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CADTH COMMON DRUG REVIEW

Clinical Review Report

TEDUGLUTIDE (REVESTIVE)

(Shire Pharmaceuticals Ireland Limited)

Indication: Treatment of adults and pediatric patients one year of age and above with short bowel syndrome who are dependent on parenteral support

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Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
EN	enteral nutrition
EOT	end of treatment
GLP	glucagon-like peptide
HRQoL	health-related quality of life
ITT	intention-to-treat
NEC	necrotizing enterocolitis
NTT	no teduglutide treatment
PP	per-protocol
PN/IV	parenteral nutrition/intravenous fluid
PS	parenteral support
RCT	randomized controlled trial
SAE	serious adverse event
SBS	short bowel syndrome
SD	standard deviation
SOC	standard of care
TEAE	treatment-emergent adverse event
TED	teduglutide
URTI	upper respiratory tract infection
WDAE	withdrawal due to adverse event

Drug	teduglutide (Revestive)
Indication	Treatment of adults and pediatric patients 1 year of age and above with short bowel syndrome (SBS) who are dependent on parenteral support
Reimbursement Request	Treatment of pediatric patients 1 year of age and above with SBS who are dependent on parenteral support
Dosage Form(s)	Powder for solution, 5 mg/vial, subcutaneous injection
NOC Date	August 13, 2019
Manufacturer	Shire Pharmaceuticals Ireland Limited

Executive Summary

Introduction

Short bowel syndrome (SBS) is a rare but serious condition that results from extensive resection of the small intestine, congenital abnormalities, or disease-associated loss of absorption. SBS is also the most common cause of intestinal failure, which is the state when a patient's gastrointestinal function is inadequate to maintain nutrient, growth, and hydration status without intravenous or enteral supplementation. In children, the most common causes of SBS include necrotizing enterocolitis (NEC), congenital intestinal atresia, gastroschisis, volvulus, extensive Hirschsprung disease, and inflammatory bowel disease. Clinical manifestations of SBS in children may include excessive fluid and electrolyte loss, inability to absorb adequate energy and nutrients (e.g., protein, carbohydrates, fats, necessary vitamins, and minerals), poor weight gain, and growth failure. Patients' and caregivers' quality of life is subsequently impaired. Those with moderate to severe disease may have a reduced lifespan due to the underlying condition, severe clinical manifestations of malabsorption, or treatment-related life-threatening complications. Survival of children with SBS has been substantially improved since the introduction in the 1960s of parenteral support (PS) in the form of parenteral nutrition (the intravenous feeding of nutrients) and intravenous hydration, also known as PN/IV (parenteral nutrition/intravenous fluid). Estimated mortality rates for infants and children with SBS vary substantially. Mortality of pediatric patients has decreased in recent years from between 20% and 40% to 10% or less, due to advances in nutritional support, neonatal intensive care, anesthesia, surgical techniques, and adoption of the intestinal rehabilitation program. In Canada, the number of pediatric patients with SBS who are dependent on PS was estimated to be [redacted].

The clinical management of SBS in children includes close monitoring of nutritional status and growth, steady and early introduction of enteral nutrition (EN), identification of patients at risk for long-term PS dependency, and prevention, diagnosis, and treatment of long-term PS-related complications such as central venous catheter sepsis and bacterial overgrowth. During the first few months after intestinal resection, PS is provided to the patients to meet energy needs and promote growth. Continued PS is required for patients with poor weight gain or fluid and electrolyte losses that are too extensive to be replaced enterally. However, prolonged PS is associated with reduced lifespan, life-threatening complications such as intestinal failure-associated liver disease, sepsis, hemorrhage, and compromised quality of life for patients and caregivers. Medications may be needed during the nutritional management of SBS to address specific symptoms and complications. Surgical therapies

such as intestinal lengthening procedures may be considered for selected patients with the aim of helping promote intestinal adaptation and enteral autonomy. Patients who fail medical and surgical therapy, those with little potential for intestinal rehabilitation, or those who develop intractable complications are potential candidates for intestinal transplantation. However, surgeries are associated with significant morbidity and mortality.

