDA.

Figure 8. CDF of Percent Change From Baseline in PN Volume Based on Diary Data



CDF = cumulative distribution function
Source: Reviewer's analysis

The efficacy results for the primary endpoint presented above were based on patients' diary data. The results using prescribed data were consistent with these results (see Table 14.2.1.3 on page 196 of study 006 CSR).

Efficacy Results – Secondary and other relevant endpoints

This sub-section summarizes secondary efficacy endpoints that are of clinical interest. The secondary endpoint results appeared consistent with the primary efficacy findings summarized above.

Complete Weaning

Five patients, comprising 2 of 24 (8%) in the 0.025 mg/kg/day group and 3 of 26 (12%) in the 0.05 mg/kg/day group achieved this clinically important threshold of 100% reduction in PN/IV volume (Table 21). These were patients who were severely affected and had no reasonable expectation of achieving enteral autonomy over a period of weeks, given their longstanding history of PN dependence and baseline disease characteristics and remaining bowel length. All five patients had required PN for at least the 4 preceding years and had disease onset in infancy.

Table 21. Characteristics of Patients Achieving Enteral Autonomy

Subject	Teduglutide Group	Sex/ Age/ Race	Underlying Diagnosis	Baseline PN/IV Volume (ml/kg/day)[a]	Small Bowel Length (cm)	Terminal Ileum Present/ Ileocecal valve Present (Yes/No)	% colon remaining (in continuity)	Weeks to Attain Enteral Autonomy[b]
(b) (6)	0.025 mg/kg/day	Female/ 14/ White	Midgut volvulus	29	122	No/ No	50	10
	0.025 mg/kg/day	Female/ 14/ White	Intestinal atresia	10	55	No/ No	70	8
	0.05 mg/kg/day	Female/ 4/ White	Gastroschisis, Intestinal atresia	57	120	No/ No	unknown	21
	0.05 mg/kg/day	Female/ 6/ Black	Midgut volvulus	57	40	No/ No	70	21
	0.05 mg/kg/day	Male/ 9/ White	Midgut volvulus	29	64	Yes/ Yes	90	14

[a] Based on prescription data provided by parent/caregiver

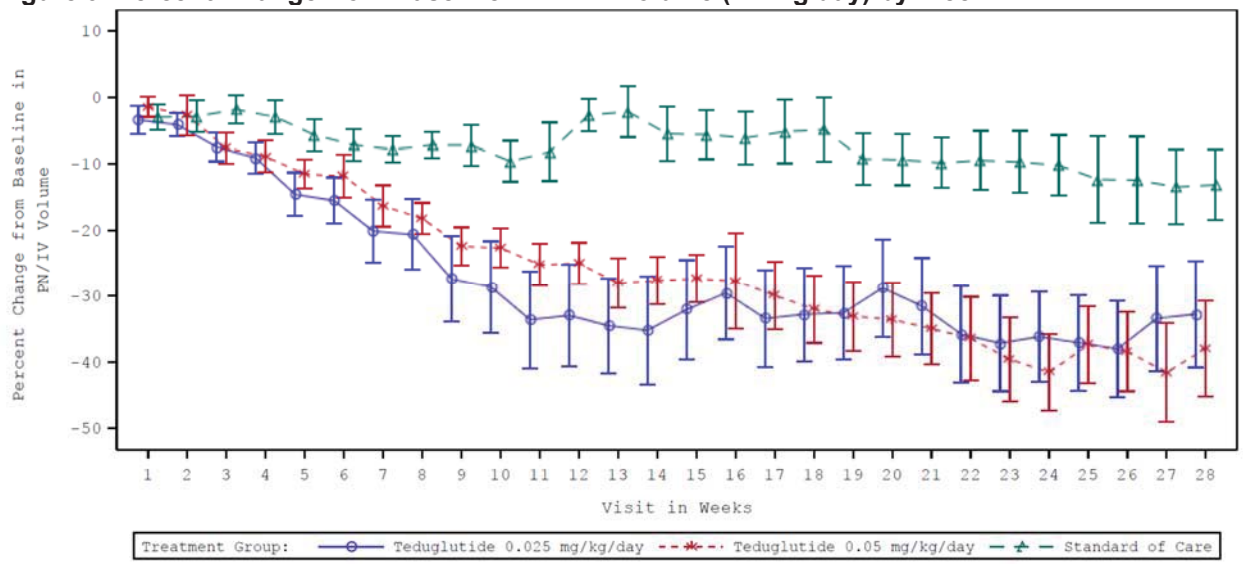
Source: Applicant's CSR for TED-C14-006 page 69/1888

Although they represent a minority of teduglutide-treated patients, those who were able to achieve this milestone derived unequivocal benefit from treatment.

Percent Change in PN volume

The Applicant also reported weekly mean percent change from baseline in PN volume by treatment arm. Given that baseline PN requirement varied widely (both total volume in L/week required as well as mL/kg/day required), the percent change in volume of prescribed PN/IV fluid (rather than discrete volume reduction) is clinically informative when considering the population as a whole.

Figure 9. Percent Change from Baseline in PN/IV Volume (mL/kg/day) by Week



PN/IV = parenteral nutrition/intravenous fluids, SE = standard error
Week 24 is end of treatment; Week 28 is end of study.
Average daily value is calculated as [(sum of non-missing daily values in the diary / number of days with non-missing values)] /last available body weight prior to the visit.
Figure illustrated mean percent change accompanied by small bars representing ± SE.
CSR for TED-C14-006, Applicant's Figure 2, page 71/1888 (intention to treat set, based on subject diary data)

The above figure indicates consistent efficacy improvement in patients who received teduglutide over time until Week 24, in both 0.025 mg/kg and 0.05 mg/kg arms. The treatment effects in the two teduglutide arms are similar. There is greater reduction in PN volume received over time in active teduglutide arms, as compared with SOC. However, these data need to be interpreted carefully since there may be potential confounding effects from imbalanced demographic and baseline characteristics between teduglutide arms and SOC.

Percent Change in PN/IV Calories

The percent change in the total weight normalized calories (kcal/kg/day) provided by PN/IV was assessed (see Figure 14.2.5.4 on page 1797 of study 006 CSR), and the pattern of reduction in PN calories from baseline appears similar to the volume reduction pattern shown in the figure above. This result suggests that the improvements in PN volume seen on treatment are a result of improved absorptive capacity, not only of fluid, but also of macronutrients.

Infusion Administration Time

One of the most clinically important benefits that a pediatric patient may attain from a treatment for SBS (outside of complete weaning from PN and ability to remove central line) is a reduction in the amount of time the child must be connected to a PN delivery device. Even a small decrease may be considered important to patients and families, as it permits increased mobility (such as opportunity to take young child out for appointments, playdate, participate in physical therapy without hinderance of being attached to infusion pole or backpack, etc.) Similarly, for older children and adolescents, an extra hour not connected to medical equipment may permit increased opportunities for socialization, recreation, extracurricular

activities, etc., that are often invaluable to patients with chronic illness who spend much of their time on their own medical care and administration of treatments.

The percentage of patients who achieved at least one day/week reduction in PN infusion time at Week 24 was 27.3% (6/22), 38.5% (10/26), and 0% (0/9), for the 0.025 mg/kg/day, 0.05 mg/kg/day, and standard of care groups, respectively.

Table 22 and Table 23 show reduction in total administration time as change from baseline in the days/week or hours/day, respectively.

Table 22. Change From Baseline in Days per Week of PN Administered (ITT, Diary Data)

	0.025 mg/kg/day N=24	0.05 mg/kg/day N=26	SOC N=9
Baseline, n	22	26	9
Mean (SD)	6.5 (1.10)	6.6 (0.79)	6.6 (1.33)
Median	7.0	7.0	7.0
Min, max	4, 7	5, 7	3, 7
Week 1 observed, n	24	25	9
Mean (SD)	6.5 (1.28)	6.6 (0.87)	6.6 (1.33)
Median	7.0	7.0	7.0
Min, max	3,7	4,7	3,7
Change from baseline, mean (SD)	-0.07 (0.377)	0 (0.222)	0 (0)
Week 12 observed, n	24	26	9
Mean (SD)	5.8 (2.45)	6.6 (0.99)	6.6 (1.33)
Median	7.0	7.0	7.0
Min, max	0,7	4,7	3,7
Change from baseline mean (SD)	-0.88 (2.257)	0.01 (0.537)	0 (0)
Week 24 observed, n	24	26	9
Mean (SD)	5.8 (2.25)	5.2 (2.47)	6.6 (1.33)
Median	7.0	7.0	7.0
Min, max	0,7	0,7	3,7
Change from baseline mean (SD)	-0.88 (1.78)	-1.34 (2.238)	0 (0)
Percent change from baseline mean, (SD)	-16.03 (31.338)	-21.33 (34.094)	0 (0)

Source: Reviewer's table, adapted from Applicant's Table 14.2.6.1 CSR for TEDC14-006 (pages 473–496/1888), data from ITT set based on diary data
SD = standard deviation; ITT = intent to treat

The above table summarizes change from baseline in total number of days per week on PN for Weeks 1, 12 and 24. On average, patients who received teduglutide 0.025 mg/kg/day and 0.05 mg/kg/day had 0.88 and 1.34 fewer days per week required on PN at Week 24, respectively. In general, there was no clear difference between the two dosages in reduction of PN time in days per week. The time needed on PN did not change in the SOC group.

Table 23. Change from Baseline in Hours of Administration Per Day (ITT, Diary Data)

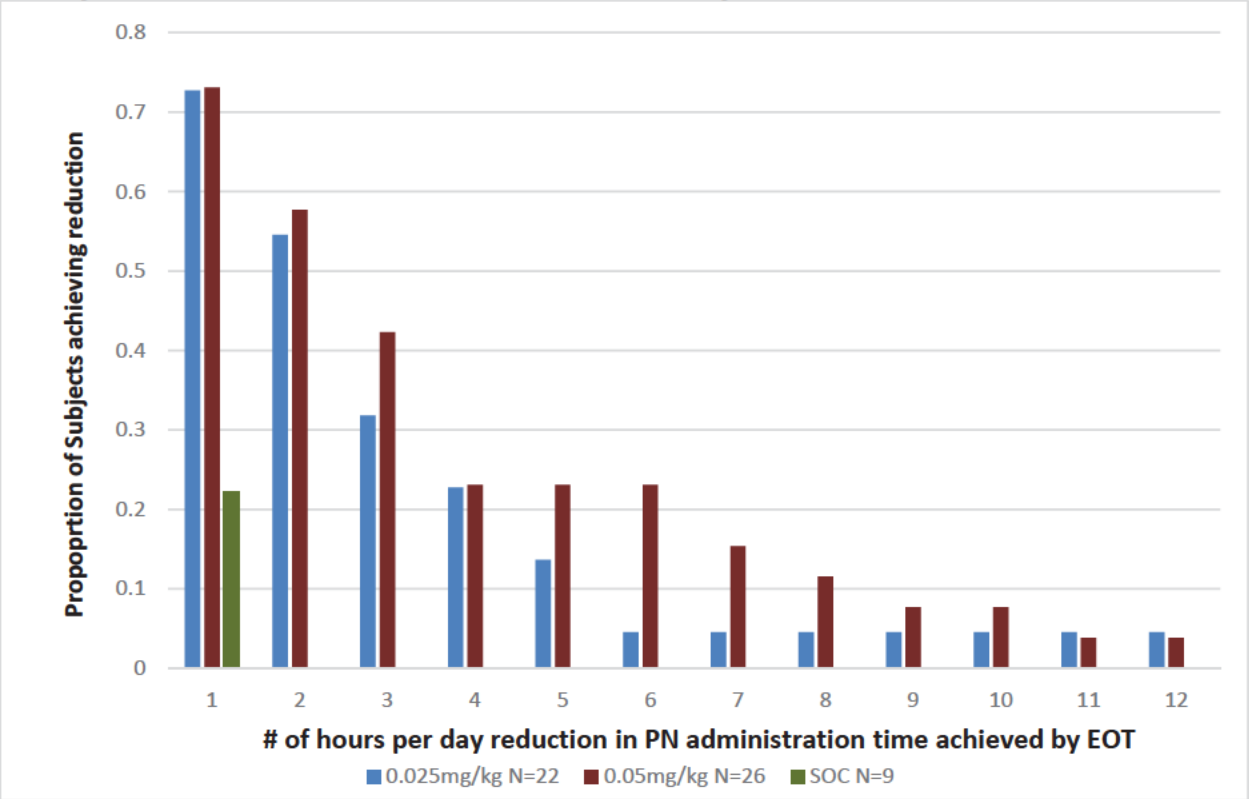
	0.025 mg/kg/day N=24	0.05 mg/kg/day N=26	SOC N=9
Baseline, n	22	26	9
Mean (SD)	11.7 (3.03)	11.2 (2.99)	12.6 (5.50)
Median	12	11.0	11.0
Min, max	5, 16	7, 20	5, 24
Week 1, n	24	25	9
Observed mean (SD)	11.9 (3.87)	11.3 (2.97)	12.2 (4.70)
Median	12.0	11.0	11.0
Min, max	4, 22	7, 20	5, 20
Change from baseline, mean (SD)	-0.26 (0.785)	0.09 (0.814)	-0.44 (1.181)
Week 12, n	24	26	9
Observed mean (SD)	9.7 (5.58)	10.3 (2.26)	12.7 (5.49)
Median	11.1	10.0	11.0
Min, max	0, 22	6, 16	5, 23
Change from baseline mean (SD)	-2.53 (3.866)	-0.84 (2.158)	0.05 (0.423)
Week 24, n	24	26	9
Observed mean (SD)	9.7 (4.88)	8.1 (4.02)	12.4 (5.42)
Median	11.0	9.2	11.0
Min, max	0, 19	0, 15	5, 23
Change from baseline mean (SD)	-2.47 (2.726)	-3.03 (3.835)	-0.21 (0.693)
Percent change from baseline mean (SD)	-26.04 (31.559)	-26.09 (36.139)	-1.75 (5.892)

Source: Reviewer's table, adapted from Applicant's Table 14.2.7.1 CSR for TEDC14-006, data from ITT set based on diary data
SD = standard deviation; ITT = intent to treat

When reporting time on PN by hours per day, teduglutide 0.025 mg/kg/day and 0.05 mg/kg/day treatment reduced the mean time on PN similarly by 2.5 and 3 hours per day from baseline at Week 24, respectively. Nine patients in the SOC arm reduced the mean time on PN by 0.21 hours per day on average from baseline. The approach to compress PN by reducing the number of hours per day (but not days per week) may be preferable in some clinical situations, and particularly in the smallest/youngest pediatric patients, who may not tolerate a full day off all IV support.

Although limited by the small sample size, the proportion of patients able to achieve a reduction of 1, 2, 3 or more hours per day off PN provides additional information on the impact of teduglutide treatment in patients. The following figure shows the proportion of patients in each arm achieving at least 1 hour, 2 hours, etc., of reduction in the total daily PN administration time, from baseline to EOT visit.

Figure 10. Proportion of Subjects Achieving Reduced Parental Nutrition by Amount of Reduction in Daily Administration Time From Baseline to EOT, Study 006



Source: Reviewer's figure, created from data provided in response to IR received January 29, 2019 (Table 2: summary number and proportion of patients that achieved the following by treatment at EOT visit, ITT set). Limited to patients with post baseline and EOT visit data available.

The figure demonstrates that the majority of patients (>70%) who received teduglutide were able to achieve a modest (1 to 2 hours) reduction in daily PN administration time. On average, about 30% and 40% of patients in teduglutide 0.025 and 0.05 mg/kg arms had 3 fewer hours per day on PN, respectively. Note that patients had varying number of hours per day on PN to start (0.05 mg/kg treated patients in study 006 had a baseline mean duration of PN administration 11.2 ±2.99 hours per day, ranging from 7 to 20 hours). The ability to compress administration over a shorter number of hours per day also varies by age as smaller patients tend to be more sensitive to fluid shifts. However, as previously discussed, patients and caregivers of patients who are PN dependent have indicated that even a modest decrease in the number of hours per day in PN administration time is still important in improving quality of life.

Dose/Dose Response

Based on evaluation of the primary and secondary endpoints, it is unclear that 0.05 mg/kg dose outperforms 0.025 mg/kg. There are small numerical differences that may favor 0.05 mg/kg, but the number of patients in each treatment arm is too small to make direct comparisons with any certainty. However, clinical pharmacology and pharmacometrics reviews indicated that the systemic exposure pediatric patients achieved from the 0.05 mg/kg dose was lower than that achieved by adults. Thus, there is uncertainty surrounding whether choosing the lower

0.025 mg/kg dose would maintain the level of efficacy demonstrated in adults. As there was no differential safety signal for 0.05 mg/kg dose compared with 0.025 mg/kg, the selection of the 0.05 mg/kg dose appears reasonable for pediatric patients.

Durability of Response

The end of study visit occurred approximately 4 weeks after the week 24 visit for the majority of patients in this trial. Based on the primary and secondary endpoints described above, benefits derived at week 24 generally persisted to week 28 (end of study). More meaningful data on the need for, and efficacy of, long term treatment past 24 weeks was collected in the extension study 304 and is described in Section 7.3.7. Because of the limitations of the extension study 303 (mainly the 2-year gap between the end of study 003 and patients' ability to enroll in the extension study), the assessment of long-term efficacy and durability of response is focused on the extension of treatment for patients from study 006 into extension study 304.

7.3.5. Study SHP633-303: A Retrospective and Prospective, Open-Label, Long-Term Safety and Efficacy Study of Teduglutide in Pediatric Subjects With Short Bowel Syndrome Who Completed TED-C13-003

Trial Design

SHP633-303 (study 303) was designed as an extension study to provide continued treatment, and collect long term efficacy and safety data, on patients initially enrolled in study TED-C13-003. Because there was a lag of 2 years between completion of study 003 and initiation of this extension study, there was also a retrospective data collection period, from which data for patients treated in study 003 and then off treatment during the intervening time was collected. The prospective portion of the study is illustrated in Figure 11.

Figure 11. Study Design for Prospective Portion of SHP633-303

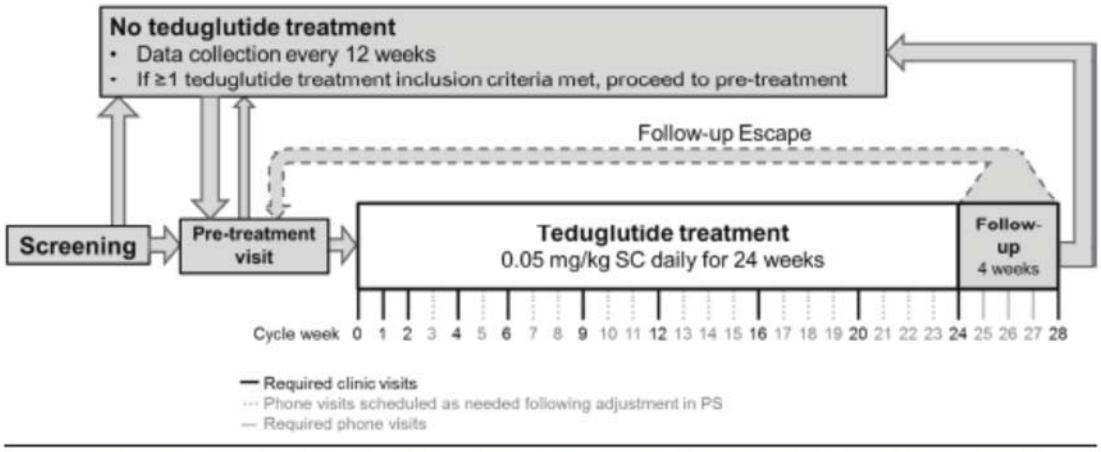


Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment were captured approximately every 12 weeks, but subjects might proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects entered a 28-week teduglutide cycle. During this cycle, subjects returned to the site for safety and efficacy assessments at Weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (solid black lines). Phone visits were required approximately 1 week after adjustments in PS during the intervening weeks between Weeks 2 and 24 (dashed grey lines). Subjects discontinued teduglutide at Week 24 and entered a 4 week follow-up (no-treatment) period, during which phone visits were performed weekly (solid grey lines). If an escape criterion was met during the follow-up period, subjects might proceed directly to another pretreatment visit.

Source: Applicant's interim CSR synopsis for study SHP633-303 (page 2/12)

Study 303 was designed to provide ongoing treatment to those who needed it, while including periodic "off treatment" trial periods, to determine whether continued teduglutide treatment was necessary. At screening, a determination of whether to start treatment was made, based on one or more "Teduglutide Treatment Inclusion Criteria". Patients who did not meet criteria for continued treatment were followed and re-assessed for the need for teduglutide treatment resumption every 12 weeks.

Teduglutide Treatment Inclusion Criteria:

1. Receiving PN and unable to reduce PN or advance feeds (less than 10% change in PN or feeding advancement) for the past 3 months.
2. Previously treated with teduglutide and meet at least one of the following:
   a. Increasing PN requirement following teduglutide discontinuation
   b. Decreasing PN requirements during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation
   c. Deteriorating nutritional status (weight loss or growth failure) despite maximal tolerated EN after teduglutide discontinuation
   d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation
   e. Severe diarrhea related to teduglutide discontinuation

Each extension "treatment cycle" was comprised of a 28-week period (24 weeks treatment and 4 weeks follow-up). If escape criterion[3] was met during the follow-up, patients could proceed directly to another pre-treatment visit. Safety evaluation continued throughout, and PN adjustments were made as needed (following standardized guidelines within the protocol for weaning criteria). Patients who did not meet criteria for treatment were followed in no teduglutide treatment (NTT) periods. Patients could escape from NTT for a pre-treatment visit to re-assess eligibility for treatment at any time if clinically indicated.

Endpoints
Efficacy and safety endpoints analogous to those collected for Study TED-C13-003 were collected.

7.3.6. Study SHP633-304: A Prospective, Open-Label, Long-Term Safety and Efficacy Study of Teduglutide in Pediatric Patients With Short Bowel Syndrome Who Completed TED-C14-006

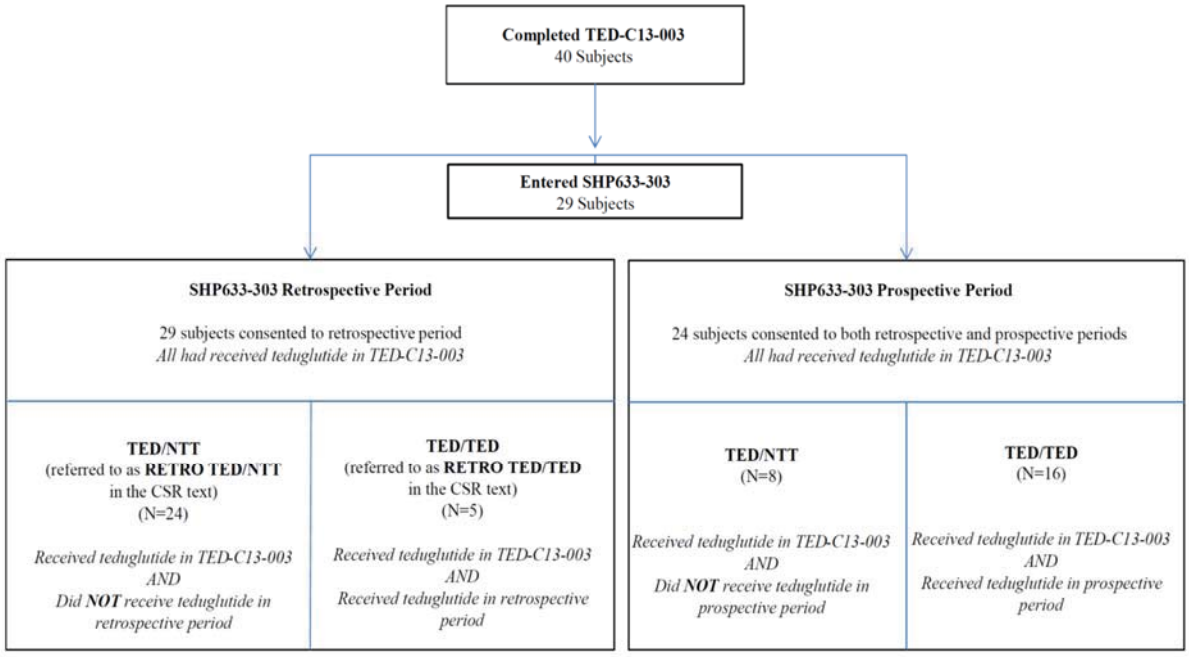
Trial Design
The design of study 304 closely mirrored that of extension study 303. The reader is referred to the preceding section for detailed description. The protocols followed similar assessment schedules, PN adjustment guidelines, visit frequency, and criteria for initiating a treatment cycle with teduglutide. The key difference was that there was no "retrospective period" for study 304. All study 304 patients had completed study 006 and met the additional "teduglutide treatment inclusion criteria" as outlined above.