Teduglutide is a 33-amino acid recombinant analogue of human glucagon-like peptide-2 (GLP-2). It was approved in 2015 by Health Canada for the treatment of adult patients with SBS who are dependent on PS. Teduglutide was reviewed by CADTH Common Drug Review (CDR) in 2016 and was recommended to be reimbursed for adult patients with SBS who are dependent on PS. On August 13, 2019, teduglutide was approved by Health Canada for the treatment of pediatric patients one year of age and above with SBS who are dependent on PS. The recommended daily dosage of teduglutide for children with SBS is 0.05 mg/kg body weight administered by subcutaneous injection once daily.

The objective of the current CDR review was to perform a systematic review of the beneficial and harmful effects of teduglutide subcutaneous injection (Revestive) for the treatment of pediatric patients one year of age and above with SBS who are dependent on PS.

Stakeholder Engagement

Patient Input

One patient group, the Gastrointestinal (GI) Society, submitted the input for this review. Information for the submission was obtained from interviews, published information, and expert and patient opinion. The parent of a child involved in the Revestive pediatric clinical trial, and two health care professionals involved in the aforementioned trial or experienced working with children with SBS, were interviewed through telephone or in person. Additionally, information was obtained from medical studies, expert opinion, and the 2015 Short Bowel Syndrome Oley Conference Roundtable in the US.

SBS is a potentially fatal condition in which patients are unable to absorb sufficient nutrients and fluids through the intestines, resulting from a birth defect, trauma, disease, or when too much intestine is surgically removed. Common symptoms of SBS include vitamin and mineral deficiencies, frequent diarrhea, extreme fatigue, cramping, dehydration, failure to thrive, and weight loss. These symptoms can lead to further complications including peptic ulcer disease, kidney stones, gallstones, small bowel bacterial overgrowth, and metabolic bone disease. The social consequences can be particularly dire for children, as the cumbersome feeding schedule and equipment, fatigue, and abdominal pain brought on directly or indirectly by malnourishment can negatively affect childhood activities such as play, school, self-care, and most social activities. Finally, living with SBS, restricted social interactions, and the ensuing isolation can lead to significant stress, anxiety, and depression.

Current therapy for patients with SBS includes one or a combination of the following: dietary adjustments, PS, EN, enteral feeding, and surgery. Each treatment is associated with different drawbacks, and the choice of therapy is determined upon the individual needs of the patients. Parenteral nutrition is generally suitable for children without adequate bowel growth or functioning gut, given to prevent atrophy of the organs necessary for digestion. Another treatment, EN, is often given to children in combination with parenteral nutrition. Finally, a limited number of surgical treatments are available to increase the absorptive properties of the intestine. However, severe and sometimes fatal post-surgical complications

can arise, which may result in frequent hospitalizations due to infections, while transplantation may cause serious damage to the liver or gallbladder.

Feedback for teduglutide was primarily provided by the parent of a child suffering from SBS resulting in the destruction of almost 90% of her intestine. The child had experienced great clinical benefits since starting the treatment. She was able to consume a wide variety of oral foods and nutritional supplements, thus decreasing her need for gastrostomy tube (G-tube) feeding. As a consequence, she had more unencumbered play and socializing time. The family of the child also benefited significantly. There were reportedly financial benefits, due to reduced requirements for ostomy supplies, which are not covered by health insurance. Minimizing the use of PS may also lower the risk of long-term complications such as the development of gallstones and liver damage to the point of needing transplant.

Based on the input from patients and their families, two areas of unmet needs were identified. There currently is a shortage of effective treatments for the following groups of SBS patients: 1) adult patients who have failed other treatments; and 2) children at a higher risk of long-term complications from an early onset of SBS, and children whose inability to grow bowel may prevent any clinical improvements. Treatments that enable children to develop a functional bowel are of particular importance for their normal growth. In addition, a treatment option that can circumvent the need for PS or EN feeding apparatuses will enable children to live their day-to-day lives more comfortably, allowing for normal physical and social development.

Clinician Input[1]

There is no single directed medical therapy beyond supportive care available in the management of SBS in pediatric patients. In general, surgical care and non-surgical supportive care are available for the study population. With the current standard of care of surgical and non-surgical management by specialized multidisciplinary intestinal failure centres, approximately 50% to 80% of children with SBS are able to achieve enteral autonomy. The most important goals for treatment in children with SBS are to improve survival, to achieve enteral autonomy from PS while maintaining optimal nutritional status and health, and to minimize the complications associated with the disease and treatments of intestinal failure.

The panel discussed the unmet needs. Currently, no medication is available to stimulate intestinal differentiation and growth, or to address the main treatment goals such as elimination of PS, increase in oral and/or enteral feeding, and therefore lowering the risk of long-term complications, need for intestine transplantation, or death. In addition, there are no treatments available to adequately treat the underlying physiologic basis of the disease. Treatments that are more effective and better tolerated are needed to manage the issues associated with SBS, especially related to feed tolerance, dysmotility, and small intestinal bacterial overgrowth.

The experts indicated that approximately 50% to 80% of the pediatric population would be able to achieve enteral autonomy after being treated in a multidisciplinary specialized centre with an intestinal rehabilitation program. Teduglutide may improve the rates of enteral autonomy and/or reduce PS usage in these patients. Unfortunately, the conducted clinical

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

trials were not helpful in identifying the specific subgroup of patients who may have better response to teduglutide.

The experts suggested the following criteria in defining SBS patients who have the greatest unmet need:

- above one year of age
- more than one year on PS therapy
- stable PS requirements or no progression in EN for more than three months
- require PS that provides more than 30% of caloric fluid, and/or electrolyte needs
- severe intestinal failure-associated complications such as PS-related liver disease or central line-related complications like infections and venous thromboembolic events.

In addition, once the treatment with teduglutide starts and is effective it may require long-term therapy because of the significant rebound after discontinuation of the treatment.

Teduglutide is not a first-line medication. It should only be provided to children who have already been treatment-optimized for their intestinal failure, and remain dependent on PS for fluid, electrolyte, or nutritional requirements. Teduglutide should be prescribed only by physicians working in a specialized multidisciplinary intestinal rehabilitation program. After the initiation of treatment and the conditions are stable, patients may also receive monitoring and treatment in a pediatric medical centre with appropriate expertise, with continued consultation care with their primary intestinal rehabilitation program.

An important question is to find out which patients would be best suited for treatment with teduglutide and the predictors for better prognosis. Unfortunately, there is insufficient data to allow the identification of patients who will respond optimally to teduglutide treatment due to the small sample of the current pediatric clinical trials. In addition, the baseline patient characteristics in the included studies for the current review did not allow the prediction of which patients will be more responsive. In the current clinical trials in pediatric SBS patients, the study participants had received more than one year of PS and required persistent parenteral nutrition. Children may not be suitable for teduglutide therapy if they receive PS for less than one year, unless serious complications associated with current treatment develop. Other subgroups that are not appropriate for teduglutide therapy are patients with inadequate remaining small intestinal length, intestinal failure from non-SBS causes, and those who do not require PS and are achieving adequate growth and development using EN.

A number of outcome measures are reported in the trials included in the current CDR review, such as reduction in PS volume, reduction in infusion time for parenteral support, increase in EN, and achievement of normal growth while weaning off PS. The experts indicate that these are all clinically relevant outcomes and are measurable in practice. The ability of reducing PS volume and infusion time is an important outcome to determine whether the treatment should continue. The threshold of greater than and equal to 20% reduction in PS volume is considered clinically meaningful change.

Treatment with teduglutide needs to be discontinued if any of the following occurs:

- Lack of efficacy: experts suggest using a less than 20% reduction in PS volume (minimal clinically important improvement) at month six to define lack of efficacy
- Allergic reaction to teduglutide
- Side effects of treatment become intolerable.

Re-assessment should be conducted every two to three months to evaluate the treatment effect, side effects, and complications.