7.3.7. Extension Studies 303 and 304: Efficacy Results

Disposition
As shown in Figure 12, of the 40 patients who completed study 003, 29 consented to the retrospective period in extension study 303 and 24 consented to participation in both the retrospective and prospective periods of study 303. Sixteen patients received teduglutide during the prospective period (TED/TED treatment group), 13 of whom had completed at least 24 weeks of extension treatment as of the interim analysis.

[3] Escape criteria were same as "teduglutide treatment criteria" items 2a, c, d, e as described in paragraph above.

Figure 12. Disposition of Patients in Extension Study 303



NTT=no-teduglutide treatment; TED=teduglutide

Source: SHP633-303 Interim Study Report Body, page 7-8/2041

Of the 55 patients who completed teduglutide treatment in study 006, 47 met the requirements to receive teduglutide in extension study 304 as of the time of interim analysis.

Durability of Benefit

Forty-seven patients were treated with teduglutide for 24 weeks in study 006 and 44/47 (94%) received additional treatment in extension study 304. Of the 31 patients who achieved at least 20% reduction in PN during study 006, 26 (84%) entered at least one "treatment cycle" in extension study 304 as of the interim analyses of the February 2, 2018, data cut. Receiving additional treatment in the extension study required meeting one or more specific criteria of disease worsening and loss of previously achieved benefit (as described above). The large percentage of patients who required additional treatment indicates that most patients did not have persistence of benefit once treatment was discontinued, after their first 24 weeks treatment.

Seventy-one patients who received teduglutide treatment in studies 003 and 006 enrolled in the respective extension studies as of the interim analyses, and 60 patients received additional teduglutide treatment in the extension study. The majority of patients who received teduglutide treatment in studies 003 and 006 started a teduglutide treatment cycle shortly after enrolling in an extension study. Minimal gaps were observed between treatment cycles for these patients. Notably, 19 patients who had completed the first 24-week treatment period in the extension studies at the time of data cut-off escaped the 4-week follow-up period early due to deteriorating nutritional status when teduglutide treatment was interrupted per report.

The Applicant notes that these results align with existing data on GLP-2 physiology and its role in driving intestinal adaptation and maintaining optimal intestinal function. In addition, the Applicant reports that most children with SBS who remain dependent on PN after the 2-year period of intestinal adaptation are expected to remain chronically dependent on GLP-2 supplementation to maintain optimal intestinal function. The data available to date appear to support the assertion that teduglutide in this population does not represent a "cure" of SBS for most patients, but rather a medication that may be effective to help manage the condition (by reducing the need to PN support) with chronic use.

Persistence of Effect

There were five patients who achieved enteral autonomy with the 24-week treatment period in study 006, as evidence by no PN use recorded in patient diaries during the week prior to the EOT visit and no prescribed PN at EOT. All five patients consented to extension study 304 and received additional teduglutide treatment as they met at least one of the teduglutide treatment inclusion criteria. Again, this suggests that teduglutide treatment, even in the patients who achieved maximal benefit within 24 weeks, is likely to be needed chronically.

Table 24 summarizes the effects of teduglutide on patients who achieved enteral autonomy and the persistence of this effect on PN requirement and their continued ability to maintain the enteral autonomy.

Table 24. Effects of Teduglutide on Patients Who Achieved Enteral Autonomy

Patient	Teduglutide Group (mg/kg/day)	Underlying Diagnosis	Baseline PN/IV Volume (mL/kg/day)	Small Bowel Length (cm)	Week to Attain Enteral Autonomy	Loss of Enteral Autonomy	Additional Weeks of Teduglutide Treatment After Achieving Enteral Autonomy
(b) (6) 14y/o	0.025	Midgut volvulus	29	122	10	Not to date	Resumed TED 4 weeks after treatment in core study. Sustained enteral autonomy since week 10 of core study, currently in Cycle 4. Required >75 weeks of TED treatment after attaining enteral autonomy
(b) (6) 14y/o	0.025	Intestinal atresia	10	55	8	Not to date	Resumed TED 6 weeks after end of treatment in core study, for a total 48 weeks cumulative TED treatment. Sustained enteral autonomy for ~1 year without additional TED treatment
(b) (6) 4y/0	0.05	Gastroschisis, intestinal atresia	57	120	21	Resumed PS within 6 weeks after end of treatment in core study	Re-attained enteral autonomy after 20 weeks of treatment. Required >31 weeks of treatment after achieving enteral autonomy for the second time
(b) (6) 6y/o	0.05	Midgut volvulus	47	40	21	Resumed PS within 10 days of Cycle 2 of extension study.	Resumed TED 4 weeks after end of treatment in core study. Re-attained enteral autonomy after 10-weeks of additional treatment in Cycle 2. Required >86 weeks of TED treatment after attaining enteral autonomy
(b) (6) 9y/o	0.05	Midgut volvulus	29	64	14	Not to date	Resumed TED 6 weeks after end of treatment in core study Received ~ 58 weeks of TED treatment after attaining enteral autonomy as of last datacut. Requirement for additional treatment is unknown per Applicant (report pending from investigator).

Source: Reviewer's Table, adapted from Applicant's IR Response, dated January 29, 2019

The data from study 006 and extension study 304 indicate that children who attain enteral autonomy on teduglutide require additional treatment with teduglutide for at least 6 to 12 months, thereafter, and potentially chronically. Longer term follow-up data are being collected but are not yet available.

According to the Applicant, as of the February 2, 2018 data cut, three additional patients achieved enteral autonomy after EOT in the study 006, one of whom did not participate in extension study 304. Table 25 summarizes parenteral support and teduglutide treatment requirement for these three patients.

Table 25. Additional Patients Who Achieved Enteral Autonomy After End of Treatment in Study 006

Patient	Teduglutide Dose	Underlying Diagnosis	Baseline PN/IV Volume (mL/kg/day)	Small Bowel Length (cm)	% Colon Remaining in Continuity	Weeks to Attain Enteral Autonomy	Additional Weeks of Teduglutide Treatment After Achieving Enteral Autonomy
(b) (6) 9y/o M white	0.05	Gastroschisis	28	60	100	1 week into extension study 304. Resumed teduglutide treatment 6 weeks after completion of study 006.	Maintained enteral autonomy for about 12 months before requiring additional teduglutide treatment in Cycle 2. Continues to maintain enteral autonomy, having received >42 weeks of teduglutide treatment after attaining enteral autonomy (including 19 weeks so far in Cycle 2).
(b) (6) 6y/o M Asian	0.05	Intestinal atresia	42	35	100	Enteral autonomy achieved by Week 27; 3 weeks after completing treatment	Patient was followed for only one week off parenteral support (PS). The patient did not consent to the extension study per Applicant, so it is unknown how long enteral autonomy was sustained.
(b) (6) 9y/o M white	0.025	Midgut volvulus	17	17	72	28 Per Applicant, PN was discontinued following Week 28 visit. Patient had achieved enteral autonomy 2 months later (upon entry into extension study 304).	Required approximately 48 weeks of TED treatment after attaining enteral autonomy.

Source: Reviewer's Table, adapted from Applicant's IR Response, dated January 29, 2019, and TED-C14-006 Demographics Data Short Bowel Syndrome History Listings 16.2.4.3

7.4. Integrated Assessment of Effectiveness

Efficacy of teduglutide in pediatric patients with SBS relies upon partial extrapolation of efficacy from adult data, and is also supported by two open-label studies in pediatric patients contained within this supplement. These pediatric studies had limited sample sizes due to the feasibility of recruitment for pediatric patients with SBS. There were no planned formal statistical comparisons between the teduglutide arms and the SOC arm in these two descriptive studies.

The efficacy of teduglutide is supported by the evaluation of improvement from baseline in efficacy endpoints in teduglutide treated patients.

The 0.0125 mg/kg/day dose was evaluated in study 003 and did not provide evidence of efficacy (only one out of eight patients achieved at least a 20% reduction in PN volume from baseline).

The 0.025 mg/kg/day and 0.05 mg/kg/day doses were evaluated in studies 003 and 006 and had similar effect in reduction in PN volume. Both doses combined showed response rates of 62% (18/29) in study 003 and 62% (31/50), (Table 20) in study 006 on the primary efficacy endpoint (20% reduction in PN from baseline). In light of similar rates of response, the selection of the higher (0.05 mg/kg) dose in pediatric patients is supported by the following:

1. Although response rates were similar on the primary endpoint, the performance of the two doses appeared to separate to a small degree at thresholds greater than 50% reduction, with the higher dose resulting in a small numeric difference in rates of response for 50%, 75% and 100% reduction, favoring the 0.05 mg/kg dose.
2. The 0.05 mg/kg dose is the approved dose in adults and it is noted that systemic exposure with the same mg/kg dose are lower in pediatric patients than adults (with the greatest difference in exposure occurring the in youngest/lowest body weight patients). Thus, accounting for lower exposures, it is unclear if the lower (0.025 mg/kg) dose would demonstrate efficacy long term. The 0.025 mg/kg dose was not evaluated in adults.
3. The safety profile for the 0.05 mg/kg dose appeared comparable to that of the 0.025 mg/kg dose; therefore, the demonstrated safety profile does not warrant limiting the dose to the lower dose in pediatric patients, given the additional uncertainty regarding efficacy of this lower dose.

Efficacy results from the selected 0.05 mg/kg dose in pediatric patients support expanding the approved indication to include pediatric patients 1 year (and 10kg) and older. The teduglutide 0.05 mg/kg/day arm had at least 50% of responders (study 003: 53%; study 006: 69%) achieving at least 20% reduction in PN volume from baseline in both core studies. Efficacy results for the secondary endpoints supported clinical improvement experienced by the patients on teduglutide 0.05 mg/kg/day (Sections 7.3.2. and 7.3.4. The clinically relevant endpoints included percentage of patients with enteral autonomy, reduction in mean time on PN (days/week or hours/day), and reduction in PN calorie etc.

Although information collected from patients on SOC is informative, patients were not randomized into SOC arm and the sample sizes in the SOC arms were very limited (i.e., five patients in study 003 and nine patients in study 006). Hence, this review did not perform a direct comparison between teduglutide and SOC arm.

Complete weaning
Enteral autonomy (complete weaning off PN) was defined as no PN prescribed at EOT and no PN recorded in subject diaries during the week prior to the EOT visit in both studies. According to this common definition, 5.4% (2/37) of patients treated with teduglutide in TED-C13-003 and 10% (5/50) of patients treated with teduglutide in TED-C14-006 achieved enteral autonomy. No patients in the SOC group of either study achieved enteral autonomy. Of the patients who achieved enteral autonomy in TED-C13-003, one had received 0.025 mg/kg/day and one had received 0.05 mg/kg/day. Of the patients who had achieved enteral autonomy in TED-C14-006, two had received 0.025 mg/kg/day and three had received 0.05 mg/kg/day. As previously described, there were also 3 additional patients who achieved this clinically important milestone during treatment in the extension study following study 006.

As detailed above, complete weaning from PN results in dramatic improvement to patient quality of life, potentially with the ability to remove central venous catheter, and related reduction in the risk of mortality due to central line related sepsis and parenteral nutrition associated-liver disease. Although a small number of patients, these results indicate that there is a subset of pediatric patients with SBS who appear to garner clinical benefit from treatment, and that this benefit is of a magnitude which is of clear importance. Further, because large changes in required PN volume are a clinical benefit that is easily recognizable to both providers and patients, it is reassuring that patients, working closely with prescribers, will be able to determine if treatment benefit is occurring, and thus make an informed decision as to whether the risk-benefit supports continued treatment with teduglutide.

8. Review of Safety

8.1. Safety Review Approach

This review was based on independent analysis of the Applicant's data sets and study reports.

The safety analysis focuses on pooled safety data from studies 003 and 006 (hereafter referred to as "core studies") and the prospective portion of the extension studies 303 and 304, which may have included periods of either no teduglutide treatment (NTT) or teduglutide (TED) treatment followed by periods of teduglutide treatment in 24 week treatment cycles.
The safety population was defined as "patients who received at least one dose of teduglutide and have undergone at least one post-baseline safety assessment." There are 101 patients in the safety population of the ISS. The safety review focuses on 87 pediatric patients with SBS

who were exposed to at least one dose of teduglutide in core studies 003 or 006. The remaining 14 patients in the core studies were in the SOC arm.

The ISS included analysis of the pooled safety data from the core studies, extension study 304, and the prospective portion of the extension study 303.

Integrated analysis of the core studies includes:

- Adverse events (AEs)
- Vital signs and growth parameters: weight, height, and body mass index (BMI)
- Laboratory safety data: biochemistry, hematology and urinalysis
- Antibodies to teduglutide

Of note, the core studies differ in design. Assignment of treatment arm (TED versus SOC) was open label in both studies. However, the assignment of the dose level for teduglutide was double blinded in study 006 and open label for study 003.

While there are several limitations to pooling the safety data from studies 003 and 006, including the differences in design, the relatively small number of patients in these two studies makes pooling essential to assess for possible trends in adverse events after exposure to teduglutide. Because of the limitations of the study design and implicit bias in the SOC group (which self-selected), a focus on this safety review is to describe the safety profile for the to-be-marketed (0.05 mg/kg) dose. Comparisons of safety between the 0.025mg/kg and 0.05mg/kg dose were also conducted in support of the selected dose.

8.2. Adequacy of the Safety Database

In this analysis, the core safety population was defined as the population of all patients in studies 003 and 006 who were randomized to at least one dose of teduglutide or SOC. Within this population, the remainder of the safety review focuses on describing the safety profile and findings for the proposed 0.05mg/kg/day dose (to be marketed dose), and in some analyses, safety findings for the 0.025mg/kg/day dose are presented side by side for comparison, in support of the dose selection. Given the small numbers of patients treated with 0.0125mg/kg/day, and that the safety of a dose much less than that which is intended for marketing is less relevant, those data are not presented in detail below.

8.2.1. Extent of Exposure

In the core studies 003 and 006, 87 patients were treated with teduglutide while 14 patients were treated with SOC. Table 26 summarizes the extent of teduglutide exposure in the core studies.

Table 26. Teduglutide Exposure in Core Studies 003 and 006

Parameter	0.0125 mg/kg/day (N=8)	0.025 mg/kg/day (N=38)	0.05 mg/kg/day (N=41)	Total Teduglutide (N=87)
Extent of exposure (weeks)				
Mean (SD)	11.2 (2.51)	19.7 (5.88)	19.5 (5.95)	18.9 (6.15)
Median	12.0	23.9	23.9	23.7
Min, max	5, 13	12, 25	8, 24	5, 25
Exposure by time period (weeks)				
≤12 weeks, n (%)	6 (75.0)	7 (18.4)	5 (12.2)	18 (20.7)
12 to ≤24 weeks, n (%)	2 (25.0)	17 (44.7)	31 (75.6)	50 (5.75)
>24 weeks, n (%)	0	14 (36.8)	5 (12.2)	19 (21.8)

Extent of exposure is calculated as (date of last teduglutide administration − date of first teduglutide administration + 1)/7.
Percentages are based on the number of subjects in the safety population for each treatment groups.
Source: Reviewer's table adapted from Applicant's Summary of Clinical Safety, NDA 203441, s13

Exposure to teduglutide was shorter in the 0.0125 mg/kg/day dose group as this dose was only included in study 003. The 0.025 mg/kg/day and 0.05 mg/kg/day groups had similar mean and median duration of exposure to teduglutide. The majority of patients in the core studies had received between 12 and 24 weeks of treatment.

Extension studies 303 and 304 followed the core studies 003 and 006, respectively. Patients could participate in multiple NTT periods and/or multiple 28-week TED treatment cycles. Patients enrolled in the extension studies were classified into four treatment groups; NTT/NTT, NTT/TED, TED/NTT and TED/TED:

- NTT/NTT – Patients in the SOC arm of the core studies who never received teduglutide treatment in the prospective portions of the extension studies
- NTT/TED – Patients in the SOC arm of the core studies who received teduglutide treatment in the prospective portions of the extension studies
- TED/NTT – Patients who received teduglutide treatment in the core studies but not in the prospective portions of the extension studies
- TED/TED – Patients who received teduglutide treatment in both the core and prospective portions of the extension studies

Table 27 summarizes the extent of teduglutide exposure in the extension studies.

Table 27. Teduglutide Exposure in Extension Studies 303 and 304

Parameter	NTT/TED (N=2)	TED/TED (N=62)
Extent of exposure (weeks)		
Mean (SD)	37.1 (15.9)	40.7 (14.2)
Median	37.1	44.0
Min, max	25.9, 48.4	3.6, 73.1
Exposure by time period (weeks)		
≤12 weeks	0	2 (3.2)
12 to ≤24 weeks,	0	8 (12.9)
24 to ≤48 weeks	1 (50.0)	34 (54.8)
48 to ≤96 weeks	1 (50.0)	18 (29.0)
>96 weeks	0	0

NTT/TED-Patients in SOC arms of the core studies who then received teduglutide treatment in the prospective portions of the extension studies
TED/TED-Patients who received teduglutide treatment in both the core and prospective portions of the extension studies.
For each cycle, the teduglutide exposure will be calculated as: extent of exposure (weeks) = (date of last teduglutide administration − date of first teduglutide administration + 1) / 7. The total extent of exposure is the sum of the exposure in all the cycles.
Percentages are based on the number of subjects in the safety population for each treatment groups.
Source: Reviewer's table adapted from Applicant's Summary of Clinical Safety, 90 days update, NDA 203441, s13, submitted December 7, 2018.
SD = standard deviation; NTT = no teduglutide treatment, TED = teduglutide

Table 28. Teduglutide Exposure in All Studies

Parameter	Total Teduglutide (N=89)*
Extent of exposure (weeks)	
Mean (SD)	47.6 (24.6)
Median	51.7
Min, max	5, 94.7
Total extent of exposure (weeks)	
≤12 weeks, n (%)	9 (10.1)
12 to ≤24 weeks, n (%)	16 (18.0)
24 to ≤48 weeks, n (%)	11 (12.4)
48 to ≤96 weeks, n (%)	53 (59.6)
>96 weeks, n (%)	0

Total extent of exposure in weeks is calculated by adding the exposure in the core studies and the sum of exposure in all the teduglutide treatment cycles in the prospective portions of the extension studies.
Percentages are based on the number of subjects in the safety population for each treatment groups.
Source: Reviewer's table adapted from Applicant's Summary of Clinical Safety, 90 days update, NDA 203441, s13, submitted December 7, 2018

The total mean exposure in all studies was 47.6 ±24.6 weeks (range: 5 to 94.7 weeks), and there were 53 (59.6%) patients who had 48 to ≤96 weeks of treatment according to a 90-day safety update submitted on December 7, 2018. This represents a higher number than discussed in the pre-sNDA meeting. While a sample size of 53 patients is generally low to make a long-term assessment of safety, given that this is a rare condition and the totality of evidence has not shown a new safety signal, the overall number of patients' exposure for at least 48 weeks appears reasonable.

8.2.2. Demographics of the safety database

Table 29 shows the baseline demographics in the core safety population, focusing on those who received 0.025mg/kg or 0.05mg/kg/day dosage, as the comparison between these two arms is a focus of the safety review.

Table 29. Baseline Demographics in Core Safety Population, Studies 003 and 006

Parameter	Total TED 0.025mg/kg/day (N=38)	Total TED 0.05 mg/kg/day (N=41)	SOC (N=14)
Age at baseline (years), mean (SD)	6.0 (3.6)	5.6 (3.6)	4.4 (4.1)
Age group at baseline of TED-C13-003/ TED-C14-006, (n, %)			
1 to <12 years	35(92.1)	38 (92.7)	13 (92.9)
<2 years	3(7.9)	1 (2.4)	0
2 to <6 years	17(44.7)	24 (58.5)	11 (78.6)
6 to <12 years	15(39.5)	13 (31.7)	2 (14.3)
12 to <18 years	3(7.9)	3 (7.3)	1 (7.1)
Sex (n, %)			
Male	27(71.1)	27 (65.9)	9 (64.3)
Female	11(28.9)	14 (34.1)	5 (35.7)
Race (n, %)			
White	27 (71.1)	34 (82.9)	5 (35.7)
Black or African American	4(10.5)	4 (9.8)	2 (14.3)
Asian	1(2.6)	2 (4.9)	2 (14.3)
Other	2(5.3)	0	2 (14.3)
Not allowed based on local regulations	3(7.9	1 (2.4)	3 (21.4)
Ethnicity (n, %)			
Hispanic or Latino	11(28.9)	8 (19.5)	4 (28.6)
Not Hispanic or Latino	23(60.5)	31 (75.6)	6 (42.9)
Not reported	3(7.9)	1 (2.4)	3 (21.4)
Not applicable	1(2.6)	1 (2.4)	1 (7.1)
Weight z-score at baseline, mean (SD)	-0.72 (1.1)	-0.83 (1.02)	-0.29 (0.98)
Height z-score at baseline, mean (SD)	-1.2 (1.2)	-1.24 (1.27)	-0.44 (1.55)
BMI z-score at baseline, mean (SD)	0.07 (1.0)	-0.02 (1.08)	0.05 (0.77)

Percentages are based on the number of subjects in the safety population for each treatment groups.
BMI is calculated as body weight in kg divided by height in meters squared, when both body weight and height are collected.
Z-score is calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention (age ≥2 years old) and World Health Organization (age <2 years old) Z-score calculation charts are used for calculation.
Source: Reviewer's table, adapted from Applicants Summary of Clinical Safety, Table 7, page 28, submitted for sNDA 203441, s13 and Applicant's IR response, dated January 29, 2019 and ISS ADSL dataset.

Generally, the demographics of the 0.025mg/kg and 0.05mg/kg/day dosages were comparable.

Detailed discussion of the demographics and imbalances/limitations between groups was discussed for the individual studies in Section 7 above. Notably, there were few patients <2 years and >12 years in the safety population, which is a limitation. Regarding the adolescents,

given that PK is expected to be comparable between adolescents and adults in most scenarios, and that adolescents with longstanding SBS are much more likely to be comparable to adult patients (in their anticipated refractory nature and potential for response to therapy) as compared to young children who may have more opportunity for growth and adaption, this limitation of the population in the core studies was deemed acceptable. Regarding the paucity of patients in the 1 to 2-year old group, this is likely due to a combination of factors, including necessary minimum duration of disease and PN dependence for this protocol limited enrollment of 1-year-olds, and that the youngest patients have the greatest opportunity for improvement without pharmacological therapy. It may be reasonable and in a patient's best interest, given the potential AEs associated with teduglutide treatment, for providers to wait until they are certain that a patient will not attain enteral autonomy on their own before pursuing a treatment such as teduglutide. Given that adaptation takes time and set-backs are common in young children in the process of weaning from PN due to intercurrent illness, etc., it is likely that in clinical practice the majority of patients using teduglutide may be closer to 2 years and older. Thus, the age representation in this population was deemed acceptable.

BMI Z-scores in the TED/NTT and TED/TED groups were near zero and do not suggest nutritional deficiency. BMI percentile for age is also consistent with normal weight status across all dosing arms, and was approximately ~50%, supporting the assertion that most patients were not underweight at time of enrollment.