The clinical experts strongly recommended that children with SBS undergo consultation in a recognized multidisciplinary specialized intestinal rehabilitation program with assessment by members of a team that includes a pediatric gastroenterologist or pediatric surgeon with expertise in SBS management for disease diagnosis, treatment, and follow-up, prior to teduglutide being prescribed.

The clinical experts also noted the following evidence gaps: 1) lack of long-term efficacy, effectiveness and safety of teduglutide therapy in the trial populations and the real world; 2) the unknown clinical benefits associated with a greater than and equal to 20% reduction in PS volume; and 3) the unknown clinical and patient characteristics that predict response to teduglutide; and 4) the impact of teduglutide discontinuation on children who adapted and weaned off PS.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

Two phase III studies (Study 006, double-blind RCT, N = 59; and Study 003, open-label non-RCT, N = 42) submitted by the manufacturer are included in this systematic review. The trials included pediatric patients (greater than one year of age) with SBS as a result of major intestinal resection. They required PS that provided at least 30% of caloric, fluid and/or electrolyte needs for at least three months prior to screening and was stable for more than three months prior to and during screening. The two studies evaluated the efficacy and safety of 24-week (Study 006) or 12-week (Study 003) teduglutide therapy (0.0125 mg/kg/day, 0.025 mg/kg/day, and 0.05 mg/kg/day) in children with SBS compared with standard of care (SOC). Teduglutide 0.05 mg/kg/day is the only Health Canada–approved dosage for the study population. The main outcome in both studies was change in parenteral feeding from baseline, with response defined as a greater than and equal to 20% reduction in PS volume from baseline to study end point (week 24 for Study 006 and week 12 for Study 003). Other efficacy outcomes include change in enteral feeding and change in nutritional status (measured with height and weight for age) from baseline. Harm outcomes associated with the use of teduglutide were also examined.

The major limitations of the included studies are the study design and the lack of a statistical comparison between treatment groups. Patients were not randomized to receive teduglutide and comparator. Patients and their caregivers decided which treatment they wanted to receive. Therefore, systematic differences in age, race, nutritional status, underlying causes for SBS, and remaining small intestinal length were observed between treatment groups and had an impact on data interpretation. Statistical testing was not performed, and data were descriptively summarized only. Subgroup analysis and sensitivity analysis were performed; however, the results should be interpreted with caution given the small sample size.

Efficacy results

In the two studies, parenteral feeding was evaluated by measuring the proportion of patients with a greater than and equal to 20% reduction in PS volume at study end point (week 24 for Study 006 and week 12 for Study 003), change from baseline in PS volume, and the change from baseline in PS infusion time (days per week or hours per day).

In Study 006, 54.2% of patients in the teduglutide 0.025 mg group, 69.2% in the teduglutide 0.05 mg group, and 11.1% in the SOC group were responders (defined as patients who achieved greater than and equal to 20% reduction in PS volume at the end of treatment [EOT]) based on patient diary data. Analysis of investigator-prescribed PS volumes gave consistent results. The percentage of patients achieving greater than and equal to 20% reduction in PS volume at EOT was higher in the two teduglutide dosage groups compared with SOC (54.2% versus 69.2% versus 22.2%, respectively). The experts consulted on this review considered these differences between treatment and SOC to be clinically meaningful, even though a statistical comparison was not performed. Treatment with both teduglutide dosages (0.025 mg and 0.05 mg) was related to greater reduction in PS volume from baseline to EOT compared with the SOC group. In addition, patients in the teduglutide dosage groups experienced shorter infusion time (fewer PS days per week and fewer PS hours per day) as compared with the SOC group at EOT.

In Study 003, 12.5% of the patients in the teduglutide 0.0125 mg group, 71.4% in the teduglutide 0.025 mg group, 46.7% in the teduglutide 0.05 mg group and no patient in the SOC group achieved a greater than and equal to 20% reduction in PS volume at week 12, based on patient diary data. When analyzed using the investigator-prescribed data, the percentage of patients achieving a greater than and equal to 20% reduction in PS volume at week 12 was [redacted]. The experts considered these differences between teduglutide and SOC to be clinically meaningful, even though a statistical comparison was not performed. All teduglutide dosage groups were related to greater reduction in PS volume from baseline to week 12 compared with the SOC group. In addition, patients in the teduglutide dosage groups (0.025 mg and 0.05 mg groups) experienced shorter infusion time (fewer PS days per week and fewer PS hours per day) as compared with the SOC group at week 12. Change in the infusion time from baseline to week 12 reported in the teduglutide 0.0125 mg group was similar to the SOC group.

Additional efficacy outcomes were examined. For change in EN, results of Study 006 showed that both teduglutide groups (0.025 mg and 0.05 mg) experienced greater increase in EN volume from baseline to EOT compared with the SOC group (percentage change of 76.89%, 79.52% and 2.50% for teduglutide 0.025 mg, teduglutide 0.05 mg group and the SOC group, respectively). [redacted]

In Study 006, two patients (8.3%) in the teduglutide 0.025 mg group and three (11.5%) patients in the teduglutide 0.05 mg group achieved enteral autonomy, which was defined as complete weaning off PS at EOT. No patients from the SOC group achieved enteral autonomy. In Study 003, one patient (7.1%) in the teduglutide 0.025 mg group and [redacted] in the teduglutide 0.05 mg group achieved enteral autonomy at week 12.

[redacted] The clinical experts consulted for this review indicated that the change in weight and height from baseline was small and not considered clinically meaningful.

Harms results

Almost all patients reported treatment-emergent adverse events (TEAEs) in Studies 006 and 003. The majority of the adverse events (AEs) were mild or moderate in severity. The most common AEs reported in Study 006 by the pediatric patients treated with 0.05 mg/kg teduglutide were pyrexia (42%), cough (39%), vomiting (31%), upper respiratory tract infection (URTI) (31%), abdominal pain (23%), and nasopharyngitis (23%). Although the proportion of patients with AEs was higher in the teduglutide groups for most of the reported AEs, the risk of certain AEs was higher in the SOC group, such as vomiting, pyrexia, and URTI.

In Study 006, the incidence of serious adverse events (SAEs) was higher in teduglutide-treated groups (63% to 77%) than in the SOC group (44%), while in Study 003, treatment with teduglutide 0.05 mg/kg/day or SOC was associated with more SAEs, as compared with teduglutide 0.0125 mg/kg/day or teduglutide 0.025 mg/kg/day. The common SAEs in the included studies were pyrexia, dehydration, and central line-related breakage or infection.

No patients withdrew due to AEs in either study. No deaths were reported in either study. In terms of AEs of special interest, during the study, there were no reports of gastrointestinal tract polyp formation, biliary complications, neoplasia, or intestinal obstruction in either study. At the end of the study, antibody development was detected in eight patients in Study 006 (three in the teduglutide 0.025 mg group; five in the teduglutide 0.05 mg group) and one patient (in the teduglutide 0.025 mg group) in Study 003.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Efficacy Outcomes							
Patients with ≥ 20% reduction in PS volume, n (%)							
Number of patients analyzed, n	20	25	9	7	14	14	5
Patients with ≥ 20% reduction in PS volume at EOT from baseline, n (%)[a]	13 (54.2)	18 (69.2)	1 (11.1)	1 (12.5)	10 (71.4)	7 (46.7)	0
Number of patients analyzed, n	24	26	9	8	14	15	5
Patients with ≥ 20% reduction in PS volume at EOT from baseline, n (%)[b]	13 (54.2)	18 (69.2)	2 (22.2)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in PS volume							
Number of patients analyzed, n	24	26	9	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD) 006: mL/kg/day 003: L/week	56.84 (25.24)	60.09 (29.19)	79.59 (31.12)	[redacted]	[redacted]	[redacted]	[redacted]