Table 30 summarizes the relevant disease specific factors impacting the SBS history of patients in the core safety population

Table 30. Short Bowel Syndrome History in the Core Safety Population

Parameter	Total Teduglutide 0.025mg/kg/day (N=38)	Total Teduglutide 0.05 mg/kg/day (N=41)	SOC (N=14)
Primary reason for the diagnosis of SBS (n, %)			
Necrotizing enterocolitis	7 (18.4)	6 (14.6)	4 (28.6)
Midgut volvulus	12 (31.6)	11 (26.8)	5 (35.7)
Intestinal atresia	5 (13.2)	3 (7.3)	1 (7.1)
Gastroschisis	12 (31.6)	17 (41.5)	2 (14.3)
Hirschsprung disease	1 (2.6)	3 (7.3)	2 (14.3)
Multiple	1 (2.6)	1 (2.4)	0
Patients with a stoma (n, %)	7 (18.4)	6 (14.6)	3 (21.4)
Type of stoma (n, %)			
Jejunostomy	4 (57.1)	4 (66.7)	2 (66.7)
Ileostomy	1 (14.3)	2 (33.3)	1 (33.3)
Colostomy	2 (28.6)	0	0
Patient with any remaining colon (n, %)	36 (94.7)	39 (95.1)	11 (78.6)
Estimated percentage of colon remaining, mean (SD)	62.2 (35.6)	71.1 (30.1)	63.2 (31.0)
Colon in continuity (n, %)	33 (91.7)	36 (92.3)	11 (100.0)
Total estimated remaining small intestinal length (cm), mean (SD)	49.4 (40.0)	42.0 (26.4)	42.5 (28.5)
Distal/terminal ileum present (n, %)	11 (28.9)	13 (31.7)	4 (28.6)
Ileocecal valve present (n, %)	8 (72.7)	11 (84.6)	4 (100.0)
Duration of prior parenteral nutrition dependence (years), mean (SD)	5.5 (3.2)	4.8 (3.2)	4.8 (4.2)
Baseline parenteral support volume requirements			
<50 mL/kg/day (n, %)	11 (28.9)	16 (39.0)	2 (14.3)
≥50 mL/kg/day, (n, %)	23 (60.5)	23 (56.1)	12 (85.7)
Missing	4 (10.5)	2 (4.9)	0

Duration of prior parenteral nutrition dependence (years) = ([baseline visit date – start date of parenteral nutrition dependency] + 1)/ 365.25
Percentages are based on the number of subjects in the population for each treatment group.
[a] Percentages are based on subjects with a stoma in each treatment arm.
[b] Percentages are based on the number of subjects who have remaining colon in each treatment group.
[c] Percentages are based on the number of subjects with distal/terminal ileum present in each treatment group.
SBS = short bowel syndrome, SOC = standard of care, SD = standard deviation,
Source: Reviewer's table adapted from Applicant's Summary of Clinical Safety Table 9 and ISS Table 3.1 and 4.1, NDA 203441, s13

The most common causes of SBS in all patients in the core studies were gastroschisis (31.7% [32/101]), midgut volvulus (29.7% [30/101]), and necrotizing enterocolitis (17.8% [18/101]. The mean total estimated remaining small intestinal length of all patients in the core studies was 44.7 ±33.00 cm. An ostomy was present in 17.8% (18/101) patients, most of whom had a jejunostomy (61.1%, 11/18 patients], followed by ileostomy (27.8%, 5/18 patients) and colostomy (11.1%, 2/18 patients). The majority (92.1%, 93/101) of patients in the core studies had at least some remaining colon, with six (6.5%) who had remnant colon that was not in continuity. The mean duration of prior PN dependence of all patients in the core studies was 5.0 ±3.35 years, and the majority (61.4%) of these patients required ≥50 mL/kg/day of PN volume at baseline. In general, the study demographics appear representative of the SBS population. Although formal comparison against the SOC arm is limited by the bias introduced in permitting self-selection to this arm, it is noted that for the key parameters anticipated to

affect prognosis (length of residual intestine, presence or absence of IC valve, and colon in continuity), the distribution of patients within the SOC group is comparable to that of the treatment arm.

8.2.3. Categorization of Adverse Events (AEs)

The Applicant's method for recording, coding and categorizing adverse events (AEs) met established standards. The Applicant provided appropriate definitions of adverse events and serious adverse events (SAEs) in the protocols.

Only treatment emergent adverse events (TEAEs) were analyzed in the ISS. TEAEs were defined as AEs that started or worsened during or after administration of treatment for patients in the teduglutide arms and AEs that started or worsened at or after the baseline visit for patients in the SOC arms. For AEs that started or worsened on the first administration date of teduglutide, events with a start time at or after the first dosing time of teduglutide were considered treatment emergent. AEs were coded with Medical Dictionary for Regulatory Activities, Version 19.1.

An AE was defined consistent with 21 CFR 312.32(a) as any untoward medical occurrence in a clinical investigation subject administered a medicinal product, whether or not it had a causal relationship with the study drug.

AEs defined in the protocol included:

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

AEs in the protocol did not include:

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

An SAE was defined appropriately consistent with 21 CFR 312.32(a).

The protocol further clarified that scheduled and/or elective hospitalizations occurring under the following circumstances were not defined as SAEs for these clinical studies:

- planned before entry into the clinical study;

- are for elective treatment of a condition unrelated to the studied indication or its treatment;
- occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria); or
- are part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

See Appendix (Section 14.4.4.) for the schedules of procedures and assessment in the protocols for studies 003 and 006. Schedule of testing and panel of routine clinical tests was acceptable.

8.3. Safety Results

8.3.1. Rates of Adverse Events

Table 31 summarizes types of TEAEs in the core studies among patients who had received 0.05 mg/kg/day of teduglutide, 0.025 mg/kg/day of teduglutide, or SOC. The overall percentages of any TEAEs are similar even if the number of patients with these TEAEs were lower in SOC compared to patients treated with teduglutide 0.05 mg/kg/day or 0.025 mg/kg/day. There appeared to be a higher percentage of patients with severe TEAEs and serious TEAEs in patients treated with teduglutide 0.05 mg/kg/day or 0.25 mg/kg/day compared to SOC. Caution is needed in making any direct comparison between treatment groups and SOC, given the lack of randomization. However, further analysis revealed that TEAEs in the treatment group were mostly not related to teduglutide administration, but rather to underlying SBS and total parenteral nutrition (TPN) (discussed further below). There were no TEAEs leading to treatment discontinuation or death in the core studies.

Table 31. Treatment Emergent Adverse Events in Safety Population, Studies 003 and 006

Treatment Emergent Adverse Events (TEAEs)	0.025 mg/kg/day Teduglutide (N=38)		0.05 mg/kg/day Teduglutide (N=41)		Standard of Care (N=14)	
	N	%	N	%	N	%
Patients with any TEAEs	38	100.0	40	97.6	14	100.0
Patients with any severe TEAEs	9	23.7	15	36.6	1	7.1
Patients with any serious TEAEs	22	57.9	28	68.3	7	50.0
Patients with any TEAEs leading to death	0	0	0	0	0	0
Patients with any TEAEs leading to treatment discontinuation	0	0	0	0	0	0

Source: Reviewer's Table, derived from ISS Pediatrics S13 Analysis Adam datasets: ADAE and ADSL; JReview 11.0.
Including pooled datasets of patients from the two core studies (TED-C13-003 and TED-C14-006) who received 0.05 mg/kg/day teduglutide and standard of care. ISS Table 6.1 page 63/3547.

The safety profile of 0.05mg/kg/day was generally comparable to that of the 0.025mg/kg/day dose. The incidence of TEAEs and serious TEAEs were similar between patients treated with 0.025 mg/kg/day and 0.05 mg/kg/day. The majority of patients in the core studies had mild or moderate TEAEs. There were no trends in the severity of TEAEs across dose groups, although

severe TEAEs were more common in teduglutide-treated patients compared to SOC treated patients. There were no TEAEs leading to treatment discontinuation or death.

8.3.2. Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts and/or discontinuations due to adverse events in patients who received teduglutide 0.025mg/kg/day, 0.05 mg/kg/day or in the SOC arm in the core studies. There was one patient who withdrew in the teduglutide 0.05 mg/kg/day arm (b) (6) (b) (6) on day 57. Review of individual patient narratives notes that the patient's reported adverse events were dehydration and irritability on day 27 and day 28 prior to withdrawal from the study on day 57. The exact reason for withdrawal was not specified in the narratives; however, it was stated that it was not due to an adverse event.

There was a total of two TEAEs leading to treatment discontinuation in two patients in the extension studies, both in the TED/TED group. There was one patient who initially received 0.025mg/kg/day teduglutide (b) (6) with a history of cholestasis who discontinued teduglutide due to increased blood bilirubin. The event was assessed as related to iatrogenic iron overload and not related to teduglutide by the investigator. While teduglutide treatment was discontinued, the patient remains in the study. The other treatment discontinuation was due to ileus in a patient who received 0.05mg/kg/day and had enterocutaneous fistula. The patient was placed on parenteral nutrition and off teduglutide treatment. Ileus and/or obstruction are reported adverse events associated with teduglutide use and are already described in the prescribing information based on the adult data.

Of note, there was one additional patient in extension study 304 (b) (6) who discontinued due to worsening SBS that was assessed as severe in intensity and not related to teduglutide, and the patient later died due to this event (described below under "Deaths").

8.3.3. Deaths

As described below, there was one death during the clinical studies of pediatric patients with SBS and it was not considered related to the study drug.

Patient (b) (6) (Study 006 Followed by Extension Study 304)
The patient was a 16-year-old, white male with SBS since (b) (6) and a medical history of midgut volvulus, cerebral palsy, hydrocephalus and seizure disorder. He received 0.05 mg/kg/day teduglutide from (b) (6), to (b) (6), before transitioning to extension study 304 from (b) (6), to (b) (6)

On (b) (6), an SAE of worsening SBS was reported. The patient was enrolled in hospice care, at which time TPN was stopped. Per the investigator, the patient's family elected to pursue end-of-life care and home hospice due to the patient's inability to wean off TPN, comorbid conditions not related to study drug, and impaired quality of life related to SBS and comorbid conditions. No treatment was provided during the SAE. The Applicant reported that on (b) (6), the patient died due to withdrawal of enteral and parenteral fluid and

nutritional support. The Applicant assessed the event as not being related to the study drug.

The Applicant's assessment that the patient's death is not related to the study drug appears reasonable, given that the patient experienced worsening of underlying disease and decision to withdraw life-sustaining nutritional support occurred when patient was off treatment; the cause of death appeared directly related to withdrawal of nutritional support.

8.3.4. Serious Adverse Events (SAEs)

There was a total of 61 treatment emergent serious adverse events (TESAEs) in 28 (68.3%) patients who received teduglutide 0.05 mg/kg/day and 50 TESAEs in 22 (57.9%) patients who received teduglutide 0.025mg/kg/day in the core studies, while there were 16 serious TEAEs in seven (50%) patients in the SOC arm. Table 32 shows TESAEs by system organ class and preferred term (PT) that occurred in ≥2 patients in the teduglutide 0.05 mg/kg/day arm and standard of care arm. The incidence of TESAEs was similar in the 0.025mg/kg/day and 0.05mg/kg/day dose groups and in the SOC group, with a slightly lower rate of pyrexia and infections/infestations in the 0.025mg/kg/day.

Table 32. Treatment Emergent Serious Adverse Events in ≥2 Patients in Teduglutide 0.025 mg/kg/day, 0.05 mg/kg/day and Standard of Care Arms (Safety Population, Studies 003 and 006)

System Organ Class *Preferred Term*	0.025mg/kg/day Teduglutide (N=38) n (%)	0.05 mg/kg/day Teduglutide (N=41) n (%)	Standard of Care (N=14) n (%)
Number of patients with any TESAE	22 (57.9)	28 (68.3)	7 (50)
General disorders and administration site conditions	5 (13.2)	11 (26.8)	3 (21.4)
Pyrexia	5 (13.2)	*10 (24.4)*	*3 (21.4)*
Infections and infestations	13 (34.2	18 (43.9)	5 (35.7)
Device-related infection	5 (13.2)	*6 (14.6)*	*0*
Influenza	2 (5.3)	*2 (4.9)*	*1 (7.1)*
Upper respiratory tract infection	2 (5.3)	*2 (4.9)*	*2 (14.3)*
Viral infection	0	*2 (4.9)*	*2 (14.3)*
Catheter site infection	0	*3 (7.3)*	*0*
Catheter sepsis	0	*1 (2.4)*	*0*
Device-related sepsis	1 (2.6)	*1 (2.4)*	*0*
Metabolism and nutrition disorders	4 (10.5)	3 (7.3)	0
Metabolic acidosis	1 (2.6)	*1 (2.4)*	0
Dehydration	4 (10.5)	*1 (2.4)*	0
Hypokalemia	1 (2.6)	*1 (2.4)*	0
Product issues	5 (15.8)	6 (14.6)	2 (14.3)
Device breakage	4 (10.5)	*2 (4.9)*	*0*
Device issue	0	*1 (2.4)*	*0*
Device malfunction	0	*1 (2.4)*	*2 (14.3)*
Device occlusion	0	*1 (2.4)*	*0*
Device dislocation	2 (5.3)	*1 (2.4)*	*0*
Gastrointestinal disorders	1 (2.6)	3 (7.3)	0
Diarrhea	1 (2.6)	*1 (2.4)*	0
Frequent bowel movements	0	*1 (2.4)*	0
Hematemesis	0	*1 (2.4)*	0

Preferred Term/*Verbatim Term*:
Device Related Infection: Device related infection/*Central line infection*; Catheter site infection/*Central line infection*, *Hickman catheter infection, Central venous tunnel infection*; Device Related Sepsis/*Central line associated sepsis*; Catheter sepsis/ *Line sepsis*
Product Issues: Device breakage/*Broken central venous line*; Device issue/*Central line contamination (dog tampered with TPN tubing);* Device malfunction/*Central line malfunction*; Device occlusion/*Occluded central line;* Device dislocation/*Central line dislodged*.
Source: Reviewer's Table, derived from ISS Pediatrics S13 Analysis Adam datasets: ADAE and ADSL; JReview 11.0.
Including pooled datasets of patients from the two core studies (003 and 006) who received 0.05 mg/kg/day teduglutide and standard of care.
TESAE = treatment emergent serious adverse event

In the teduglutide 0.05 mg/kg/day arm, the system organ class with the highest percentage of patients reporting any TESAEs were infections and infestations (20, 48.8%), general disorders and administration site conditions (13, 31.7%), product issues (6, 14.6%), gastrointestinal disorders (6, 14.6%) and metabolism and nutritional disorders (5, 12.2%). Similarly, infections and infestations (5, 35.7%), general disorders and administration site conditions (7, 50%) and product issues (2, 14.3%) were the most frequently reported TESAEs in the SOC arm.

The most common TESAE in patients treated with teduglutide 0.05 mg/kg/day was pyrexia (12, 29.3%) with a similar percentage of patients in SOC arm (3, 21.4%). However, these cases of pyrexia were assessed as not related to administration of teduglutide. Based on review of the provided narratives, the Applicant's assessment seems reasonable.

Device-related AEs (listed under "product issues") were frequently reported (occurring in 14% of patients treated with 0.05 mg/kg). However, patient narratives indicate that all these device-related adverse events and product issues were complications of central venous catheters used to administer PN, and not related to the device used to prepare and administer teduglutide. Complications and malfunctions of central lines in pediatric patients with SBS are well known problems associated with this condition.

SAEs in Extension Studies

The system organ classes and preferred terms (PT) of the most frequently reported TESAEs in the extension studies were similar to those of the core studies and included infections and infestations (49.4%) and general disorders and administration site conditions (29.2%), with PT of pyrexia (28.1%), device-related infection (27.0%), influenza (10.1%), device breakage (9.0%), dehydration (7.9%), and URI (6.7%). There were no new TESAEs that had not been previously associated with use of teduglutide in the core studies.

The Applicant reported one patient with fecaloma who passed stool spontaneously without intervention; no disimpaction was performed and no laxatives were administered. The investigator denied presence of fecaloma but noted obstruction was due to result of hard stool. Given there was no fecaloma per investigator report, the Applicant updated the event term to feces hard and GI obstruction in the safety database. However, the term fecaloma remains in the clinical data table for the 90 days safety update report. This event is notable because intestinal obstruction is an adverse event of special interest (AESI) for teduglutide based on the larger controlled trial population in adults.

There was one AESI of large intestine polyp (patient (b) (6)) in a 6-year-old male with medical history of SBS, GI bacterial overgrowth, and PN-associated liver disease. He received 0.025 mg/kg/day in study 006 followed by 0.05 mg/kg/day teduglutide in extension study 304. Patient had 48 to ≤96 weeks of TED treatment in TED/TED group w (b) (6) . A sessile polyp was found on colonoscopy/EGD performed o (b) (6) . Per the Applicant, no treatment was given to the patient for the event of large intestinal polyp. On (b) (6) follow-up information indicated no cecal polyp was visualized on two subsequent colonoscopies. Repeat colonoscopies on (b) (6) with biopsies showed colonic mucosa, duodenal biopsy with focal mild active chronic gastritis, but endoscopist and investigator did not identify any colonic polyps. Given no colonic polyps identified on follow-up, the event initially identified as serious AESI was removed by Applicant. However, this event represents a reported AE of special interest, and it required multiple invasive follow-up procedures. The reason that a previously identified polyp could not be found on follow-up examination is unclear. While it may have been a misdiagnosis at onset, it is not possible to confirm or refute this. Pedunculated polyps may at times detach spontaneously, and thus may not be seen on follow-up examination. Given the concern for intestinal polyps associated with teduglutide use based upon the larger adult database, this case should not have been removed from the safety database and should be noted.

8.3.5. Common Adverse Events

In the core studies, there were 459 TEAEs in 40/41 (97.6%) patients in the 0.05 mg/kg group, 384 TEAEs in 38/38 (100%) patients in the 0.025mg/kg/group and 104 TEAEs in 14/14 (100.0%) patients in the SOC arm, majority of which were mild or moderate in severity. Table 33 summarizes the most commonly reported TEAEs seen in ≥2 patients in the core studies.

Table 33. Treatment Emergent Adverse Events in ≥2 Patients, Core Studies 003 and 006

	Pooled Trials of TED-C13-003 and TED-C14-006		
Treatment Emergent Adverse Event (TEAE)	**TED 0.025mg/kg/day (N=38) n (%)**	**TED 0.05 mg/kg/day (N=41) n (%)**	**SOC (N=14) n (%)**
Number of patients with any TEAEs	38 (100)	40 (97.6)	14 (100.0)
Upper respiratory tract infection (total)	18 (47.4)	29 (70.7)	10 (71.4)
Abdominal pain (total)	8 (21.1)	13 (31.7)	2 (14.3)
Abdominal distension	1 (2.6)	3 (7.3)	0
Nausea	5 (13.2)	5 (12.2)	1 (7.1)
Injection site reactions (total)	8 (21.1)	12 (29.3)	0
Vomiting	16 (42.1)	15 (36.6)	6 (42.9)
Cough (total)	5 (13.2)	15 (36.6)	4 (28.6)
Hypersensitivity (total)	5 (13.2)	11 (26.8)	3 (21.4)
Decreased appetite	0	3 (7.3)	0
Influenza	2 (5.3)	4 (9.8)	0
GI stoma complication	5 (13.2)	7 (17.1)	3 (21.4)
TEAEs below are not in the current approved adult labeling			
Diarrhea (total)	11 (28.9)	11 (26.8)	3 (21.4)
Fatigue	1 (2.6)	5 (12.2)	0
Medical device related reactions (total)	1 (2.6)	6 (14.6)	1 (7.1)
Pyrexia	10 (26.3)	20 (48.8)	6 (42.9)
Device related infections (total)	6 (15.8)	11 (26.8)	0
Abnormal Liver Function tests (total)	14 (36.8)	11 (26.8)	0
Anemia (total)	3 (7.9)	7(17.1)	0
Metabolic acidosis (total)	9 (23.7)	6 (14.6)	2 (14.3)
Headache	5 (13.2)	7 (17.1)	1 (7.1)

Source: Reviewer's Table, derived from ISS Pediatrics S13 Analysis Adam datasets: ADAE and ADSL; JReview 11.0.
Including pooled datasets of patients from the two core studies (TED-C13-003 and TED-C14-006) who received 0.05 mg/kg/day teduglutide (TED) and standard of care (SOC). Adapted from Applicant's ISS Table 7.1

To create the table above, the following related preferred terms were combined to define the following TEAEs:

Table 34. Combined Terms and Preferred Terms for Treatment Emergent Adverse Events

Treatment Emergent Adverse Event (Combined Term)	Included Preferred Terms
Upper respiratory tract infection (URI)	URI, pharyngitis, nasopharyngitis, rhinitis, respiratory tract infection
Abdominal pain	Abdominal pain, abdominal pain upper
Injection site reactions	Injection site bruising, injection site discoloration, injection site hematoma, injection site induration, injection site mass, injection site pain, injection site rash, injection site swelling, injection site erythema
Cough	Cough, productive cough
Hypersensitivity	Dermatitis, dermatitis atopic, dermatitis contact, dermatitis diaper, erythema, pruritis, rash
Gastrointestinal (GI) stoma complication	GI stoma complication, GI stoma output decreased, GI stoma output increased, stoma complication, stoma site erythema, stoma site hemorrhage, stoma site reaction
Diarrhea	Diarrhea, abnormal feces, fecal volume increased and frequent bowel movement
Medical device related reaction	Injury associated with device, medical device site dermatitis, medical device site erythema, medical device site pain
Device-related infections	Device-related infection, device-related sepsis
Abnormal liver function tests	Transaminases increased, AST increased, ALT increased, drug-induced liver injury
Anemia	Anemia, red blood cell count decreased, hemoglobin decreased, hematocrit decreased, microcytic anemia
Metabolic acidosis	Acidosis, metabolic acidosis, blood bicarbonate decreased

Source: Reviewer created table

TEAEs of URI, abdominal pain, abdominal distension, nausea, injection site reaction, cough and influenza were more common among teduglutide-treated patients than among patients who received SOC. These terms were also more common among teduglutide-treated patients in the placebo-controlled adult SBS studies.

Using the analysis method/grouping strategy defined above, TEAEs that were not previously noted as more common among teduglutide-treated patients than SOC-treated in adult studies but were observed to be more common among teduglutide-treated than SOC-treated pediatric patients include: fatigue, headache, diarrhea; medical device-related reactions, device-related infections, abnormal liver function test, anemia, and metabolic acidosis.

Review of individual patient narratives showed that majority of these TEAEs (those seen commonly in pediatric patients but not meeting the threshold for common AEs in adults) were not related to teduglutide administration and, as such, does not warrant inclusion in the label. Patients with SBS often have intravenous central-line catheters for chronic parenteral nutrition administrations, and these chronic indwelling devices increase a patient's risk for infection, associated pyrexia, and device-related reactions. Thus, the Applicant's proposal not to include

device related infection, pyrexia, device related reactions in the label appears reasonable.

Of the two patients with anaphylaxis reactions, one had vancomycin-related reaction of red man syndrome, of which there was a prior history, and which resolved with discontinuation of vancomycin. The second patient with anaphylaxis reaction was due to a double dose of fondaparinux, resulting in stridor and inspiratory/expiratory wheezing; the event resolved with epinephrine, diphenhydramine and racepinephrine. Teduglutide was interrupted for 2 days before continuation. Neither of the two cases of anaphylaxis reactions was related to teduglutide administration.

There was a case of elevated ALT that started on (b) (6), (level not provided) in patient (b) (6) (study 006), which was reported resolved at lowest level of 65 U/L in (b) (6) (baseline not given). ALT was reported to be higher again in (b) (6) (158 U/L) and on (b) (6) (584 U/L). Gamma-glutamyl transferase and bilirubin levels for this patient were normal. The patient was reported to be symptom free and doing well. Patient was also noted to be receiving intermittent rifaximin for small intestinal bacterial overgrowth and history of lactic acidosis. The investigator noted that given rifaximin was started prior to ALT elevation, rifaximin was likely causing the event and it was stopped on (b) (6) The outcome for the intermittent adverse event of transaminases increased was reported as recovered/resolved on (b) (6) The dose of teduglutide was not changed during the event. The event was assessed by the investigator as mild in intensity and not related to teduglutide. The most likely cause of the elevated ALT is the progression of the patient's underlying SBS, in addition to patient's dependence on parenteral nutrition, and concurrent administration of rifaximin. While the elevated level of ALT of 584 at the highest is concerning, given that the dose of teduglutide was unchanged while the ALT level was fluctuating, it is less likely that the ALT elevation was due to the study drug. Thus, the investigator's assessment was deemed acceptable, as elevated ALT is one of the listed adverse reactions on the label of rifaximin that can occur with a frequency of 2 to 10%.