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)[a]	–16.16 (10.52)	–23.30 (17.50)	–6.03 (4.55)	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change, mean (%)[a]	–36.17 (30.65)	–41.57 (28.90)	–10.21 (13.59)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients analyzed, n	24	26	9	8	14	15	5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)[b]	–11.28 (15.51)	–22.13 (17.92)	–5.84 (9.80)	–0.43 (0.86)	–2.73 (1.92)	–2.40 (3.50)	0.43 (0.75)
Per cent change, mean (%)[b]	[redacted]	[redacted]	[redacted]	–8.60 (20.38)	–35.61 (26.20)	–36.50 (40.59)	7.38 (12.76)
Change from baseline in EN volume							
Number of patients analyzed, n	23	26	9	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD) 006: mL/kg/day 003: L/week	17.80 (24.45)	27.64 (29.47)	14.04 (18.19)	[redacted]	[redacted]	[redacted]	[redacted]
EOT, mean (SD)[a] 006: mL/kg/day 003: L/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)[a]	7.69 (13.46)	10.96 (16.59)	0.74 (5.91)	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change, mean (%)[a]	76.89 (117.19)	79.52 (134.49)	2.50 (33.87)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients analyzed, n	18	22	5	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)[b]	7.67 (17.77)	8.17 (17.87)	0.33 (0.90)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete weaning off PS							

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Number of patients analyzed, n	20	25	9	8	14	15	5
Patients with 100% reduction in PS volume at EOT from baseline, n (%)	2 (8.3)	3 (11.5)	0	0	1 (7.1)	[redacted]	0
Patients with < 100% reduction in PS volume at EOT from baseline, n (%)	[redacted]	[redacted]	[redacted]	7 (87.5)	13 (92.9)	14 (93.3)	5 (100)
Harm Outcomes							
Patients with ≥ 1 AE, n (%)							
	24 (100)	25 (96.2)	9 (100)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 SAE, n (%)							
	15 (62.5)	20 (76.9)	4 (44.4)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who stopped treatment due to AEs, n (%)							
	0	0	0	0	0	0	0
Deaths, n (%)							
	0	0	0	0	0	0	0

AE = adverse event; EN = enteral nutrition; EOT = end of treatment; IV = intravenous; NR = not reported; PS = parenteral support; SAE = serious adverse event; SD = standard deviation; SOC = standard of care; TED = teduglutide.

[a] Based on patient's diary data.

[b] Based on prescribed data.

Sources: Clinical Study Reports of Studies 006[1] and 003.[2]

Critical appraisal

The rare disease nature of SBS posed a practical recruitment challenge to the included trials, and a randomized study design may not have been feasible. None of the two studies included a randomized comparison of teduglutide with SOC. Patients or their parents determined whether they would receive treatment with teduglutide or SOC. Systematic differences with respect to patients' baseline characteristics between the teduglutide treatment groups and the SOC group, e.g., age, race, nutritional status, underlying causes for SBS, and remaining small intestinal length, were observed. The imbalanced baseline characteristics may have an impact on data interpretation and bias the results. Patients in the teduglutide groups tended to be older and to have more severe conditions. Compared with younger patients with milder disease, it may be challenging for them to grow adequate bowel length and achieve enteral autonomy. The small number of study participants makes data interpretation difficult when the observed treatment effect could be due to chance, or alternatively, a true effect may not be detected due to insufficient power of the trial. Although a more severe population was within the teduglutide groups, and this may conservatively bias the results toward the non-teduglutide treatment, it is uncertain to what extent the imbalances in the patient's baseline characteristics would have influenced the relative treatment effect between teduglutide and SOC.

In addition, sensitivity analyses and subgroup analyses are not easy to perform in these small trials. Therefore, treatment effect of the study drug in the interested subgroups cannot be fully explored. Data in both studies were descriptively described without performing statistical testing; no adjustments on covariates were planned and there was no adjustment on multiple comparisons. In addition, a reduction of greater than and equal to 20% in PS volume was the main efficacy outcome measure in both studies. Although this is commonly used in clinical trials as well as in practice, there is a lack of underlying scientific basis for the use of 20% as a threshold at present.