It appeared that adverse event data in these studies were vulnerable to selection bias, reporting bias, and limited sensitivity in the SOC group, due to the much smaller sample size. Although the dose of teduglutide was blinded in the TED-C14-006 study, allocation to teduglutide treatment was open label in both core pediatric studies. Additionally, parents chose whether their children would receive teduglutide in these studies. It is likely that parents of children who have more frequent central line complications or more severe IF-associated liver disease were more motivated to try an experimental therapy. Of note is that analysis of patient narratives of the adverse reactions not currently listed in the adult label (but seen in the pediatric analysis) showed that none of the observed elevations in aminotransferases, catheter-related infection, device related issues, pyrexia and diarrhea were related to teduglutide.

No new safety signal was identified in review of TEAEs in the core studies. After review of the TEAEs in the core studies, the Applicant's proposal not to include a new table of AEs in the label is reasonable, given the common TEAEs in the pediatric core studies were similar to those seen in the adult studies. Of the additional TEAEs seen in the core studies in pediatrics, most were

not related to teduglutide, majority were related to underlying SBS and associated parenteral nutrition.

8.3.6. Significant Adverse Events

Significant AEs (AEs graded by the investigator as "severe" in intensity) occurred within the core studies, in 15 of 41 (36.6%) in the teduglutide 0.05 mg/kg/day arm, 10 of 38 (26.3%) in the teduglutide 0.025mg/kg/day arm and one of 14 (7.1%) in the SOC arm.

Table 35. Summary of Severe Treatment-Emergent Adverse Events in Total Teduglutide Arm– Safety Population in Core Studies 003 and 006

System Organ Class *Preferred Term*	0.025mg/kg/day Teduglutide (N=38) n (%)	0.05 mg/kg/day Teduglutide (N=41) n (%)	Standard of Care (N=14) n (%)
Number of patients with any severe TEAE	9 (23.7)	15 (36.6)	1 (7.1)
Gastrointestinal disorders	0	2 (4.9)	0
Diarrhea	0	*1 (2.4)*	*0*
Hematemesis	0	*1 (2.4)*	*0*
General disorders and administration site conditions	3 (7.9)	4 (9.8)	1 (7.1)
Pyrexia	3 (7.9)	*4 (9.8)*	*1 (7.1)*
Immune system disorders	0	1 (2.4)	0
Anaphylactic reaction	0	*1 (2.4)*	*0*
Infections and infestations	5 (13.2)	8 (19.5)	1 (7.1)
Upper respiratory tract infection	1 (2.6)	*1 (2.4)*	*0*
Device-related infection	2 (5.3)	*2 (4.9)*	*0*
Viral infection	0	*1 (2.4)*	*0*
Gastroenteritis viral	1 (2.6)	*0*	*1 (7.1)*
Influenza	1 (2.6)	*1 (2.4)*	*0*
Catheter site infection	0	*1 (2.4)*	*0*
Device-related sepsis	1 (2.6)	1 (2.4)	*0*
Parainfluenza virus infection	0	1 (2.4)	*0*
Respiratory tract infection	0	1 (2.4)	*0*
Pneumonia	0	1 (2.4)	*0*
Investigations	0	1 (2.4)	0
Blood albumin decreased	0	*1 (2.4)*	0
Metabolism and nutrition disorders	1 (2.6)	1 (2.4)	0
Dehydration	1 (2.6)	*1 (2.4)*	0
Nervous system disorders	1 (2.6	1 (2.4)	0
Depressed level of consciousness	0	*1 (2.4)*	0
Generalized Tonic-Clonic Seizures	1 (2.6)	*0*	
Product issues	3 (7.9)	3 (7.3)	0
Device breakage	3 (7.9)	*1 (2.4)*	*0*
Device malfunction	0	*1 (2.4)*	*0*
Device occlusion	0	*1 (2.4)*	*0*
Psychiatric disorder	0	1 (2.4)	0
Irritability	0	*1 (2.4)*	0

Source: Reviewer's Table, derived from ISS Pediatrics S13 Analysis Adam datasets: ADAE and ADSL; JReview 11.0.
Including pooled datasets of patients from the two core studies (TED-C13-003 and TED-C14-006) who received 0.05 mg/kg/day teduglutide and standard of care. Adapted from Applicant's ISS Table 10.1

The majority of severe TEAEs in the core studies for patients treated with teduglutide occurred in one patient. Severe TEAEs that occurred in two or more patients were pyrexia, device related infection, device breakage, URI, influenza, device-related sepsis, and sepsis. Severe TEAEs (pyrexia and gastroenteritis viral) that occurred in the SOC arm were in one patient. Of note, the majority of TEAEs that occurred during the core studies were mild or moderate in severity.

There was a total of 11 (15.1%) patients with severe TEAEs who received teduglutide in the extension studies (SHP633-303 and SHP633-304) safety population (N=73). The majority of severe TEAEs in the extension studies were similar to those in the core studies, with pyrexia representing the most common preferred term in five (6.8%) of all patients treated with teduglutide, followed by two (2.7%) with device related infections. All the other patients in the extension with severe TEAEs occurred in one patient each.

There were no trends in the frequency of severe TEAEs by total duration of treatment. Of note, all device-related events were related to central venous catheters used to administer parenteral nutrition, and not related to the teduglutide injection device.

8.3.7. Adverse Events of Special Interest

The protocol for TED-C13-003 and TED-C14-006 defined an AESI as the following: growth of pre-existing polyps of the colon, benign neoplasia of the GI tract including the hepatobiliary system, tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system).

These AESIs were selected based on the known and/or anticipated potential risks associated with teduglutide, informed by the adult development program.

There were no AESIs, serious AESIs or related AESIs in the core and extension studies for patients treated with teduglutide.

8.3.8. Laboratory Findings and Additional Safety Assessments

Clinical laboratory tests to include summary of serum chemistry, hematology and urinalysis values and change from baseline for the core and extension studies were analyzed. There were no clinically meaningful changes in laboratory tests during the core and extension studies. In addition to mean change from baseline, proportion of patients experiencing any post-baseline value that was considered “markedly abnormal” was reviewed for key laboratory tests of interest; results are shown in the Appendix, Section 14.4.2. Assessment of Post-Baseline Chemistry Abnormalities (Table 36), . Results of this analysis were generally consistent with findings from mean change from baseline analysis. Notable findings were 11/89 patients identified to have markedly elevated ALT (defined as ALT>8x ULN), and 9/89 patients reported to have lipase >3X ULN. These findings are discussed further below.

Liver Enzymes

On January 23, 2019, the FDA requested narratives for all patients with markedly abnormal laboratory values that may be suggestive of drug-induced liver injury (DILI). The Applicant responded on January 29, 2019, with narratives for 13 patients (12 with teduglutide exposure) whose laboratory values met one or more of the following standard laboratory criteria for potential DILI: AST >8X ULN, ALT >8X ULN, ALP>5X ULN and TB >2X ULN. The majority of these were elevations of ALT. Of note, patients with IF who are PN dependent have high rates of PN-related liver disease. Further, it is not uncommon for patients with some degree of baseline liver disease to have intermittent spikes in liver enzymes, often precipitated by other triggers such as intercurrent illness, dehydration, anesthesia administration, and/or concomitant medications. As a result, it is not surprising that within this patient population several cases of marked elevation of liver enzymes occurred. Reassuringly, none of these required study drug discontinuation or represented a marked worsening in liver function (as captured by lack of concomitant, persistent rise in bilirubin, or other signs of progression of liver disease). The investigators involved in this trial (who were experienced with PN dependent patients) generally considered these cases unlikely to be treatment related, and the review team agrees with this interpretation. Detailed narratives with relevant laboratory profiles are including in the Appendix (Section 14.4.3.) for cases of markedly abnormal LFTs that may potentially be associated with DILI.

In conclusion, after review of patient narratives that the Applicant provided for all patients with markedly abnormal laboratory values, teduglutide does not appear to be associated with DILI. Changes in AST, ALT, bilirubin and/or alkaline phosphatase that occurred during the trials appeared more likely related to the underlying disease and intercurrent illnesses.

Lipase

Of all patients treated with teduglutide in the clinical development program, 9 (10.1%) had lipase >3x ULN; however, none was reported as a serious adverse event. To correlate the elevated lipase with a clinical diagnosis of potential pancreatitis, the clinical database was reviewed for patients with abdominal pain and elevated lipase >3xULN. Three patients were identified by the applicant to have abdominal pain and elevated lipase, none of whom had pancreatitis and none were related to teduglutide use. See section 14.4.1. in Appendix for more information.

Hematology

Of the patients treated with teduglutide in the core studies, there were four patients who had markedly low leukocytes (<2 X 10^9/L) value, three patients with markedly low platelet count (<75 X 10^9/L) value, and two patients with markedly low neutrophils (<0.5 X 109/L) value. There was also one patient in the SOC group with a markedly low neutrophils (<0.5 X 109/L). Of the patients who had teduglutide treatment during/after treatment in the extension studies, there was one patient each with: neutrophils <0.5 10^9/L, leukocytes <2 10^9/L, and leukocytes >30 10^9/L. For the patients in NTT periods, a markedly abnormal hemoglobin <70 g/L was noted in one (6.7%) patient. These abnormal hematology laboratory values seem to occur irrespective of whether they received teduglutide treatment or not. In addition, the overall low number of

patients with markedly abnormal post-baseline hematology values limits any conclusion that can be drawn from the analysis.

Vital Signs
Vital signs were measured at screening, baseline, Week 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 15, Week 18, Week 21, Week 24 (End of Treatment: EOT) and Week 28 (End of Study: EOS) in study 006 and screening, baseline, Week 1, Week 2, Week 3, Week 4, Week 6, Week 8, Week 10,Week 12 (End of Treatment: EOT) and Week 14 (End of Study: EOS) in study 003. There were no clinically relevant changes from baseline in pulse rate, systolic blood pressure, diastolic blood pressure or temperature.

Electrocardiograms
ECG was obtained at screening and Week 12 in core studies. Summary of ECG findings by visit showed no clinically meaningful changes in patients treated with teduglutide.

Immunogenicity
Immunogenicity data are summarized by clinical pharmacology reviewer in Section 6.3.2.4. There was no apparent relationship between presence of anti-drug antibody and safety (adverse events) or efficacy (loss or lack of efficacy), though the immunogenicity data were limited.

8.3.9. Safety Analyses by Demographic Subgroups

The total sample size for the pediatric studies was small; thus, further subgroup analysis was not conducted since it is unlikely to yield meaningful results.

8.3.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
New studies on carcinogenicity or tumor development potential were not required nor submitted in this application. The nonclinical data reflected in the approved prescribing information highlights concern for potential carcinogenicity (increased incidence of adenomas of bile duct, jejunum, and papillary adenoma of gallbladder) seen in rats at high doses. This potential risk to patients is included in labeling, which recommends a colonoscopy to assess for colonic polyps at baseline and regular post-baseline intervals, as well as a repeat colonoscopy to assess new-onset lower GI bleeding. The pediatric data did not identify any cases of malignancy. There was one potential case of GI tract polyp, which resolved (discussed above).

Human Reproduction and Pregnancy
No new data on pregnancy or fertility were submitted with this application. No patients within the pediatric development program became pregnant while on treatment.

Pediatrics and Assessment of Effects on Growth
The clinical program design was insufficient to meaningfully assess linear growth because of the small numbers, short duration and lack of control. In general, pediatric patients with SBS may

have impaired growth and/or be underweight due to years of malabsorption and difficulties with intestinal function. BMI% and height Z scores were summarized by the Applicant for the baseline and EOT visits within the study 006 safety population. Mean values showed minimal change over this duration. However, unless strict protocol-mandated procedures were in place for measurement of height such as using stadiometry, variability in technique may limit interpretability of such results. Further, this analysis was not conducted stratified by Tanner stage, which is important when considering linear growth rates across various stages of pubertal development. The Applicant also provided (in response to IR received February 12, 2019) individual patient profiles for height, weight and BMI% for the seven patients who achieved enteral autonomy (regardless of dose) across the pediatric program. No consistent trend in growth parameters for these subjects was noted.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Per the Applicant, one patient in study 006 received an approximate six-fold overdose of study drug (0.03 mL/kg/day of assigned volume instead of 0.005 mL/kg/day due to miscommunication among investigator staff) at the baseline visit. The dosing error was immediately recognized, and the patient was monitored closely for the following week. No AEs were associated with the overdose. Treatment with teduglutide was not interrupted and the dose group allocation of the patient was not prematurely unblinded. The patient had been allocated to the 0.05 mg/kg dose group, meaning that the patient had received approximately 0.30 mg/kg at the baseline visit without any apparent adverse effects per report.

The Applicant provided a postmarketing safety report that identified two cases of overdose (both from Germany; vial strength unknown) out of the 136 pediatric cases of adverse events reported in the postmarket setting globally. One patient with SBS received 3-fold overdose of the prescribed dose of teduglutide of 0.05 mg/kg for 5 months and no adverse events were reported in association with the overdose. No other information was provided. Another patient received a 2-fold overdose about 4 months after starting treatment with teduglutide 0.05 mg/kg. Double dose was prescribed during hospitalization; no reason was provided. No adverse events were reported in relation to this prescribed overdose. No other relevant information was provided.

None of the cases of reported overdose during the clinical trials and postmarketing safety review were associated with adverse events.

8.4. Safety in the Postmarket Setting

8.4.1. Safety Concerns Identified Through Postmarket Experience

Based on the Applicant's most recently submitted periodic safety update report (PSUR) including the reporting period from August 29, 2017 and August 30, 2018, the cumulative worldwide patient exposure to teduglutide is 4,740 patient years. Six hundred ninety-eight subjects were exposed in the context of a clinical trial. The PSUR identified 3 potential new safety signals from the reporting period – namely cholestasis/hyperbilirubinemia, D-lactic

acidosis, and ileus/fecaloma/constipation. All three of these were identified as a result of reports in patients included in the pediatric program (described previously in this review) and the Applicant's further assessment of the larger safety database, focused on these 3 issues did not identify a clear signal that any of these are new safety signals related specifically to teduglutide.

8.4.2. Expectations on Safety in the Postmarket Setting

There is an ongoing non-interventional study TED-R13-002: A Prospective, Multicenter Registry for Patients with Short Bowel Syndrome where separate analyses of adult and pediatric patients enrolled have been completed. A total of 733 adult patients were enrolled in this study from 66 sites located in seven countries (Canada, Denmark, France, Germany, Norway, United Kingdom, and United States (265 teduglutide ever-treated patients, 189 teduglutide currently-treated patients, and 468 teduglutide never-treated patients (defined as patients with SBS who are PN dependent for at least 6 months and have never received teduglutide as an internal control group) as of June 30, 2018. The primary objective of the study is to assess the risk of colon cancer in adult patients exposed to teduglutide, and is assessed in comparison to external registry-based estimates of colon cancer risk. However, secondary objectives include occurrence of other AESI identified for teduglutide, as well as efficacy assessments. To date, the observed AEs and SAEs are consistent with previously reported safety data for teduglutide and are consistent with the known safety profile of teduglutide according to the Applicant.

Please refer to Division of Epidemiology I Review by Dr. Monisha Billings, dated February 1, 2019, for further details on the TED-R13-002 registry study.

The Applicant provided postmarketing pediatric safety review on February 1, 2019. This summary is based on post-marketing commercial sales for pediatric patients across the European Union and South Korea. As of December 2018, an estimated (b) (4) pediatric patients have been treated with commercially available teduglutide globally. There were 387 adverse events in (b) (4) pediatric patients over the period of December 21, 2012, through December 31, 2018, in Spain (b) (4)), Germany (b) (4), Unites States (b) (4), Argentina ((b) (4), Austria (b) (4), and (b) (4) in France, Israel, Italy, Norway and United Kingdom. The most commonly reported adverse event in the pediatric postmarketing population was abdominal pain, the proportion of which was similar to cases reported in the adult population. Pyrexia, abnormal feces, and erythema are proportionately more commonly reported to all adverse events in pediatric patients compared to adults. There were no new safety signals identified in the postmarketing report.

Of the (b) (4) pediatric cases, vial strength was provided in (b) (4) (55%) of cases; (b) (4) (77%) cases reported the use of 5-mg vials and (b) (4) (23%) cases reported the use of 1.25-mg vials. The 5-mg vial was used in children aged 3 to 11 years. The 1.25-mg vial was used in children aged 1 to 9 years.

8.5. Integrated Assessment of Safety

A total of 101 patients were included in the pediatric clinical development program for teduglutide, of which 99 were unique subjects. Of the 99 patients, 89 received teduglutide, while 14 were in the SOC arm. The long-term safety update was based on a mean of 74 weeks of prospective observation and 48 weeks of prospective teduglutide treatment among the 89 pediatric patients who received teduglutide. Of the 89 patients exposed to teduglutide, 41 received 0.05 mg/kg/day and 38 received 0.025mg/kg/day. The mean duration of exposure across all studies was 47.6 ±24.6 weeks (range: 5 to 94.7 weeks). Across the combined controlled and extensions study period, Nine (10.1%) patients had ≤12 weeks of treatment, 16 (18.0%) patients had 12 to ≤24 weeks of treatment, 11 (12.4%) patients had 24 to ≤48 weeks of treatment, and 53 (59.6%) patients had 48 to ≤96 weeks of treatment, which may have included exposure to one or more doses of teduglutide. Given the rare condition of SBS, the small number of pediatric patients treated with teduglutide in this clinical development program appears reasonable, in addition to the totality of evidence from the adult development program.

Nearly all patients experienced one or more TEAE during the course of treatment. There were 384 events in 38/38 (100%) patients in 0.025mg/kg, 459 TEAEs in 40/41 (97.6%) patients in the 0.05-mg/kg group and 104 TEAEs in 14/14 (100.0%) patients in the SOC arm, the majority of which were mild or moderate.

The most common TEAEs for patients treated with 0.025mg/kg/day and 0.05mg/kg/day teduglutide in the core studies were similar for both dose groups. The common TEAEs include URI, abdominal pain, abdominal distension, nausea, injection site reaction, vomiting, cough, hypersensitivity, decreased appetite, influenza and GI stoma complication, pyrexia, diarrhea, fatigue, medical device related reactions, device related infections, abnormal liver function tests, anemia, metabolic acidosis and headache. Most of these TEAEs were similar to those observed in the placebo-controlled adult SBS studies. However, there were some TEAEs that were observed in the pediatric studies that were not in the adult studies; these TEAEs were generally not related to teduglutide administration.

In the 0.05mg/kg/day teduglutide dose, there were two reported events of anaphylaxis in two patients, both of which were not related to teduglutide administration. One was related to vancomycin administration (red-man syndrome) and the second one was related to double-dose of fondaparinux. There was one death during the clinical studies of pediatric patients with SBS and it was not considered related to the study drug.

Based on review of clinical and laboratory safety data, there were no new safety signals identified as associated with teduglutide treatment in the core and extension studies. There was a single potential AESI in the case of a large polyp that was noted after a patient had completed teduglutide in the core and extension studies; however, the polyp was no longer visible on multiple repeat colonoscopy and the AESI was removed per Applicant. In addition,

there was a case of peripheral edema in a patient who received 0.025 mg/kg/day teduglutide, which the Applicant reported as non-serious and did not affect teduglutide administration.

In summary, the available data were sufficient to characterize the safety profile of teduglutide in the pediatric population. Based on available data, teduglutide treatment demonstrated an acceptable benefit versus risk profile for use in pediatric SBS, with precautions in place to mitigate the known risks through labeling and REMS. Additional long-term safety data will be collected in the ongoing registry, which is already established as a postmarketing requirement issued at the time of adult approval. The safety profile, as summarized above, appears to be favorable, and the benefit-risk balance supports approval.

9. Pediatrics

This supplemental NDA application includes data for teduglutide with a proposed indication for the treatment of pediatric patients 1 year and older with SBS who are dependent on PN. This study was conducted in response to a PWR. The PWR outlined two clinical efficacy/safety studies followed by an open-label safety extension study of up to 3 years. Efficacy of teduglutide in patients with SBS is supported by extrapolation of efficacy from adequate and well-controlled studies in adults, supplemented by PK, PD, efficacy and safety data in pediatric patients 1 year and older. Although common causes of SBS in children may be different than those in adults, the manifestation, complications and management of SBS are sufficiently similar between adults and children to support extrapolation of efficacy (Carroll et al., 2016; Squires et al., 2012a). Therefore, data from controlled studies in adults supplemented by dosing (PK), qualitative efficacy (PD) and safety data in pediatric patients were deemed adequate to support expansion of the use of teduglutide to pediatric patients 1 year and older. The Applicant has evaluated multiple dose arms over an adequate dose range as outlined in the PWR. Data from the clinical studies described above support the proposed dose of 0.05 mg/kg/day, same dose as the approved adult dose.

The Applicant developed a 1.25-mg vial (b) (4) n the extension studies 303 and 304, this lower strength was used to dose children weighing less than 15 kg. In the PK/PD studies 003 and 006, the currently approved 5-mg strength was used down to 10 kg. (b) (4) the pediatric dosing administration will be limited to the 5 mg strength. Refer to the finalized Product Quality DS-DP reviews in Panorama for additional detail. The 5-mg/vial kit includes a syringe for administration with a needle size of 5/8”, which is considered acceptable for SC administration in pediatric patients 1 year and older (Centers for Disease Control and Prevention, 1994; Smith et al., 1991). The Applicant provided data to describe the

variability in dosing by weight that would be expected in the pediatric population using this presentation. The variability is greatest at low body weights, and the Applicant proposed a body weight cutoff of ≥10 kg for use of this presentation. As described, the variability (maximum of 32% for a 10-kg patient) is considered acceptable from a safety and efficacy standpoint.

Since the product will be indicated for treatment of pediatric patients 1 year and older with SBS who are dependent on PN, the relevant efficacy and safety information will be described throughout labeling as appropriate and summarized in 8.4 Pediatric Use. (b) (4) The prescribing information will therefore recommend that an adult caregiver must administer the medication to pediatric patients. (b) (4)

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information

Key changes to the prescribing information included, but were not limited to, (b) (4) throughout the label and limiting the use to patients who weigh at least 10kg. The reader is referred to the approved label for the final language.

Below are points of discussion between the Applicant and the Division during review of the label:

- Section 1: The indication was revised to add pediatric patients 1 year of age and older
- Section 2: Important administration information
  - Added lower body weight limit (at least 10kg)
    (b) (4)
  - Added a statement that Gattex is for adult self-administration or care-giver administration, and that self-administration in pediatric patients has not been tested.
  - Added that colonoscopy/sigmoidoscopy is recommended for all children/adolescents after 1 year of treatment and every year thereafter while

on continuous treatment with Gattex, and if they have new or unexplained bleeding.

(b) (4)

- Section 6: Addition of statement that overall safety profile in pediatric patients was similar to that seen in adult studies.
    - Number of patients exposed during the studies was revised to reflect data from patients who received only 0.05mg/kg/day teduglutide and SOC.
- Section 8: The Pediatric Use subsection was updated based on the studies in the teduglutide pediatric program.
- Section 12: Added pediatric PK profile.
- Section 14: Added descriptive efficacy data of pediatric patients who received the to-be-marketed dose in study 006.

Patient labeling has been updated in accordance with the final agreed upon prescribing information in the Package Insert.

11. Risk Evaluation and Mitigation Strategies

11.1. Introduction

This section of the review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) modification for teduglutide (Gattex), NDA 203441/S-013, submitted by Shire-NPS Pharmaceuticals, Inc. (Shire) on September 11, 2018. The modification proposes changes to the Gattex REMS document, REMS materials, and REMS supporting document to align with labeling changes related to the proposed pediatric indication.

11.2. Background

Gattex was originally approved with a REMS on December 12, 2012.[4] The goals of the Gattex REMS are to mitigate the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex by:

1. Informing patients about the risks listed above associated with the use of Gattex
2. Informing healthcare providers about the risks listed above associated with Gattex

The currently approved REMS consists of elements to assure safe use (ETASU), which includes training that must be provided to healthcare providers who prescribe Gattex (not linked to distribution). It also contains a timetable for the submission of assessments.

11.3. Results of Review of Applicant-Proposed REMS Modification

11.3.1. General Comments

The proposed modifications to the Gattex REMS reflect incorporating information about the new indication into the existing REMS. Language was inserted throughout the REMS materials to align with the proposed pediatric indication, (b) (4) Shire also proposed formatting and editorial changes, typographical corrections, and administrative changes throughout the REMS document, REMS materials, and REMS supporting document.

11.3.2. REMS Document

There were no changes to the REMS goal with this modification. In addition, Shire listed the Gattex REMS Post-Training Knowledge Assessment Questions as an approved REMS material in the REMS document based on the Agency's comments.

11.3.3. REMS Materials

As part of the REMS modification proposal, the following REMS materials were revised to include the new proposed indication in addition to formatting and structure updates: Gattex REMS Prescriber Education Slide Deck, Gattex REMS Dear Healthcare Provider Letter, Gattex REMS Post-Training Knowledge Assessment Questions, and the Gattex REMS Patient and Caregiver Counseling Guide. Further, the Agency instructed Shire to submit the Gattex REMS

[4] Gattex (teduglutide), Approved Risk Evaluation and Mitigation Strategies (REMS). December 18, 2018; https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=21.

Post-Training Knowledge Assessment Questions, that were in the REMS supporting document, as a separate and distinct REMS material.

11.3.4. REMS Supporting Document

The proposed Gattex REMS supporting document was revised to include pediatric clinical information supporting the expansion of the US indication. Additionally, the Applicant submitted a revised REMS assessment plan to include survey metrics for caregivers.

11.4. Conclusions and Recommendations

DRISK finds the proposed REMS modification for Gattex, as submitted on May 10, 2019, acceptable and recommends approval of the Gattex REMS. For a detailed account of the REMS modification review, refer to the Division of Risk Management's Review of May 15, 2019 (Reference ID: 4433118).

12. Postmarketing Requirements and Commitment

No new safety concerns were identified during this review cycle that warrant additional postmarketing requirements. In addition, no additional postmarketing commitments are recommended.

13. Signatory Authority (DGIEP) Comments

I concur with the recommendation of the review team to approve supplemental NDA 203441/S-013 for Gattex (teduglutide) to expand the indication to include pediatric patients 1 to 17 years of age with short bowel syndrome (SBS) who are dependent on parenteral support. The pediatric studies contained in this sNDA were conducted in response to a pediatric written request, and Gattex will be the first product to be approved to treat pediatric patients with SBS who are PN-dependent. The recommended dosage is 0.05 mg/kg once daily by subcutaneous injection, which is same as the approved adult dosage. (b) (4)

(b) (4)

review team assessed the potential impact on the safety and efficacy of using the currently marketed 5 mg vial kit in pediatric patients from potential dosing variability that could result from tolerance and device-related issues. I concur with the review team's assessment that the

currently marketed presentation is acceptable for use in patients with a minimum body weight of 10 kg. The dosage and administration section of the labeling will indicate that the use of the Gattex 5 mg kit is not recommended in pediatric patients weighing less than 10 kg.

Efficacy of Gattex in pediatric patients with SBS 1 to 17 years of age is supported by extrapolation of efficacy from adequate and well-controlled studies in adults, supplemented by PK, PD, efficacy and safety data in pediatric patients 1 year and older. Disease progression and anticipated response to therapy are sufficiently similar between adult and pediatric patients with SBS to support extrapolation of efficacy. The pediatric program had a limited sample size due to the feasibility of recruitment for this rare pediatric population with SBS who remain PN-dependent. The pediatric trial assessed same efficacy/PD endpoints as the adult program (including the primary endpoint of the proportion of patients achieving at least 20% reduction in the volume of parenteral support after 24 weeks of treatment), and results were consistent with those of the adult phase 3 program. In addition, a small subset of pediatric patients achieved complete enteral autonomy. However, ongoing extension studies have shown that most patients require continued treatment with Gattex beyond 24 weeks to maintain clinical benefit.

The safety of Gattex treatment in pediatric patients with SBS was similar to that in adults; no new safety signals were identified in extension studies. A REMS was implemented at the time of initial approval and remains in effect to mitigate the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex. It consists of training for prescribers as well as informational materials for patients and their caregivers to ensure understanding of the known and potential risks associated with Gattex. The existing REMS was modified to account for the addition of the pediatric indication.

I concur with the review team that data submitted in this sNDA support the conclusion that the benefits of treatment with Gattex outweigh the identified risks in the intended population, with precautions in place to mitigate the known risks through labeling and REMS. Additional long-term safety data will be collected in the ongoing registry, which is already established as a postmarketing requirement issued at the time of original approval. No post-marketing studies will be required.

14. Appendices

14.1. References

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14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): TED-C13-003, TED-C14-006, SHP633-303 and SHP633-304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): 0 Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in 0 Sponsor of covered study: Shire-NPS Pharmaceuticals, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.3.1. Applicant's Population PK Analyses

A population PK analysis was conducted using data from Study TEDC13-003 and Study TED-C14-006 as well as from data from adult subjects from clinical studies. A total of 459 subjects from 12 clinical studies were evaluable for the population PK analysis.

The PK of teduglutide was described using a one-compartmental model with linear elimination. An allometric component accounting for the effect of body weight on Ka, CL/F and Vc/F was included in the base PK model.

Applicant's conclusion on covariate effects:

- The CL/F of teduglutide was dependent on body weight. Lower CL/F values are expected in lighter/younger subjects. For example, typical subjects with body weight values of 10.1 and 127 kg are expected to have CL/F values 68% lower and 42% higher relative to a typical subject with a body weight of 70 kg, respectively.
- The CL/F of teduglutide was dependent on baseline eGFR capped to 150 L/min/1.73m2 (eGFRT). Lower CL/F values are expected in subjects with lower eGFRT. For example, typical subjects with eGFR values of 4.43 and 473 mL/min/1.73m2 are expected to have CL/F values 64% lower and higher relative to a typical subject with an eGFRT of 102 mL/min/1.73m2, respectively.
- The CL/F of teduglutide was dependent on ALT levels. Lower CL/F values are expected in subjects with lower ALT levels. For example, typical subjects with ALT levels of 3 and 412 U/L are expected to have CL/F values 23% lower and 43% higher relative to a typical subject with an ALT level of 24.0 U/L, respectively.
- The Vc/F of teduglutide was highly dependent on body weight. Lower Vc/F values are expected in lighter subjects. For example, typical subjects with body weight values of 10.1 and 127 kg are expected to have Vc/F values 96% lower and 2.7-fold higher relative to a typical subject with a body weight of 70 kg, respectively.
- The Vc/F of teduglutide was dependent on age. Higher Vc/F values are expected in pediatric patients. For example, typical subjects of 1 and 79 years of age are expected to have Vc/F 3-fold higher and 24% lower values relative to a typical subject 34 years of age, respectively.
- The Ka of teduglutide was dependent on body weight. Higher Ka values are expected in subjects with lower body weight (i.e., pediatric patients). For example, typical subjects with body weight values of 10.1 and 127 kg are expected to have a Ka values 3.3-fold higher and 31% lower (0.975 and 0.223 h-1, respectively) relative to a typical subject with a body weight of 70 kg, respectively.

The parameter estimates for the final model are listed in Table 36. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 13.

Table 36. Population PK Parameters of Teduglutide (Final Model Including M3 Method)

PK Parameters	Typical Values	BSV (%)	Shrinkage
CL/F (L/h)	13.6 x (Body Weight/70)$^{0.590}$ x (eGFRT/102)$^{0.322}$ x (ALT /24.0)$^{0.125}$ x 0.833 if not SBS or Crohn's Disease	26.3	14.0%
Vc/F (L)	33.1 x (Body Weight/70)$^{1.65}$ x (Age/34.0)$^{-0.332}$	39.2	21.4%
Ka (h^{-1})	0.318 x (Body Weight/70)$^{-0.624}$ x 0.690 for SC administration other than abdomen	26.1	35.0%
ALAG (h)	0.207	0, Fixed	NA
Error Model			
Additive Error (ng/mL)	7.16	NA	NA
Proportional Error (%)	24.4	NA	NA

ALAG = Lag time; ALT = alanine aminotransferase; BSV = between-subjects variability; CL/F = apparent clearance; eGFRT = estimated glomerular filtration rate capped to 150 mL/min/1.73m^2; Ka = first-order rate constant of absorption; PK= Pharmacokinetic; Vc/F = apparent central volume of distribution; NA= Not applicable.

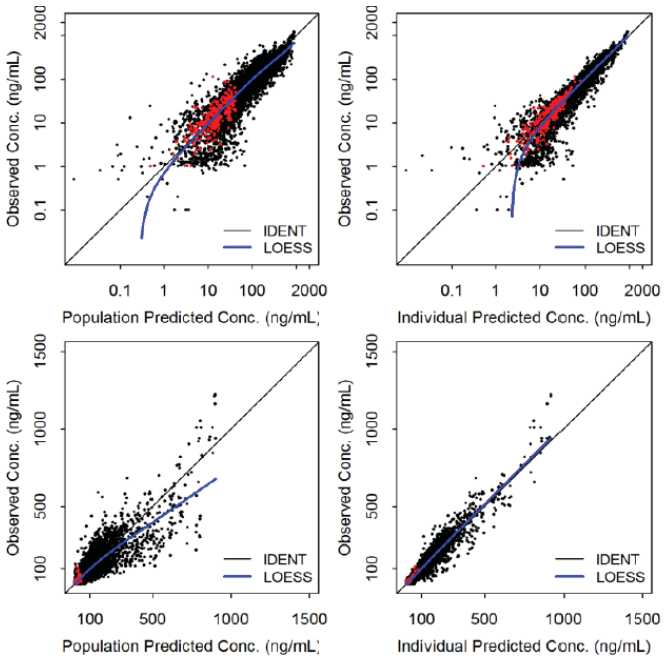
$$CL/F = 13.6 \times \left(\frac{Body\ Weight}{70}\right)^{0.590} \times \left(\frac{eGFRT}{102}\right)^{0.322} \times \left(\frac{ALT}{24.0}\right)^{0.125} \times 0.833\ if\ not\ SBS\ or\ Crohn's\ Disease$$

$$Vc/F = 33.1 \times \left(\frac{Body\ Weight}{70}\right)^{1.65} \times \left(\frac{Age}{34}\right)^{-0.332}$$

$$Ka = 0.318 \times \left(\frac{Body\ Weight}{70}\right)^{-0.624} \times 0.690\ for\ SC\ administration\ other\ than\ abdomen$$

Source: Applicant's Population PK Analysis, Table 4

Figure 13. Goodness-of-Fit Plots (Final Population PK Model Including M3 Method)



Line of identity, LOESS: Locally weighted smoothing scatterplot function; IDENT= Line of identity.
Conc = Concentration; PK= Pharmacokinetic. Note: only values above the LOQ are presented in the above figure
Samples collected between the first dose and the lagtime of absorption had PRED and IPRED=0. Those samples are not presented on the log-scale plots

Source: Applicant's Population PK Analysis, Figure 3

In summary, the Applicant's population PK analysis is generally acceptable. The goodness-of-fit plots and the visual predictive check indicate that the population PK model is adequate in characterizing the PK profile of teduglutide in adult and pediatric subjects. The inter-individual variability for CL/F and Vc/F is modest. Shrinkages for CL/F, Vc/F and Ka are reasonable. Organ maturation was not incorporated in the model since the youngest patient was 1 year of age and kidney function is expected to reach 90% maturation at this age. The disease status (SBS versus CD) was not a significant covariate on PK.

14.3.2. Applicant's Simulation for Renal Impairment

No pediatric patients with renal impairment (RI) were enrolled in studies 003 or 006. To support the recommended dose reduction for pediatric patient with moderate and severe RI, the applicant conducted simulation using the updated population PK model, and actual demographic data from the pediatric patients with SBS treated with a 0.05 mg/kg dose (n=40). The dosing regimen simulated is 0.05 mg/kg/day of teduglutide administered by SC injection. The definition of renal function is based on eGFR:

- Moderate renal impairment: ≥ 30 to 59 mL/min/1.73m^2
- Severe renal impairment: ≥ 15 to 29 mL/min/1.73m^2

Simulations results are shown in Table 37 and Table 38 for following typical eGFR values: 15, 22.5, 29, 30, 45, and 59 mL/min/1.73m^2. For comparison, the PK parameters of teduglutide in pediatric patients (1 to 17 years) with normal renal function from studies 003 and 006 are presented in Table 39.

Table 37. Predicted PK Parameters of Teduglutide in Pediatric Patients (1 to 17 years) with Short Bowel Syndrome–Moderate Renal Impairment

Parameters	Moderate Renal Impairment		
	Lower Range	Mid-Point	Upper Range
	eGFR = 30 mL/min/1.73m^2 (n=40)	eGFR = 45 mL/min/1.73m^2 (n=40)	eGFR = 59 mL/min/1.73m^2 (n=40)
CL/F (L/h)			
Mean (CV%)	4.71 (34.0%)	5.54 (37.8%)	6.02 (32.7%)
Median [Min, Max]	4.24 [2.64, 8.30]	4.86 [3.19, 11.7]	5.81 [2.86, 12.6]
90% PI	[2.82 - 8.09]	[3.40 - 9.46]	[3.34 - 9.00]
Cmaxss (ng/mL)			
Mean (CV%)	45.5 (29.1%)	43.7 (30.5%)	39.0 (27.8%)
Median [Min, Max]	43.4 [22.8, 79.1]	44.7 [16.3, 71.0]	38.8 [17.7, 69.2]
90% PI	[28.8 - 70.1]	[20.3 - 64.7]	[25.5 - 56.0]
AUCss (ng*h/mL)			
Mean (CV%)	216 (30.5%)	182 (23.2%)	172 (37.1%)
Median [Min, Max]	202 [111, 372]	187 [115, 288]	155 [81.1, 375]
90% PI	[125 - 349]	[127 - 252]	[96.5 - 277]

Source: Applicant's Response to FDA Information Request, GATTEX (S-013) IR dated January 29, 2019, Table 8

Table 38. Predicted PK Parameters of Teduglutide in Pediatric Patients (1 to 17 years) with Short Bowel Syndrome–Severe Renal Impairment

Parameters	Severe Renal Impairment		
	Lower Range	Mid-Point	Upper Range
	eGFR = 15 mL/min/1.73m^2 (n=40)	eGFR = 22.5 mL/min/1.73m^2 (n=40)	eGFR = 29 mL/min/1.73m^2 (n=40)
CL/F (L/h)			
Mean (CV%)	3.76 (30.9%)	4.53 (30.0%)	4.80 (31.8%)
Median [Min, Max]	3.60 [1.79, 7.17]	4.22 [2.56, 8.09]	4.61 [2.65, 8.92]
90% PI	[2.16 - 5.82]	[2.68 - 6.88]	[2.89 - 7.53]
Cmaxss (ng/mL)			
Mean (CV%)	49.4 (26.3%)	44.2 (27.9%)	43.4 (24.0%)
Median [Min, Max]	47.5 [29.4, 84.8]	44.9 [23.1, 70.1]	43.5 [22.0, 63.8]
90% PI	[34.2 - 73.9]	[25.8 - 66.8]	[24.9 - 60.8]
AUCss (ng*h/mL)			
Mean (CV%)	270 (35.3%)	222 (29.6%)	215 (38.5%)
Median [Min, Max]	236 [155, 524]	210 [109, 408]	205 [105, 459]
90% PI	[165 - 479]	[126 - 316]	[128 - 366]

Source: Applicant's Response to FDA Information Request, GATTEX (S-013) IR dated January 29, 2019, Table 8

Table 39. PK Parameters of Teduglutide in Pediatric Patients (1 to 17 years) with Short Bowel Syndrome–Normal Renal Function

Parameters	Normal Renal Function		
	0.0125 mg/kg (n=9)	0.025 mg/kg (n=35)	0.05 mg/kg (n=40)
CL/F (L/h)			
Mean (CV%)	7.53 (39.5)	8.18 (30.5)	**7.87** (32.3)
Median [Min, Max]	6.55 [5.06, 14.3]	7.45 [5.17, 13.3]	7.47 [1.64, 15.6]
Cmaxss (ng/mL			
Mean (CV%)	8.49 (12.5)	16.3 (18.2)	**33.2** (33.8)
Median [Min, Max]	8.62 [6.16, 10.0]	15.6 [12.1, 23.3]	30.8 [20.7, 77.4]
AUCss (ng.h/mL)			
Mean (CV%)	28.9 (27.5)	64.1 (20.3)	**130** (42.5)
Median [Min, Max]	25.4 [21.8, 41.9]	64.0 [44.8, 94.1]	120 [63.5, 421]

Source: Applicant's Response to FDA Information Request, GATTEX (S-013) IR dated January 29, 2019, Table 6

The simulated results suggest that a pediatric patient (1 to 17 years) with moderate RI is expected to have a 17% to 37% higher $C_{max,ss}$ and 32% to 66% higher AUC_{ss} compared to patient with normal renal function. A pediatric patient with severe RI is expected to have a 31% to 49% higher $C_{max,ss}$ and 65%-2-fold higher AUC_{ss} compared to patient with normal renal function.

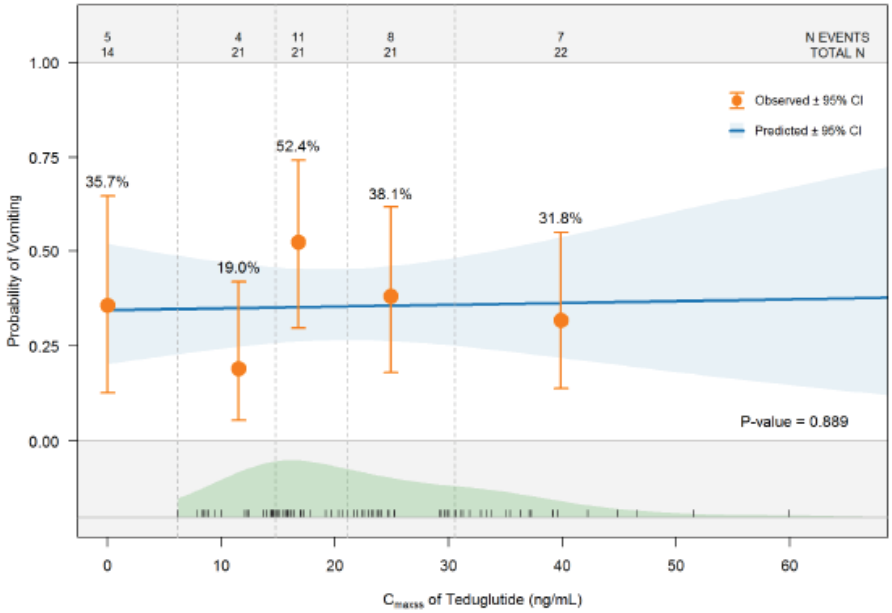
The proposed 50% dose reduction in pediatric patients with moderate or severe RI appears to be supported by the applicant's simulation. In addition, the predicted effect of RI on PK in pediatrics are generally consistent with those observed in the adult patients (section 12.3 in the label).

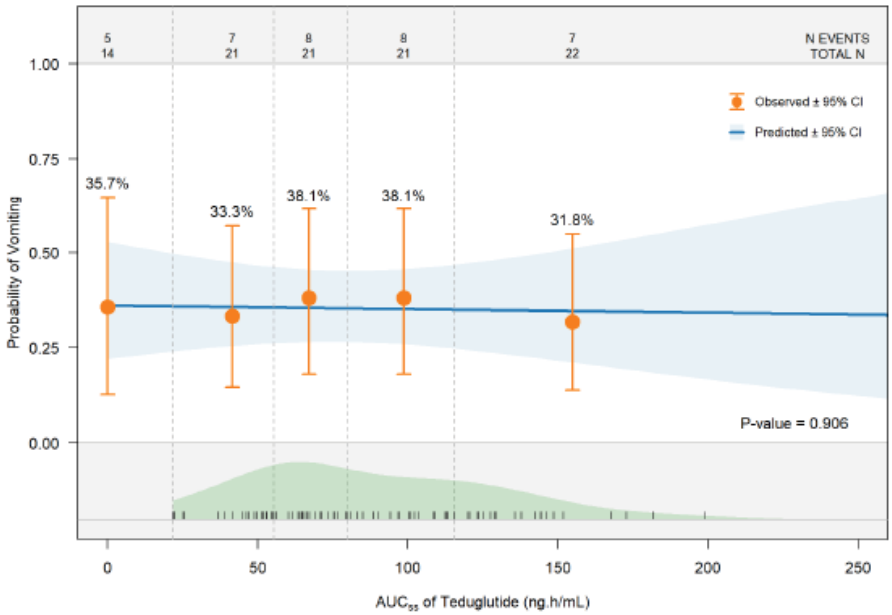
14.3.3. Applicant's Exposure-Response Analyses

Vomiting, abdominal pain and URI were among the most frequent TEAEs in pediatric patients enrolled in teduglutide studies 003 and 006. Logistic regression analyses were performed to characterize the relationship between these TEAEs and exposure parameters at steady state ($C_{max,ss}$ and AUC_{ss}) in pediatric patients with SBS. A total of 99 pediatric subjects (N=99, PK population) were included in the analysis. Overall, 35 pediatric patients (35.4%) presented at least one vomiting episode and 23 (23.2%) experienced one occasion of abdominal pain (including the preferred term abdominal pain upper). A total of 43 pediatric patients (43.3%) presented at least one episode of URI (including the preferred terms upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, laryngitis, rhinitis, viral upper respiratory tract infection). Logistic regressions on probabilities of adverse events (vomiting, abdominal pain, and URI) were performed based maximal teduglutide concentration at steady state ($C_{max,ss}$ and AUC_{ss}). The logistic regression models of teduglutide were used to evaluate the safety-exposure relationship. The logistic regression figure included 95% confidence intervals by quintiles of exposure levels. Model predictions and 95% confidence intervals was plotted, and the Wald test p-value of the logistic regression was reported on each plot. The safety-exposure relationship of teduglutide exposure parameters at steady state ($C_{max,ss}$ and AUC_{ss}) and the probability of vomiting, abdominal pain, and URI are presented in Figure 14, Figure 15, Figure 16, respectively.

Overall, no apparent ER relationship was observed since the probability of these adverse events did not significantly increase with higher $C_{max,ss}$ or AUC_{ss} values (Wald test p-value >0.05). There appears to be a numerical increase in probability of abdominal pain with increasing exposure, which is consistent with observed rate at 0.05 mg/kg (Figure 15).

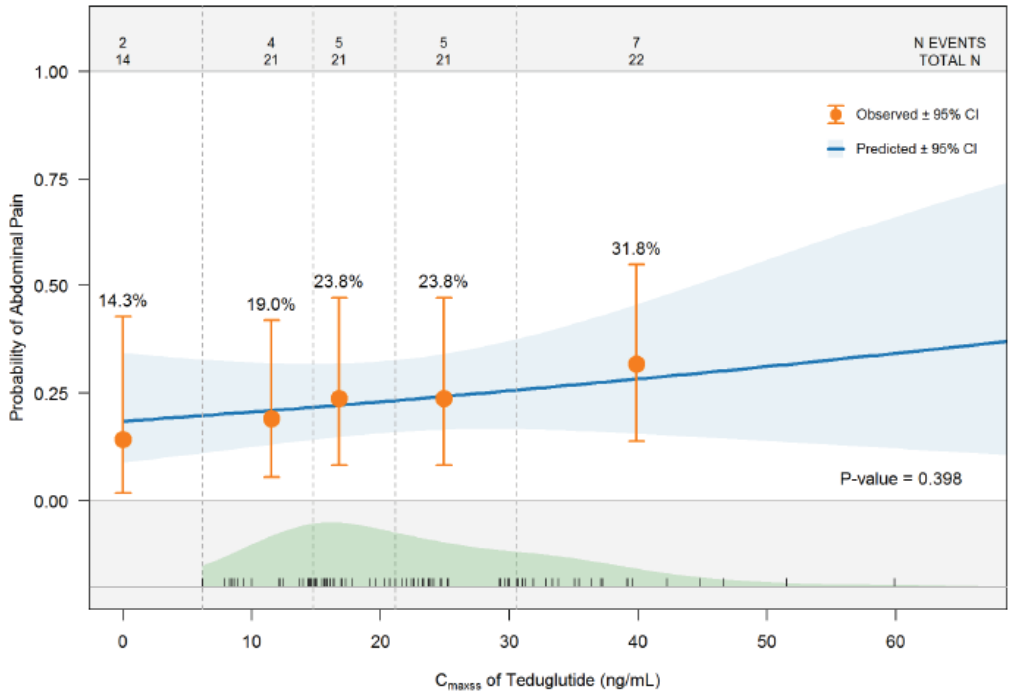
Figure 14. Exposure-Response–Impact of $C_{max,ss}$ and AUC_{ss} on Probability of Vomiting

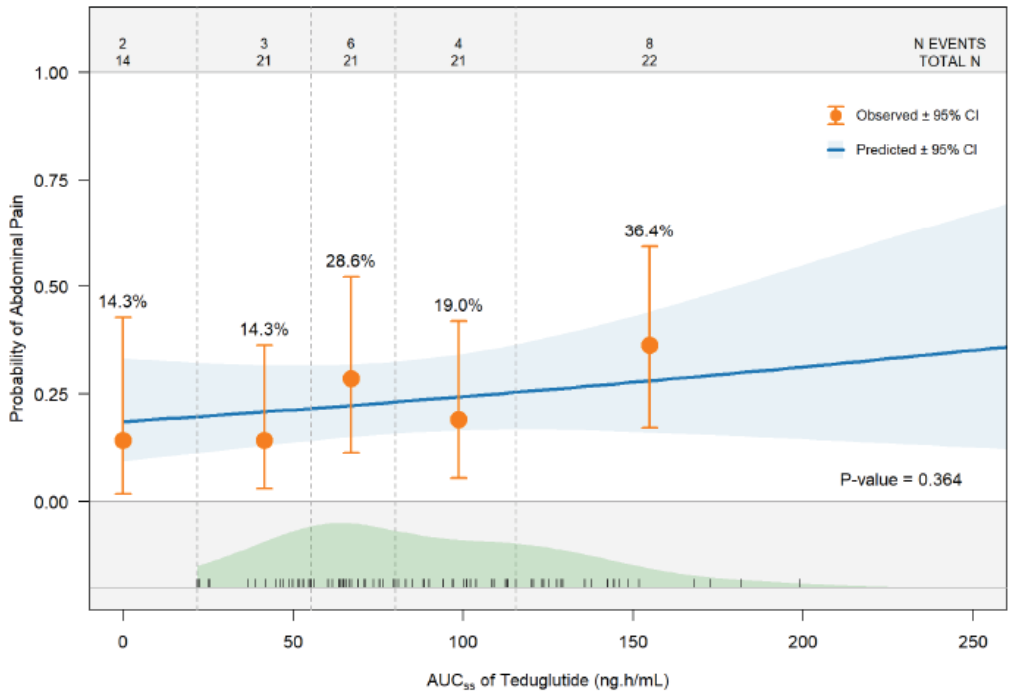




Source: Applicant's Response to FDA Information Request, GATTEX (S-013) IR dated January 29, 2019, Figure 2
$C_{max,ss}$ = peak concentration at steady state, AUC_{ss} = area under the curve at steady state

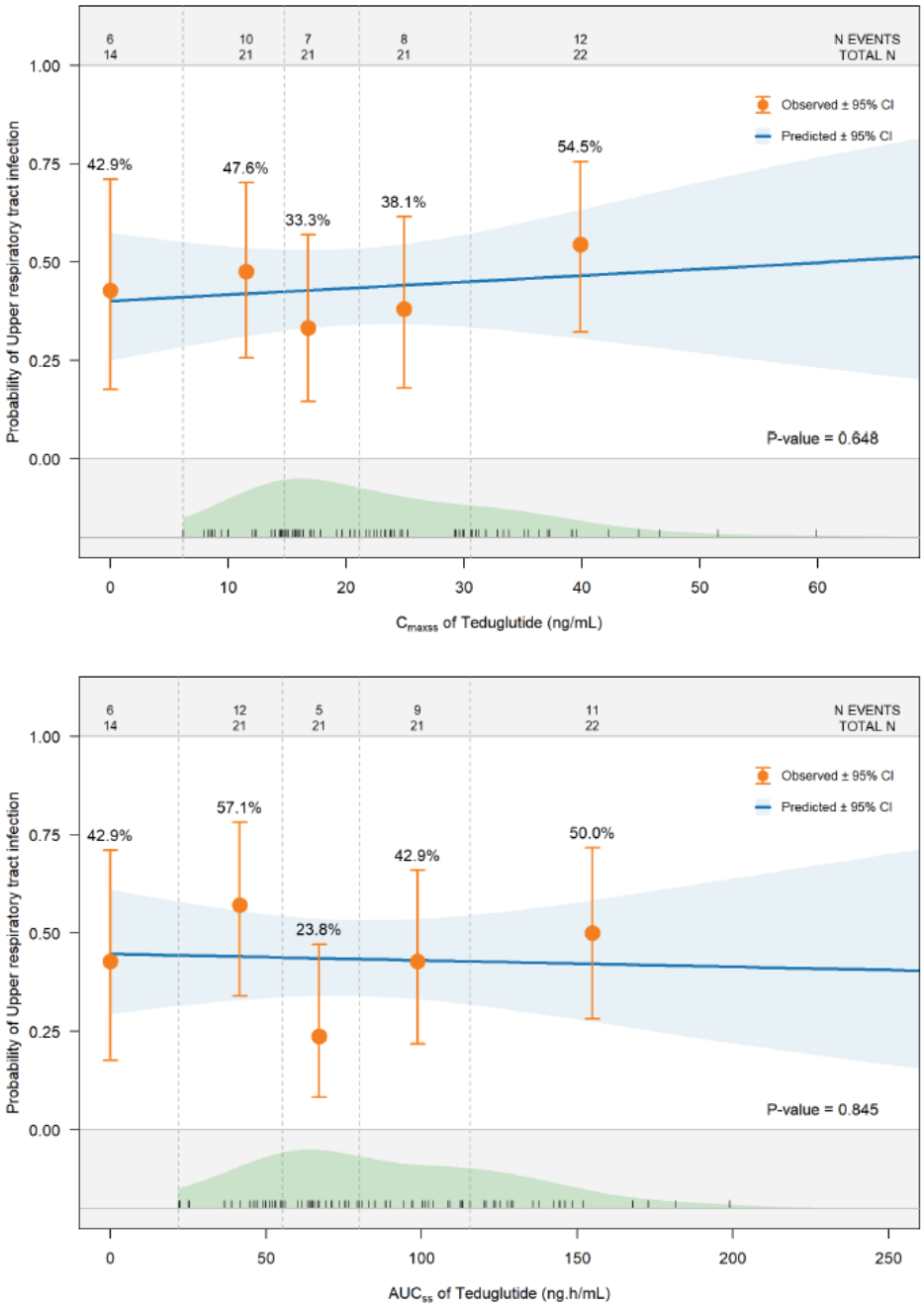
Figure 15. Exposure-Response–Impact of $C_{max,ss}$ and AUC_{ss} on Probability of Abdominal Pain





Source: Applicant's Response to FDA Information Request, GATTEX (S-013) IR dated January 29, 2019, Figure 3
$C_{max,ss}$ = peak concentration at steady state, AUC_{ss} = area under the curve at steady state

Figure 16. Exposure-Response–Impact of $C_{max,ss}$ and AUC_{ss} on Probability of Upper Respiratory Tract Infection



Source: Applicant's Response to FDA Information Request, GATTEX (S-013) IR dated January 29, 2019, Figure 4
$C_{max,ss}$ = peak concentration at steady state, AUC_{ss} = area under the curve at steady state

14.3.4. Summary of Bioanalytical Method Validation and Performance

How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?
In the pediatric studies 003 and 006, sparse PK samples were collected in pediatric patients with SBS.

In pediatric studies 003 and 006, teduglutide (ALX-0600) concentrations in human plasma (K3EDTA) were determined at [redacted] (b) (4) using liquid chromatography with tandem mass spectrometry (LC-MS/MS) method.

The bioanalytical assay measuring teduglutide in human plasma (EDTA) via LC-MS/MS method was validated at [redacted] (b) (4) (study AA04327-02). An aliquot of human plasma (EDTA) containing the analyte and internal standard was extracted using an automated protein precipitation procedure. The extracted samples were analyzed using an AB SCIEX API 4000™ and 5000™ mass spectrometer. Multiple charged positive ions (4+) were monitored in the multiple reaction monitoring mode. Quantitation was by peak area ratio.

The LC-MS/MS method employed to analyze teduglutide in studies 003 and 006 at [redacted] (b) (4) was the same validated LC-MS/MS bioanalytical method that was employed to measure teduglutide in adult population at [redacted] (b) (4)

Which metabolites have been selected for analysis and why?
No metabolites were measured in any of the studies.

What bioanalytical methods are used to assess concentrations of the measured moieties?
Summary of the Validated Analytical Methods for ALX-0600 in Human Plasma

Protocol No.	Bioanalytical Site:	[redacted] (b) (4) Validation Report No.	Assay Method	Sensitivity (ng/mL)
TED-C13-003 TED-C14-006	[redacted] (b) (4)	AA04327-02	LC/MS/MS	1.00

LC-MS/MS = liquid chromatography with tandem mass spectrometry

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used? What are the lower and upper limits of quantitation?

Study Report	Matrix	Validation report	Range of Standard Curve	LLOQ	ULOQ	Dilution factor
TED-C13-003	Plasma	AA04327-02	1.00 - 120 ng/mL	1.0 ng/mL	120 ng/mL	10

LLOQ = lower limit of quantification; ULOQ = upper limit of quantification

Linear regression with 1/concencetraiton2 weighting method was used to analyze the ALX-0600.

Samples with a concentration up to 500 ng/mL can be quantified after the application of an appropriate dilution factor.

What are the accuracy, precision, and selectivity at these limits?

Matrix	Validation report		Intra-assay	Inter-Assay
Plasma	AA04327-02	Precision (CV%)	<11.3%	<12.8%
		Accuracy	-9.1.0% to	-4.7% to 11%

Selectivity: No significant interference at the retention time of ALX-0600 or ALX-0600-IS (IS) was observed from endogenous components in human plasma (EDTA). No quantitative interference with ALX-0600 was observed in samples fortified with acetaminophen.

Recovery of sample extract is 68% at lower limit of quantification (LLOQ) (1.0 ng/mL) and 76% at upper limit of quantification (ULOQ) (120 ng/mL).

What is the sample stability under conditions used in the study?
All PK plasma samples from both studies TED-C13-003 and TED-C14-006 were stored at approximately -80°C until the analysis and analyzed within the time-period for which the long-term, short-term, freeze-thaw, or postpreparative stability has been established during the method validation.

Table 40. Stability of Teduglutide (ALX-0600) in Human Plasma (EDTA)

Stability Summary	
Long-term stability	182 days (approximately 6 months) at -20°C in polypropylene tubes 796 days (approximately 26 months) at -80°C in polypropylene tubes 265 days in polypropylene tubes at -80°C (LLOQ QC)
Short-term stability	23 hours at ambient temperature, nonUV-shielded light conditions in polypropylene tubes 24 hours in polypropylene tubes at ambient temperature under UV-shielded light
Cumulative short-term stability	50 hours in polypropylene tubes at ambient temperature under UV-shielded light (total of all thaw cycles)
Freeze-thaw stability	6 cycles at -80°C in polypropylene tubes 5 freeze (-80°C)-thaw (ambient temperature) cycles in polypropylene tubes under UV-shielded light
Post-preparative stability	113 hours in a polypropylene 96-well plate at 5°C
Processed sample integrity	362 hours at 5°C in a polypropylene 96-well plate

LLOQ = lower limit of quantification; QC = quality control
Source: Validation Of An LC-MS/MS Method for The Determination of ALX-0600 in Human Plasma (EDTA), Study: AA04327-02, Amendment 5 to Validation Final Report, Validation Summary, page 12-14

Table 41. Clinical Studies Bioanalysis (PK) Stability for Analyte Teduglutide (ALX-0600)

Shire Study No.	(b) (4) Bioanalytical Report #	First Date of Sample Collection	Last Date of Sample Collection	Start Date of Bioanalysis	End Date of Bioanalysis	Maximum Storage Time (Days)	Established Long-Term Stability (Months)
TED-C13-003	CA12892-01	12/16/13	10/15/14	04/21/14	11/25/14	345	26
TED-C14-006	CA19482-01	6/23/16	2/1/17	8/18/17	9/20/17	455	26

(b) (4) comments: Samples stored at -80°C for both studies.
Source: Applicant's Response to FDA Information Request, GATTEX (S-013) dated October 26, 2018, Table 2

Table 42. Clinical Studies Bioanalysis (Citrulline) Stability

Study No.	First Date of Sample Collection	Last Date of Sample Collection	Start Date of Bioanalysis	End Date of Bioanalysis	Maximum Storage Time (Days)	Established Long-Term Stability (Days)
TED-C13-003	12/16/13	1/9/15	12/12/14	2/9/15	420	781
TED-C14-006	6/23/16	8/18/17	8/22/17	10/3/17	467	781

Maximum storage time = first collection to last analysis
Source: Applicant's Response to FDA Information Request, GATTEX (S-013) dated October 26, 2018, Table 3

Hemolyzed Sample Integrity: No significant interference for ALX-0600 was observed in two of the three hemolyzed human plasma (EDTA) lots (fortified with 0.5% whole blood) that were fortified at the concentration of the LLOQ (1.00 ng/mL) or in any of the three hemolyzed human plasma (EDTA) lots (fortified with 0.5% whole blood) that were fortified at the concentration of the high quality control (QC) (90.0 ng/mL) samples.

Lipemic Sample Evaluation: No significant interference for ALX-0600 was observed in any of the three lipemic human plasma (EDTA) lots that were fortified at the concentration of the LLOQ (1.00 ng/mL) or in any of the three lipemic human plasma (EDTA) lots that were fortified at the concentration of the high QC (90.0 ng/mL) samples.

What is the plan for the QC samples and for the reanalysis of the incurred samples?
The concentrations of QC were 3.00**,** 30.00, and 90.0 ng/mL in study TED-C14-006 and were 3.00**,** 30.00, 90.0 ng/mL, and 500 ng/mL (dilution factor 5) in studyTED-C13-003.

All studies had at least 10% of the samples re-analyzed as the incurred samples reanalysis to demonstrate the reproducibility of quantification in all studies. The incurred sample repeats from both studies met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20% in all studies.

Table 43. In-Study Assay Performance of Teduglutide (ALX-0600) in Human Plasma (EDTA)

Clinical Study	QCs Inter-Run Precision (%CV)	QCs Inter-Run Accuracy (%RE)	% of Samples for ISR	Passed ISR
TED-C13-003	≤5.3%	-1.9% to 5.7%	11.4% (25/219)	Yes
TED-C14-006	18.1% at LQC, ≤7.6%	1.3% to 3.6%	10.6% (20/187)	Yes

ISR = incurred samples reanalysis; QC = quality control
Source: Reviewer created table based on bioanalytical study reports for studies TED-C13-003 and TED-C14-006

14.4. Clinical Appendices

14.4.1. Analysis of Adverse Events by Organ System

The Applicant analyzed treatment-emergent adverse events, which may be associated with the following identified and potential risks, to better quantify if any of these identified or potential risks were occurring in greater frequency than expected in pediatric patients.

Important Identified Risks

1. Biliary adverse events, such as cholecystitis
2. Pancreatic adverse events, such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection, and increased blood amylase and lipase
3. Cardiovascular adverse events associated with fluid overload
4. Gastrointestinal stenosis and obstruction
5. Gastrointestinal stoma complications
6. Growth of pre-existing polyps of the colon
7. Benign neoplasia of the GI tract, including the hepatobiliary system
8. Tumor promoting ability

Important Potential Risks

9. Adverse events associated with increased absorption of oral concomitant medications

The Applicant provided a listing of patients who had events which could have been associated with any of the categories listed above. On January 23, 2019, the review team requested further information including narratives on these identified adverse events, to assist in determination of whether these represent medically important events. The Applicant responded on January 29, 2019, with the following information:

i. Biliary adverse events

There were three patients with AEs listed in this category, two patients with cholelithiasis and one patient with cholestasis and concomitant abnormal laboratory values. Both events of cholelithiasis were reported as nonserious and moderate in intensity. The cholestasis event was reported as serious and moderate in intensity. None of the events were assessed as related to teduglutide by the investigator. All events were ongoing or not resolved and no action was taken in regard to teduglutide. Biliary events are summarized below.

Table 44. Summary of the Three Patients With Biliary Events

Subject ID	Cholelithiasis	Cholestasis	Serious and severity	Investigator reported causality to teduglutide	Action taken in regards to study drug	Outcome of the event
(b) (6)	X		Not serious and moderate severity	Not related	None	not recovered/not resolved
		X	Serious and moderate severity	Not related	Drug withdrawn	ongoing
	X		Non serious and moderate severity	Not related	None	not recovered/not resolved

Source: Applicant's IR Response, dated January 29, 2019

It appears reasonable to conclude that the three cases of biliary events are not related to teduglutide, based on patient narratives provided. Teduglutide treatment was withdrawn in patient (b) (6) due to bilirubin increased. However, the elevated bilirubin was attributed to iatrogenic iron overload per the investigator.

ii. Pancreatic adverse events

There were 21 unique patients who had abdominal pain or abdominal pain upper from the pediatric studies. According to the Applicant, amylase and lipase values in these 21 patients were reviewed, and there was no correlation to suggest pancreatitis.

There were three patients with AEs of amylase and/or lipase increase in all the teduglutide pediatric studies and none of the events satisfied the pancreatitis definition. Table 45 shows the summary of the three patients with amylase/lipase increased.

Table 45. Summary of Patients With Amylase/Lipase Increased

Subject ID	Lipase Increased	Amylase Increased	Elevation(s) >3xULN	Correlation of elevation to abdominal pain	Correlation of elevation to abnormal imaging
(b) (6)	X	X	No	No	No
	X		Yes	No	No
	X		No	No	No

Source: Applicant's IR Response, dated January 29, 2019

The Applicant's analysis that the three cases of reported elevation in amylase and/or lipase did not constitute cases of pancreatitis and do not represent important teduglutide related AESI appear reasonable, based on the patient narratives provided.

iii. Cardiovascular adverse events

Tachycardia, dyspnea and peripheral edema were the adverse events identified under the cardiovascular system organ class. In the teduglutide pediatric studies, there were four patients with tachycardia, two patients with dyspnea and one patient with peripheral edema. All patients had transient tachycardia of short duration that were accompanied by intercurrent illness except for patient (b) (6) who had a reported event of mild, non-serious adverse event of tachycardia from (b) (6) to (b) (6), and multiple intercurrent illnesses during that time including diarrhea, productive cough, vomiting and gastroenteritis. Review of the patient's vital signs from clinic visits provided by the Applicant showed a heart rate that

ranged from 88 to 125 beats per minute (bpm) throughout the study (screening to end of study: Week 28). This heart rate is only slightly higher than normal for a 6-year-old (normal is 75-115bpm).

Table 46. Summary of Patients With Cardiovascular Adverse Events

Subject ID (b) (6)	Tachycardia	Dyspnoea	Seriousness and severity	Investigator Causality to teduglutide	Concomitant illness with tachycardia/dyspnea
	X		Non-serious/ moderate severity	Not related	URI, hypovolemic shock
	X		Non-serious/ mild severity	Not related	hypoglycemia, and device related infection described as MRSA abscess-central line infection
	X		Non-serious/ mild severity	Not related	Dehydration, abdominal pain
	X		Non-serious/ mild severity	Not related	Multiple concomitant AEs within this period
		X	Non-serious/ mild severity	Not related	Asthma, Increased stool frequency
		X	Non-serious/ mild severity	Not related	Rhinorrhea, cough

Source: Applicant's IR Response, dated January 29, 2019

Based on the provided patient narratives, the Applicant's analysis that the tachycardia and dyspnea listed above were not related to teduglutide appear reasonable.

There was one event of peripheral edema in TED-C14-006, which occurred in patient (b) (6) (b) (6) who is an 11-year-old black male with SBS and past medical history significant for volvulus, device related infection, neutropenia, intestinal malrotation, pancreatic insufficiency, failure to thrive, type 1 diabetes mellitus, central venous catherization, GI tube insertion, small intestinal resection, and gastric bacteria overgrowth. He was treated with teduglutide 0.025 mg/kg/day from (b) (6), to (b) (6), while in study TED-C14-006 continued with teduglutide 0.05 mg/kg/day in study SHP633-304 on (b) (6).

The patient experienced peripheral edema on (b) (6) (at which time he was receiving the 0.025mg/kg dose), which was described as a non-serious adverse event; no action was taken, and it was considered recovered/resolved on (b) (6) The patient continued treatment in the core study and move onto the extension study without interruption to teduglutide and the peripheral edema did not recur.

Of note is that of all the TEAEs that could represent potential or identified potential risks in the core and extension studies, seven of the events were serious TEAEs occurring in five patients: two events of ileus in two patients, two events of cholestasis in one patient, and one event each of increased blood bilirubin, cholelithiasis, and abdominal pain in one patient (see Table 47 below).

Table 47. Serious TEAEs Representing Identified and Potential Risks for All Studies

Patient ID	Study ID	Treatment Group	Preferred Terms/ *Verbatim Term*	Action Taken With Study Drug	Outcome
(b) (6)	TED-C14-006	SOC arm	Ileus paralytic/ *Paralytic ileus**	Drug interrupted and restarted	Resolved
	SHP633-304	NTT/TED			
	TED-C14-006	TED 0.05 mg/kg/day			
	SHP633-304	TED/TED	Postoperative ileus/ *Postanesthesia ileus**	Drug interrupted due to event	Resolved
	TED-C14-006	TED 0.05 mg/kg/day			
	SHP633-304	TED/TED	Cholelithiasis/ *Gallstones**	Dose not changed	Recovered
	TED-C14-006	TED 0.025 mg/kg/day			
	SHP633-304	TED/TED	Large intestine polyp/ *Cecal polyps**	N/A. Patient not treated with TED at time of event.	Resolved
	TED-C14-006	TED 0.025 mg/kg/day	Cholestasis/ *Worsening cholestasis**	Dose not changed	Unknown
	SHP633-304	TED/TED	Blood bilirubin increased/ *Elevated bilirubin**	N/A. Event occurred in screening	Recovering

Source: Reviewer's Table, adapted from Applicant's Table 27.3, individual patient narratives for SHP633-303 and SHP633-304 and ISS Pediatrics S13 Analysis Adam datasets: ADAE and ADSL; JReview 11.0.
NTT/TED: Patients in SOC arm of the core studies who then received teduglutide treatment in the prospective portions of the extension studies
TED/TED: Patients who received teduglutide treatment in both the core and prospective portions of the extension studies
* = TEAE not related per Applicant
N/A = Not applicable, SOC = standard of care, TED = teduglutide, NTT = no-teduglutide treatment; TEAE = treatment emergent adverse event

The conclusion from the review of all these adverse events is that no new safety risks were identified in the pediatric safety population that were exposed to teduglutide.

14.4.2. Assessment of Post-Baseline Chemistry Abnormalities

Table 48. Summary of Post-Baseline Markedly Abnormal Chemistry Laboratory Results in Teduglutide Treated Population: All Studies by Duration of Total Exposure

Number (%) of patients with marked abnormal laboratory abnormality	≤12 Weeks (N=10) n/m (%)	12 to ≤24 Weeks (N=18) n/m (%)	24 to ≤48 Weeks (N=37) n/m (%)	48 to ≤96 Weeks (N=24) n/m (%)	Total (N=89) n/m (%)
Alkaline Phosphatase (U/L)					
>5x ULN	0/10 (0.0)	0/18 (0.0)	1/37 (2.7)	0/24 (0.0)	1/89 (1.1)
Alanine Aminotransferase (U/L)					
>8x ULN	1/10 (10.0)	1/18 (5.6)	4/37 (10.8)	5/24 (20.8)	11/89 (12.4)
Aspartate Aminotransferase (U/L)					
>8x ULN	0/10 (0.0)	0/18 (0.0)	1/37 (2.7)	0/24 (0.0)	1/89 (1.1)
Direct Bilirubin (umol/L)					
>34.208	0/10 (0.0)	0/18 (0.0)	1/37 (2.7)	0/24 (0.0)	1/89 (1.1)
Bilirubin (umol/L)					
>3x ULN	0/10 (0.0)	0/18 (0.0)	1/37 (2.7)	0/24 (0.0)	1/89 (1.1)
Blood Urea Nitrogen (mmol/L)					
>12.495	1/10 (10.0)	0/18 (0.0)	2/37 (5.4)	2/24 (8.3)	5/89 (5.6)
Calcium (mmol/L)					
>3	0/10 (0.0)	0/18 (0.0)	0/37 (0.0)	1/24 (4.2)	1/89 (1.1)
C Reactive Protein (mg/L)					
≥100	0/10 (0.0)	0/18 (0.0)	2/37 (5.4)	2/24 (8.3)	4/89 (4.5)
Glucose (mmol/L)					
>13.875	1/10 (10.0)	0/18 (0.0)	0/37 (0.0)	1/24 (4.2)	2/89 (2.2)
Potassium (mmol/L)					
<2.5	0/10 (0.0)	0/18 (0.0)	1/37 (2.7)	0/24 (0.0)	1/89 (1.1)
>6.5	0/10 (0.0)	1/18 (5.6)	0/37 (0.0)	0/24 (0.0)	1/89 (1.1)
Magnesium (mmol/L)					
<0.4114	1/10 (10.0)	1/18 (5.6)	0/37 (0.0)	0/24 (0.0)	2/89 (2.2)
Phosphate (mmol/L)					
<0.644	1/10 (10.0)	1/18 (5.6)	0/37 (0.0)	0/24 (0.0)	2/89 (2.2)
>2.254	1/10 (10.0)	2/18 (11.1)	1/37 (2.7)	2/24 (8.3)	6/89 (6.7)
Amylase (U/L)					
>3x ULN	1/10 (10.0)	0/18 (0.0)	0/37 (0.0)	0/24 (0.0)	1/89 (1.1)
Lipase (U/L)					
>3x ULN	0/10 (0.0)	0/18 (0.0)	1/37 (2.7)	8/24 (33.3)	9/89 (10.1)

Source: Adapted from Applicant's ISS Table 17.3, Received on September 11, 2018, and Reviewer's JReview Analysis of ISS dataset.
Patient can be counted in more than one criterion for the parameter.
Percentages are based upon m, defined as the number of patients in the safety population with at least one post-baseline value for the associated parameter
ULN = upper limit of normal; U/L = unit per liter

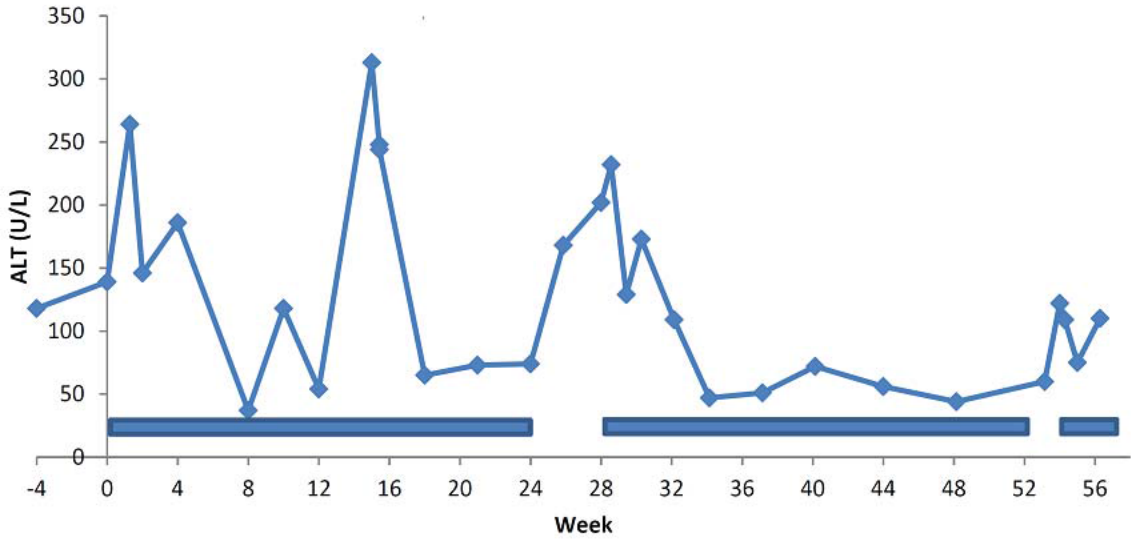
14.4.3. Narratives for Patients With Markedly Abnormal Liver Function Tests

As noted in the review above, a small number of patients experienced marked elevations in AST and/or ALT during the course of study participation. It is noted that patients with intestinal failure and long-term dependence on PN have a high rate of PN associated cholestasis and may be expected to have abnormal liver enzymes. Further because of varying degrees of liver injury related to this, they also commonly experience transient increases in liver enzymes (sometimes

of marked elevation) in association with intercurrent events such as viral infections, line infections and catheter associated sepsis.
The applicant provided the following narratives for patients identified to have marked increases in liver enzymes while participating in the teduglutide studies. Generally, the narratives are not suggestive of drug-induced liver injury. Summaries of these cases follow:

Patient (b) (6) had an ALT value of 313 U/L (9.2 times the ULN of 34 U/L) at week 15 in TED-C14-006. The investigator deemed this clinically significant and recorded an adverse event of ALT increased, mild, nonserious, and not related to teduglutide. Per report, an adverse event of food poisoning occurred 4 days prior to this event and the patient did not have any elevation in TB or direct bilirubin (DB).

Figure 17. ALT Trajectory for Patient (b) (6)



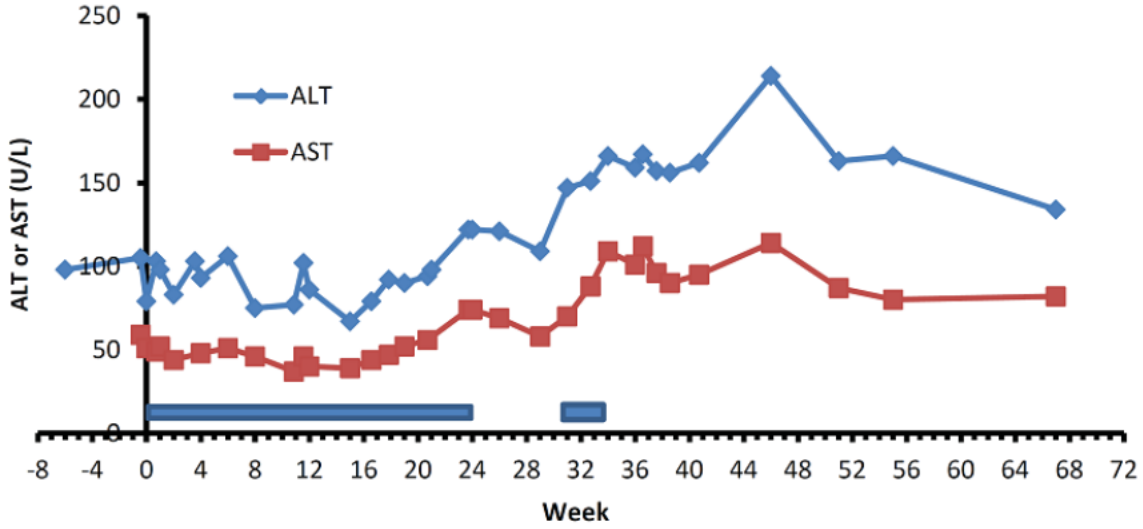
Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

There was also no interruption to teduglutide treatment due to adverse events reports. ALT returned to below the patient's baseline at the next scheduled clinic visit (week 18). After teduglutide treatment ended in TED-C14-006, ALT began to rise and was associated with adverse events of nausea, vomiting, diarrhea, and small intestinal bacterial overgrowth with a peak of 232 U/L (11.6x ULN of 20 U/L) during SHP633-304 at Cycle 1, day 1, immediately prior to resuming teduglutide treatment. During Cycle 1, ALT declined to below baseline levels, and then rose transiently again during a gap in treatment between Cycle 1 and Cycle 2. This pattern does not appear to be consistent with DILI due to teduglutide. The transient elevations in ALT were likely related to concomitant illnesses, and not teduglutide, given the dose of the study drug was not interrupted in during the study.

Patient (b) (6) had markedly abnormal values for alkaline phosphatase (ALP), TB, and DB during TED-C14-006 and markedly abnormal values for ALP, TB, DB and ALT in SHP633-304. The patient developed progressive cholestasis during TED-C14-006 study, with TB peak of 5.7

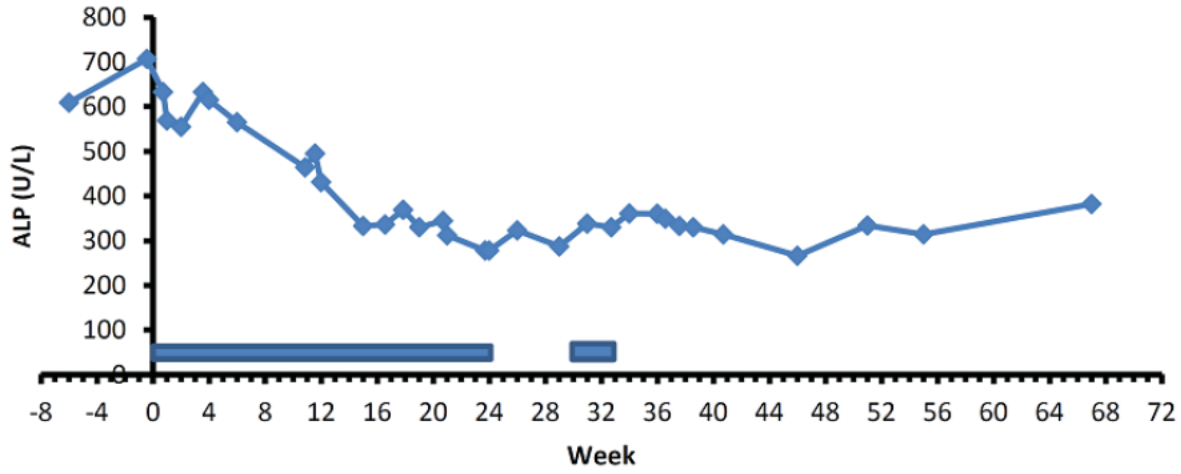
mg/dL (4.8x ULN of 1.2 mg/dL) and DB peak of 3.9 mg/dL at week 26. TB and DB values continued to trend upward during SHP633-304.

Figure 18. Transaminase Trajectory for Patient (b) (6)



Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase, AST = aspartate aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

Figure 19. Alkaline Phosphatase Trajectory for Patient (b) (6)



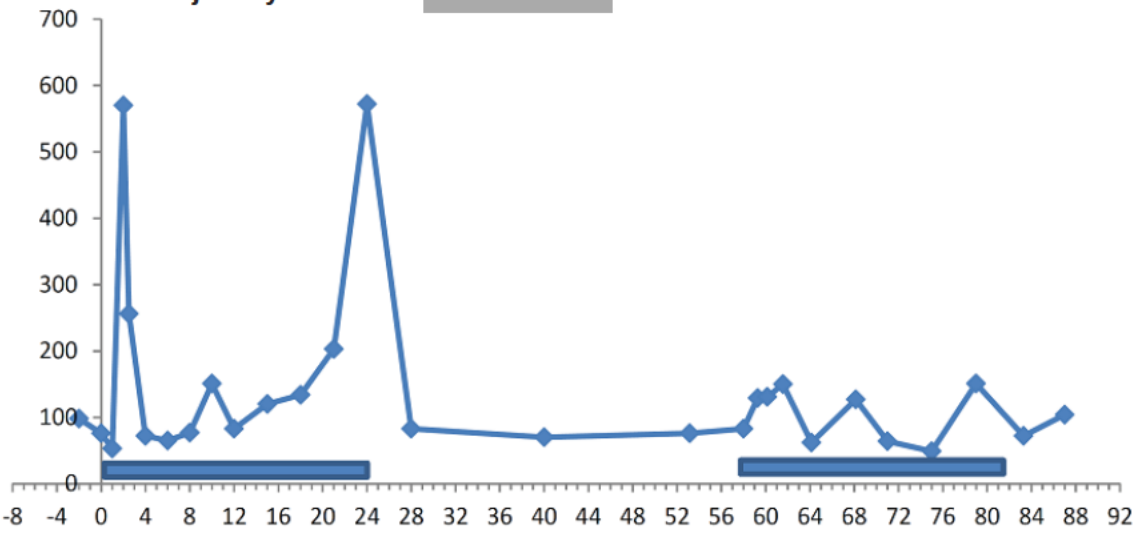
Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALP = a kaline phosphatase
Source: Applicant's IR Response, dated January 29, 2019

Baseline ALT was 79 U/L (normal range 6-34 U/L) and baseline AST was 51 U/L (normal range 10-40 U/L), rose to 121 and 69 U/L ALT/AST respectively at week 24 and continued to trend upward peaking at 214 U/L (10.7x ULN of 20 U/L) and 114 U/L (3x ULN of 37 U/L) during extension study of SHP633-304. Gamma-glutamyl transferase was stable and mildly elevated throughout TED-C14-006 with values generally 40-60 U/L (normal range 0-24 U/L). Alkaline phosphatase declined throughout the study from the 609 U/L at screening to 287 U/L at week 28 (normal range 69-325 U/L).

Per report, the investigator discovered that patient had been receiving intravenous iron infusions of 15 mg, 6 days per week despite having an elevated ferritin and iron saturation prior to the initiation of these transfusions. The iron infusions started 15 months before screening into TED-C14-006 study. Abdominal MRI was notable for iron overload in the liver, spleen, and bone marrow. Patient had liver biopsy, which showed findings consistent with hemochromatosis (diffuse, moderate hepatocellular ballooning degeneration with marked hepatocellular and reticuloendothelial iron overload consistent with grade 0-1 steatosis, and grade 1-2 fibrosis). The adverse events of ALT/AST increased in this patient were reported not to be related to teduglutide. Based on all available evidence, these events were most likely due to hepatocellular injury secondary to chronic liver disease, and iatrogenic iron overload. While contribution of teduglutide cannot be definitively excluded, the underlying identified disease process is the likely explanation for the changes noted.

Patient (b) (6) had two, transient markedly abnormal elevations in ALT. The first elevation occurred on study day 16 of TED-C14-006 with a value of 570 U/L (13x ULN of 43 U/L). The investigator assessed it as mild, serious and not related to teduglutide. Treatment with teduglutide was not interrupted and ALT/AST values returned to baseline values by week 4 (72/36 U/L respectively).

Figure 20. ALT Trajectory for Patient (b) (6)



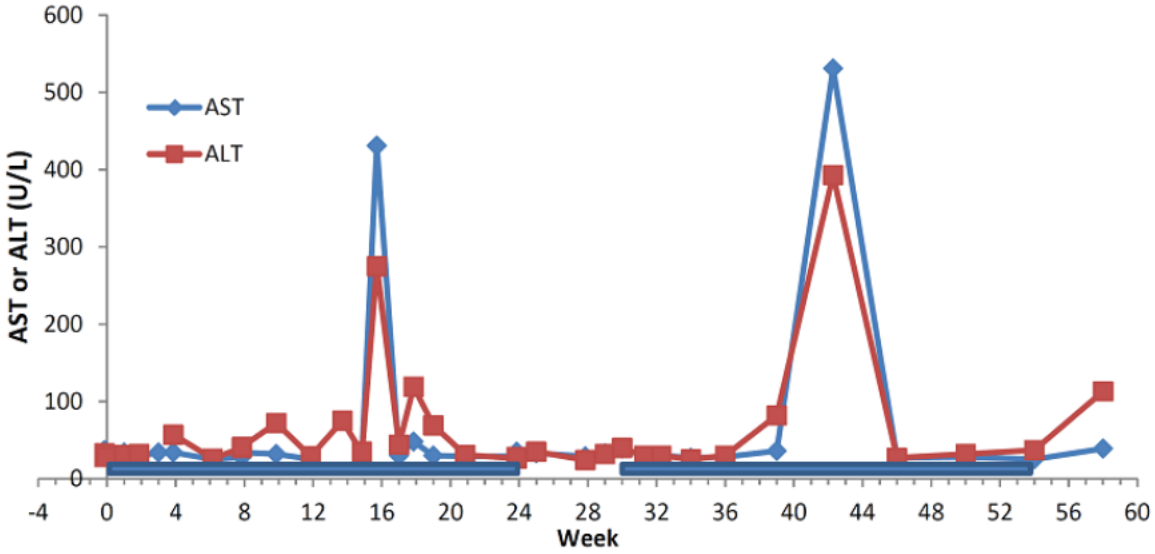
Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

Per the investigator report, the patient had nonspecific symptoms of viral airway infection prior to elevation of transaminases. Treatment with teduglutide was not interrupted. Patient subsequently had a second peak in ALT at week 24 with ALT value of 572 U/L (13x ULN), without associated change in bilirubin. The patient received additional 24 weeks of teduglutide treatment in the SHP633-304 study, during which ALT varied between 62 and 150. Per the investigator, the transaminase fluctuations were likely due to the underlying disease and

intercurrent adverse events such as URI and not due to DILI related to teduglutide. It is noted that this patient's dose of teduglutide was not interrupted during both events of transient ALT elevation. In addition, the patient's baseline ALT appears generally lower when off teduglutide treatment compared to when the patient was on treatment. Given this, the elevation in ALT is less likely related to teduglutide but rather to intercurrent viral illness and underlying SBS.

Patient [redacted] (b) (6) had transient elevation in AST/ALT that peaked at week 16 with values of 431 U/L (12.7x ULN of 34 U/L) for AST and 275 U/L (5x ULN of 55 U/L) during TED-C14-006.

Figure 21. ALT Trajectory for Patient [redacted] (b) (6)

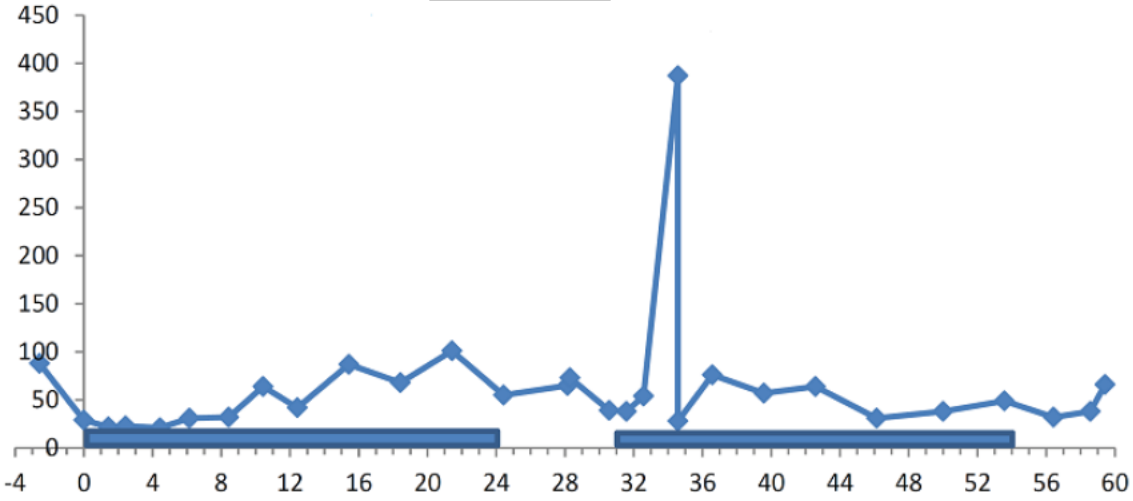


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase, AST = aspartate aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

A second transient elevation in ALT and AST occurred in SHP633-304 at Cycle 1, week 12 with peak AST of 531 U/L (14x ULN of 37 U/L) and peak ALT of 393 U/L (13x ULN of 30 U/L). In both cases, there were no associated changes in ALP or bilirubin. Per report, the investigator attributed the elevated ALT/AST to patient's TPN and intermittent infections. There was no interruption of teduglutide treatment associated with the transaminase elevation, and on both occasions, these elevations resolved by the time of the next scheduled visit. These cases of transient elevation in transaminases does not appear to be related to teduglutide, given they are transient, and teduglutide dose was not interrupted, especially in this patient with SBS, possible underlying IF-associated liver disease and intercurrent infections.

Patient [redacted] (b) (6) had a transient increase in ALT during the SHP633-304 study with a peak value of 387 U/L (19x ULN of 20 U/L) at Cycle 1, week 4. There were no associated increases in bilirubin or ALP.

Figure 22. ALT Trajectory for Patient (b) (6)

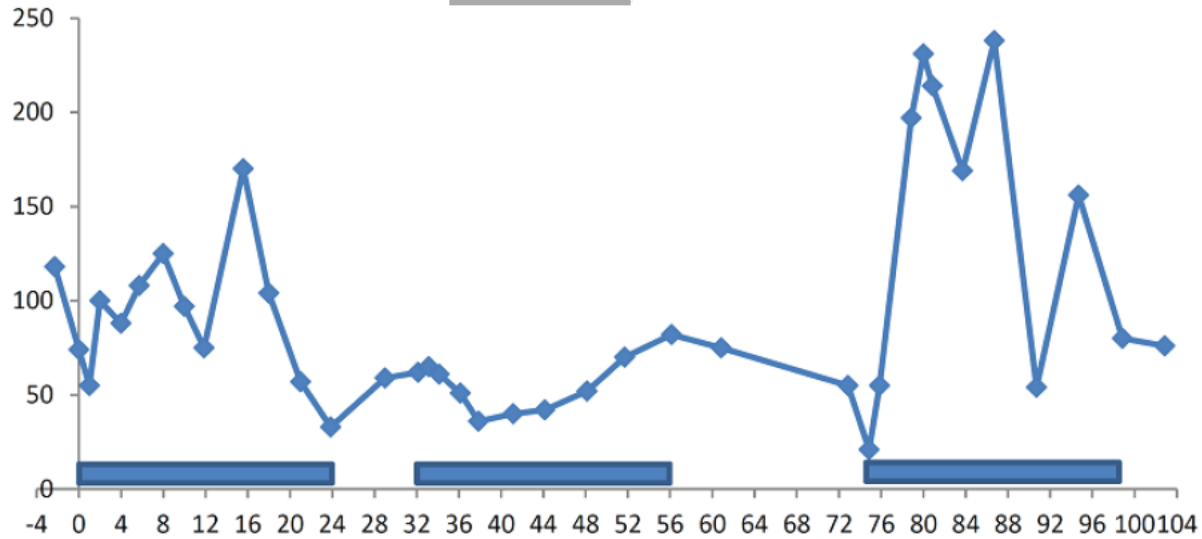


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

Per report, there were no temporally-associated adverse events, no interruption in teduglutide treatment and ALT returned to patient's baseline by the next scheduled visit at Cycle 1, week 6. This patient completed SHP633-304 Cycle 1 without additional ALT elevation. While not definitive, given the rapid return to baseline without intervention, this case is unlikely to represent DILI.

Patient (b) (6) sustained elevations in ALT during Cycle 2 from weeks 4 to 12, with a peak of 238 U/L at week 12 (11.9x ULN of 20 U/L) and resolution by week 16.

Figure 23. ALT Trajectory for Patient (b) (6)

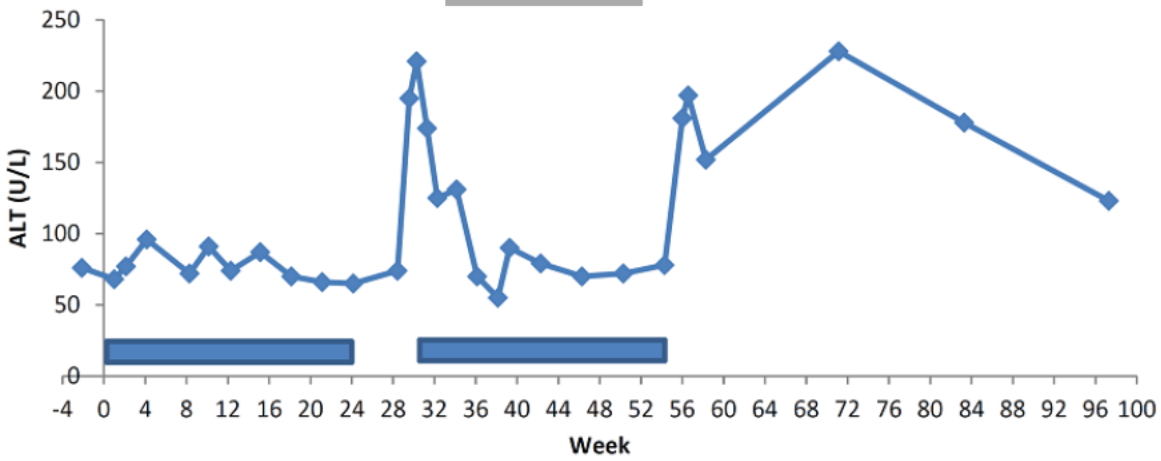


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

Patient experienced ALT elevations in Cycle 2 that were temporally associated with an adverse event of cough that was ongoing. Abdominal ultrasound revealed cholelithiasis and persistent hepatosplenomegaly with normal Doppler. Per investigator, "it is not uncommon for slow resolution of ALT back to baseline when the rise is secondary to cough/URI and DILI was not suspected," thus no interruption in teduglutide treatment. By the end of Cycle 2, ALT had returned to baseline (80 U/L). Based on the evidence, the elevations in ALT were most likely due to underlying disease and intercurrent illnesses and not related to teduglutide.

Patient (b) (6) developed a sharp rise in ALT after EOT in study 006 and prior to starting Cycle 1 of extension study 304.

Figure 24. ALT Trajectory in Patient (b) (6)

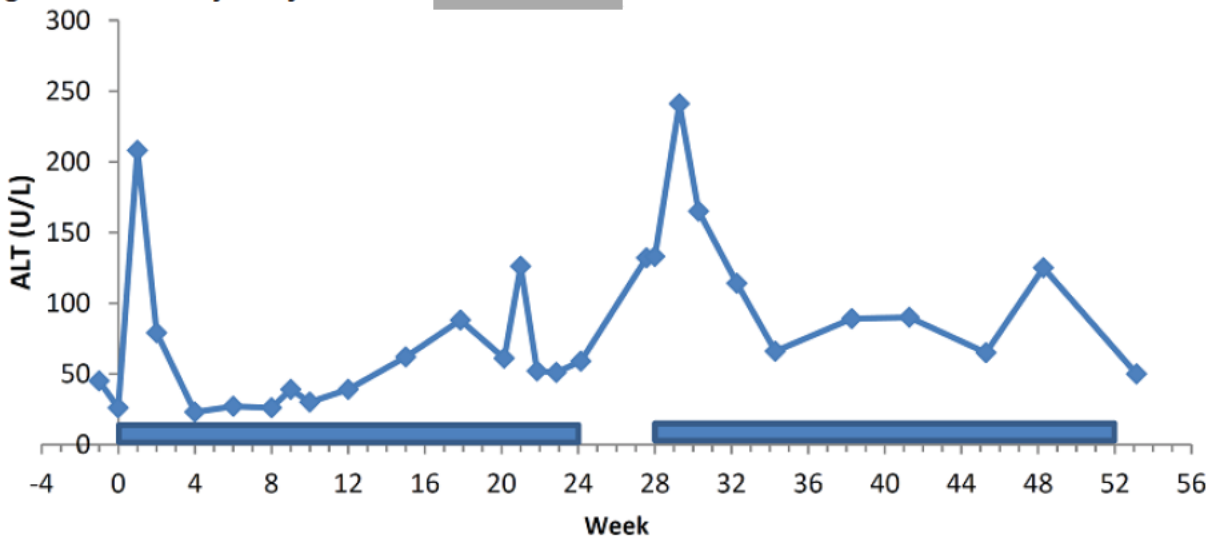


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

ALT peaked at 221 U/L (11x of 20 U/L), Cycle 1, day 1 and returned to baseline values in the 70s during teduglutide treatment in Cycle 1. ALT rose to 197 U/L two weeks after teduglutide treatment was discontinued. The elevations in ALT were noted for at least 8 months thereafter in the absence of teduglutide treatment. There were no associated changes in bilirubin or ALP. The pattern of ALT elevation does not appear related to teduglutide, given there was elevation before patient was on treatment and while off treatment.

Patient (b) (6) had a transient increase in ALT 1 week into TED-C14-006 with a peak of 208 U/L (6x ULN of 34 U/L). After discontinuation of teduglutide, ALT began to rise with a second peak at 241 (12x ULN of 20 U/L) in Cycle 1, week 1 of SHP633-304.

Figure 25. ALT Trajectory in Patient (b) (6)

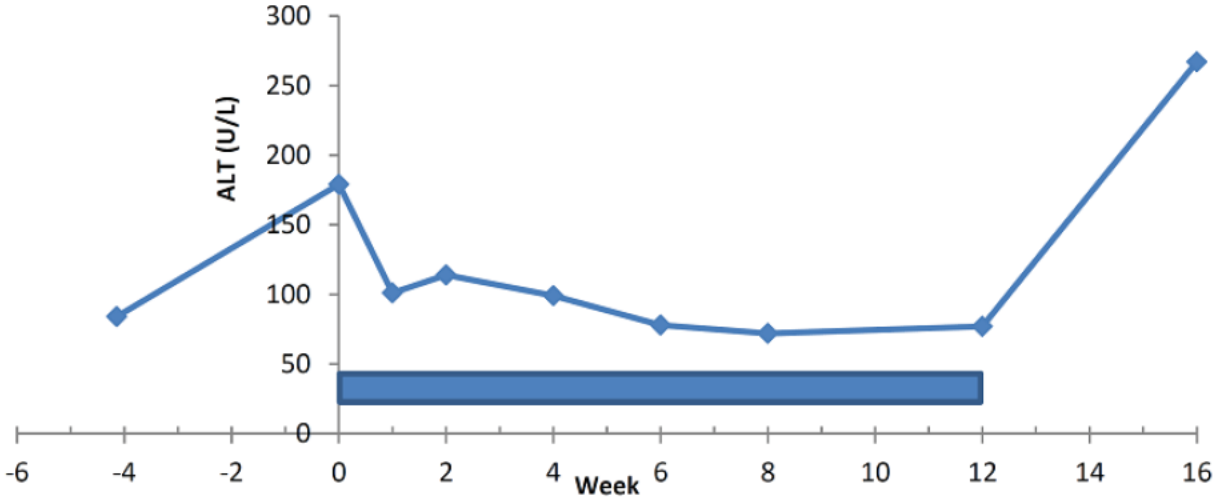


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

The investigator reported no relevant adverse events associated with either transient rise in ALT, and no associated changes in bilirubin and ALP in both instances. There was also no interruption in teduglutide in both cases and ALT returned to baseline. Given the information provided, the ALT pattern observed in this patient does not appear to support that it is related to teduglutide.

Patient (b) (6) had a rise in ALT after teduglutide treatment ended in TED-C13-003 peaking at 267 U/L (9x ULN of 29 U/L at the week 16 visit of TED-C13-003 (4 weeks after completion of teduglutide treatment). There was no associated increase in ALP or bilirubin.

Figure 26. ALT Trajectory in Patient (b) (6)

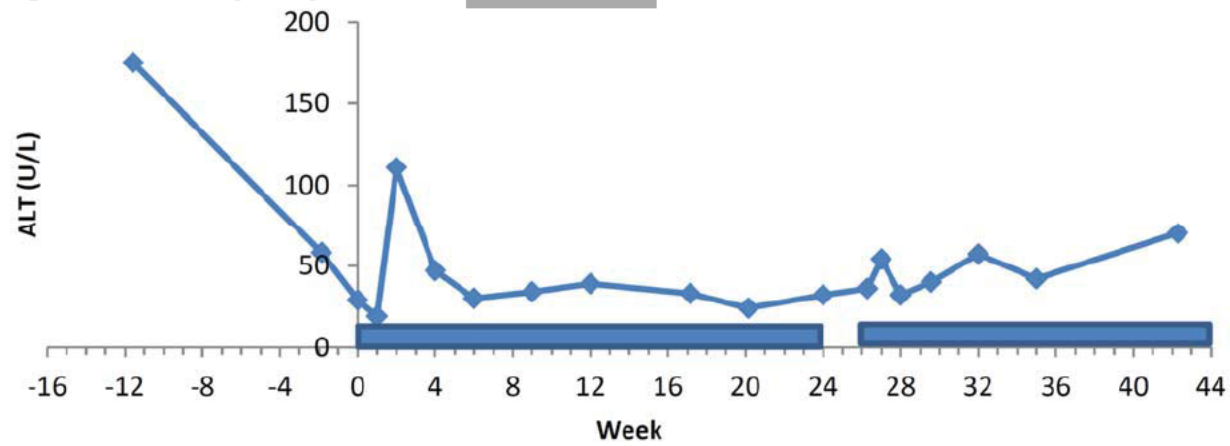


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

Given that the ALT increased 4 weeks after treatment ended, it is unlikely that this was due to teduglutide treatment.

Patient (b) (6) entered the SHP633-303 more than 3 years after teduglutide treatment had ended (in study 003) with elevated ALT of 175 (8.75x ULN of 20 U/L) and elevated ALP of 436 U/L (ULN 309 U/L), bilirubin was within normal limits (0.4 mg/dL).

Figure 27. ALT Trajectory for Patient (b) (6)

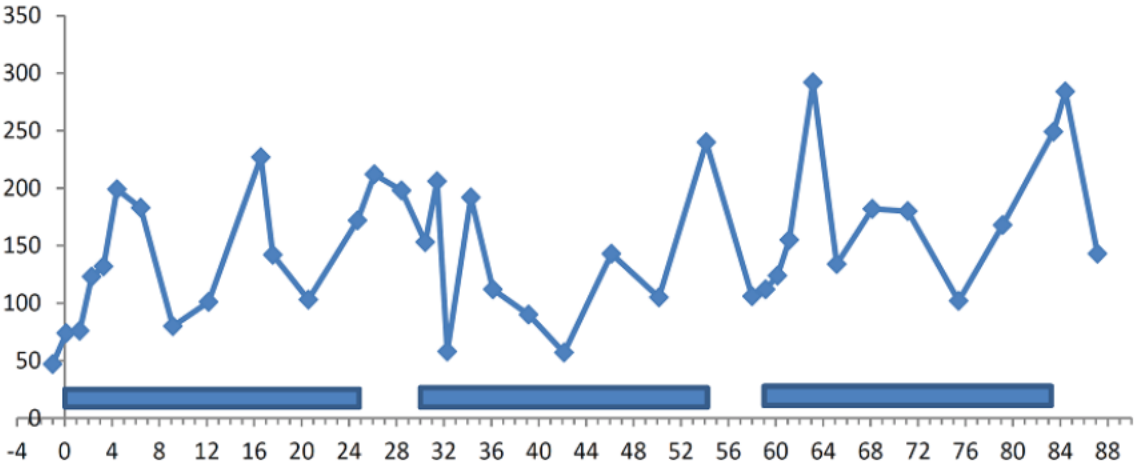


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

Of note is that patient was reported to also have a temporally associated adverse event of catheter associated device related infection (due to Malassezia, fungal infection). Given that the elevation in ALT occurred 12 weeks prior to teduglutide treatment and was temporally associated with fungaemia, this event is most likely not related to teduglutide treatment.

Patient (b) (6) had several ALT values that exceeded 8x the ULN of 25 U/L during study SHP633-303. These values occurred at Cycle 1, week 16 (227 U/L); 1 week after the end of teduglutide treatment in Cycle 1 (212 U/L); Cycle 2, week 1 (206 U/L); Cycle 2, week 24 (240 U/L); Cycle 3, week 4 (292 U/L); Cycle 3, week 24 (249 U/L); and 1 week after the end of teduglutide treatment in Cycle 3 (294 U/L). None of these values were deemed clinically significant by the investigator.

Figure 28. ALT Trajectory for Subject (b) (6)

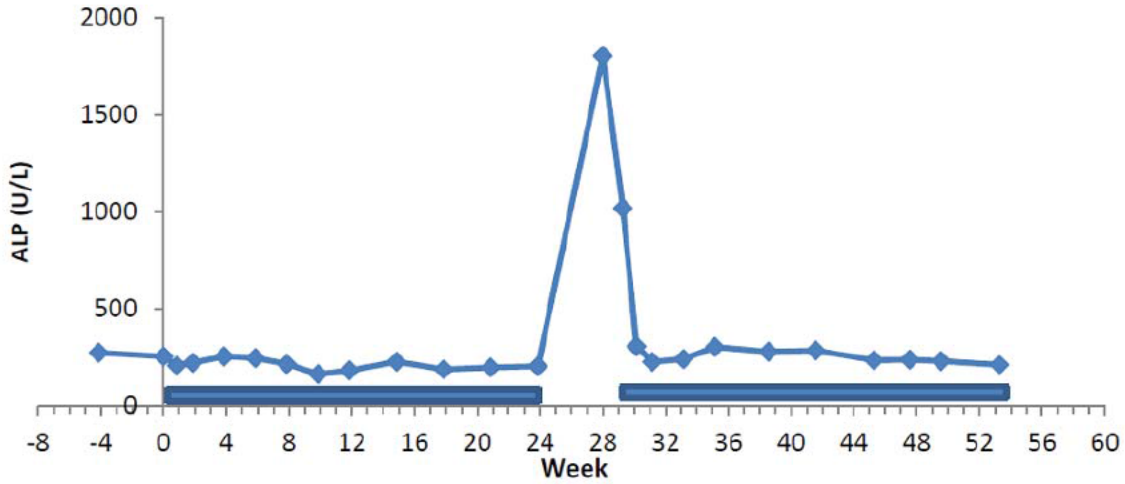


Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALT = alanine aminotransferase
Source: Applicant's IR Response, dated January 29, 2019

Per report, the patient had an adverse event of sepsis during Cycle 1, week 8, which was immediately preceded by a mild increase in bilirubin from baseline of 0.7 mg/dL to a peak of 1.8 mg/dL (1.5x ULN). No other significant changes in ALP or bilirubin report. The pattern of ALT elevation is not suggestive of being related to teduglutide.

Patient (b) (6) had stable ALP levels during teduglutide treatment period in TED-C14-006. Baseline ALP was 275 U/L (ULN 297) and 206 at week 24 (EOT).

Figure 29. Alkaline Phosphatase Trajectory for Patient (b) (6)



Teduglutide treatment periods in TED-C14-006 and SHP633-304 indicated by blue bars
ALP = a kaline phosphatase
Source: Applicant's IR Response, dated January 29, 2019

Four weeks after discontinuation of teduglutide treatment, ALP rose to 1804 U/L (6x ULN) at the end of study visit and remained elevated as the patient entered SHP633-304, with a value of 1019 U/L at Cycle 1, day 1. This event was not recorded as an adverse event per report at the initial onset of given it started while patient was off treatment per report. During teduglutide treatment in SHP633-304, ALP returned to normal levels with no associated increase in ALT, ALT or bilirubin. Given that the transient elevation of ALP in this patient correlates with periods when the patient is off teduglutide and resolution to normal ALP occurs when patient is on treatment with teduglutide, therefore the investigator analysis that the elevated ALP is most likely not related to teduglutide appears reasonable

14.4.4. Schedule of Assessments

Table 49. TED-C14-006 Protocol Schedule of Events in Teduglutide-Treated Patients From Screening to Week 28

Schedules of Events

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

	Screening Baseline		Treatment period											
Study week	**SRN**	**BL**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**
Visit Number/Type: S=site/T=telephone	**1/S**	**2/S**	**3/S**	**4/S**	**5/T**	**6/S**	**7/T**	**8/S**	**9/T**	**10/S**	**11/T**	**12/S**	**13/T**	**14/S**
Study day±window	**≥-14**	**0**	**7±2**	**14±2**	**21±3**	**28±3**	**35±3**	**42±3**	**49±3**	**56±3**	**63±3**	**70±3**	**77±3**	**84±3**
Informed consent/assent[a]	X													
Eligibility	X	X												
Demographics	X													
Medical/Surgical history	X													
Electrocardiogram	X													X
Short bowel syndrome history	X													
Upper GI with small bowel follow through and abdominal ultrasound[b]	X													
Fecal occult blood test[c]	X													X
Colonoscopy/Sigmoidoscopy[c]	(X)													(X)
Provide GI-specific symptoms history diary	X													
Review GI-specific symptoms history diary		X												
Randomization[d]		X												
Dispense drug[e]		X	X	X		X		X		X		X		X
Pharmacokinetic sampling[f]		X[f]												
Safety laboratory testing[g]	X[h]	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Pregnancy test[h]	X	X	X	X		X		X		X		X		X
Citrulline test[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)

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

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

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

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

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

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

c All subjects enrolled in a treatment arm will have an FOBT after providing consent/assent. Subjects with positive FOBT at screening for whom a readily detectable cause cannot be not identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy. Colonoscopy/sigmoidoscopy will be conducted at screening on all subjects 12 years of age and older; however if the screening FOBT is negative and the subject has undergone the procedure within 1 year before visit 1 (screening), then that result will be acceptable for the screening assessment (See Section 6.5.4). Subjects with positive FOBT results at week 12 for which a cause is not identified by a physical exam will be discussed with the Shire medical monitor (See Section 6.5.3).

d Treatment arm assignment and randomization and will be completed before dispensing teduglutide.

e The first subcutaneous injection of teduglutide will be administered under the supervision of the investigator/designee after which the subject will be observed for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) must be specified and recorded in the eCRF. Teduglutide dose may be adjusted based on weight at week 12.

f See Section 6.1 for PK blood draw timepoints. If a subject is unable to provide blood samples for PK at the baseline visit (day 0), then PK samples may be collected during any other future site visit while the subject is still receiving treatment with teduglutide.

g Safety lab assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits may be collected by a Home Health Agency and submitted to a central lab or performed locally and will consist of clinical chemistry and urinalysis only. For children in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. Safety labs must be performed approximately within 5-7 days of any adjustment to the PN/IV prescription. For all subjects in the teduglutide treatment arm, PT/INR will be tested at screening and if drug-induced liver injury is suspected thereafter.

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

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

j For antibody testing, blood will be obtained from subjects in the teduglutide treatment arm at the site before receiving the first dose of teduglutide. Blood samples may be drawn from a central line or from peripheral access (See Section 6.6.1.2).

k The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 6.6). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every clinic visit and within 1 week of each change in PN/IV prescription. (See Section 6.6 for more detail). Nutritional support includes PN/IV and EN (formula) (See Section 6.4).

l Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data and according to the guidelines provided in Appendix 1.

Source: TED-C14-006 protocol Amendment 4, Version 5, March 15, 2016, pages 52–56/78, total protocol pages 358–362/384

Table 50. TED-C14-006 Protocol Schedule of Events in Standard of Care–Treated Patients From Screening to Week 28

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

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

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

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

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

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

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

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

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

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

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

e Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data and according to the guidelines provided in Appendix 1.

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

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

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

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

a Any subject who discontinues from the study before week 24 (EOT) (ie, early terminates) will undergo EOT procedures at the time of discontinuation and will complete a follow-up visit 4 weeks later.

b The volume and hours per day of PN/IV support and EN (formula) will be recorded on the intake diary every day during the study (Section 6.6). Urine and stool output should be recorded in the output diary over a 48 hour period of PN/IV and EN stability before every clinic visit and within 1 week of each change in PN/IV prescription. (See Section 6.6 for more detail). Nutritional support includes PN/IV and EN (formula) (See Section 6.4).

c Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data and according to the guidelines provided in Appendix 1.

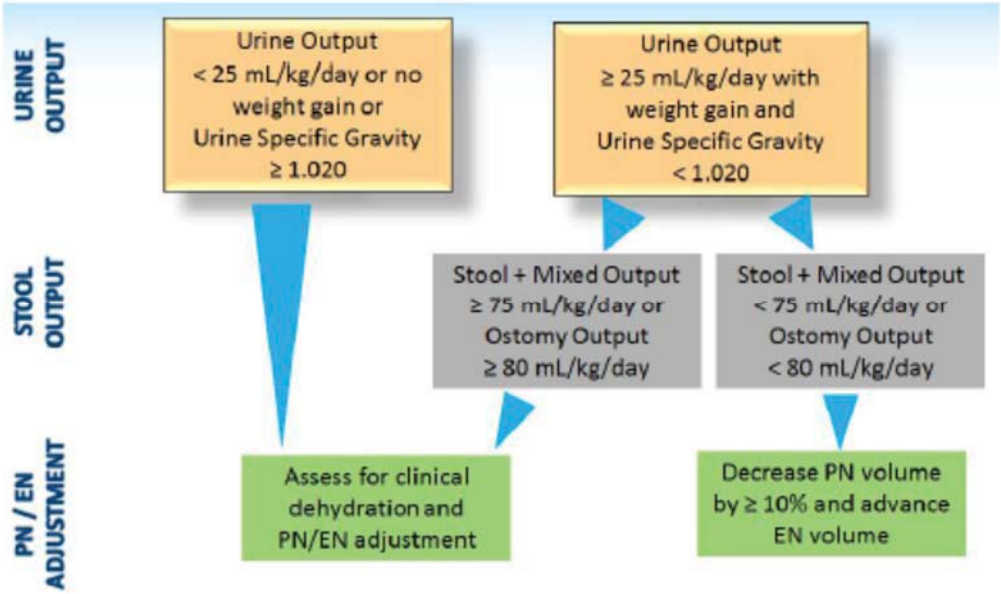
d Safety lab assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central lab. Safety labs performed at phone visits may be collected by a Home Health Agency and submitted to a central lab or performed locally and will consist of clinical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

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

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

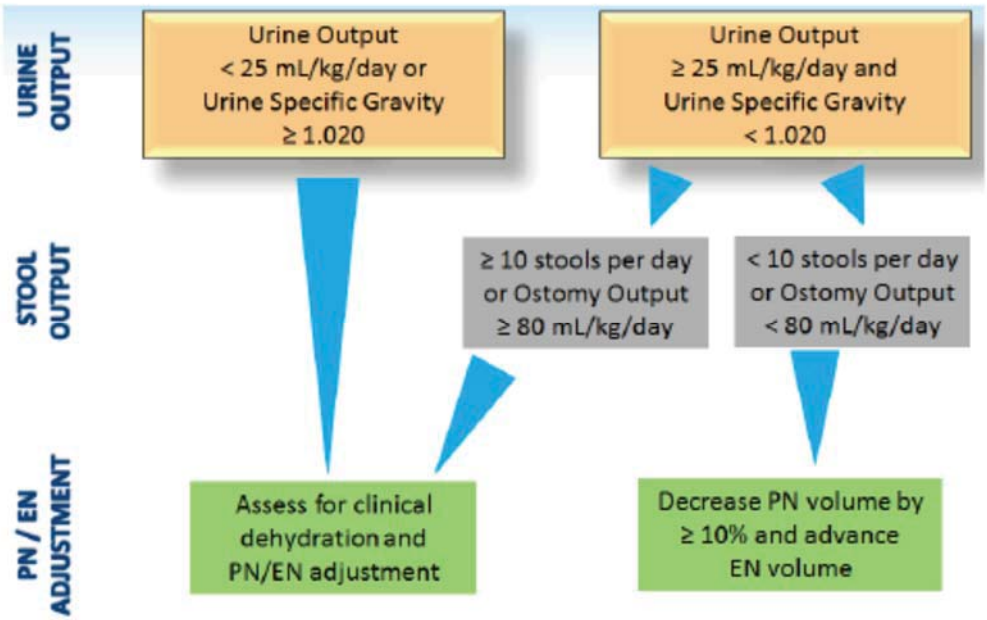
Source: TED-C14-006 protocol Amendment 4, Version 5, March 15, 2016, pages 57–59/78, total protocol pages 363–365/384

14.4.5. Parenteral Nutrition Weaning Algorithm (Non-Toilet Trained)



Source: Applicant submitted protocol for TED-C14-006 (Amendment 4/version 5.0) (page 73)

14.4.6. Parenteral Nutrition Weaning Algorithm (Toilet Trained)



Source: Applicant submitted protocol for TED-C14-006 (amendment 4/version 5.0) (page 74)

14.5. Certification of Financial Interests

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list of investigators (TED-C13-003)	See attached list of investigators (SHP633-304)
	See attached list of investigators (TED-C14-006)	
	See attached list of investigators (SHP633-303)	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Olivia Maurel, PharmD	Therapeutic Area Head, Global Regulatory Affairs
FIRM/ORGANIZATION: Shire-NPS Pharmaceuticals, Inc.	
SIGNATURE: [signature]	DATE *(mm/dd/yyyy)*: 09/03/2018

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