The two studies used more stringent exclusion criteria for patient recruitment than are usually observed in clinical practice. In addition, the study population was older and is representative of a more severe disease, compared with that usually seen in Canadian practice. However, according to the experts, the study results are likely generalizable to the Canadian patient population. Three dosages of teduglutide were evaluated in the included studies, however, only the dosage of 0.05 mg/kg/day is approved by Health Canada for children with SBS at present. Due to the relatively short duration (12 weeks to 24 weeks) of the included studies, some important clinical outcomes cannot be sufficiently examined, such as survival, growth failure, need for intestinal transplantation, and certain harm outcomes which may be related to the use of the study drug (e.g., colon polyps, neoplasia).

Other Relevant Evidence

Description of studies

Study 303 and 304 were extension periods of Studies 003 and 006 (the core study), respectively, and were designed to evaluate the safety and long-term efficacy of teduglutide in pediatric patients with SBS. Both studies were phase III, open-label, and are currently ongoing. Study 303 consisted of a retrospective and a prospective period. Once patients (or caregivers) provided informed consent and entered the open-label study, data were retrospectively collected for the period between the end of Study 003 and the beginning of Study 303 using medical reports (2.4 years to 3.3 years; N = 29). Patients were then followed up prospectively for a period of at least six months (greater than and equal to six months or 24 weeks for 21 patients; greater than and equal to 22 weeks for three patients), during which time data were collected using intake diaries and PS prescription. Patients had the opportunity to consent to retrospective data collection only. Study 304 [redacted] patients entered immediately after completing Study 006. For both studies, only interim results were reported, [redacted]

The main criteria for inclusion in the core studies were children and adolescents aged one year to 17 years with SBS who had stable PS requirements (unable to reduce PS or advance enteral feeds) for at least three months prior to screening. All patients who completed the core studies were eligible to continue in the extension period, regardless of their treatment assignment in the core studies.

Treatment during the extension period consisted of multiple recurring teduglutide or no teduglutide cycles, with crossover allowed depending on the disease course. Each teduglutide cycle consisted of a 24-week block of teduglutide treatment, followed by a 4-week follow-up period to evaluate whether continued teduglutide was needed. The duration

of the no teduglutide cycles was not pre-specified, although patients were assessed every 12 weeks during this period. At any point during the study, including during or after a no teduglutide period or follow-up period, patients could be assessed for treatment with teduglutide.

Efficacy results

Overall, the small number of patients, imbalance between the treatment arms, and provision for crossover between treatments without any information on when or how many times crossover occurred, prevent any conclusion from being drawn regarding comparative as well as long-term treatment efficacy. The retrospective period had a number of additional factors that limited the interpretability of the results, including a short duration of exposure to teduglutide relative to the total retrospective follow-up, no information on the dosage of teduglutide, and a large proportion of patients missing toward the end. For these reasons, the discussion below will primarily focus on the prospective period.

Greater than and equal to 20% reduction in weight-normalized PS volume

During the prospective period of Study 303, the number of patients [redacted] achieving a greater than and equal to 20% reduction in weight-normalized PS volume [redacted]. In Study 304, the number of patients [redacted] who achieved a greater than and equal to 20% reduction in PS volume [redacted].

Change in PS volume

During the prospective period of Study 303, among patients [redacted], the mean PS volume [redacted]. In Study 304, among patients who received teduglutide during the extension period, there was [redacted] in the mean PS volume [redacted].

Complete weaning off PS

By the end of the retrospective period of Study 303, five patients achieved enteral autonomy according to PS prescription, two in the TED (teduglutide)/TED arm and three in the TED/NTT (no teduglutide treatment) (defined as “patients who received teduglutide in the core study but not during the extension study”) arm. Notably, one of these patients achieved enteral autonomy during the core study. No patients newly achieved enteral autonomy during the prospective period until the time of cut-off date. In Study 304, a total of seven patients in the TED/TED arm achieved enteral autonomy at C1 EOT, five of whom achieved enteral autonomy during the core study. Notably, [redacted] who had achieved enteral autonomy in the core study and at cycle EOT started to receive PS during C2. [redacted].

Harms results

In Study 303, a total of [redacted] AEs were reported during the retrospective period. Device-related infection constituted the most frequently reported AEs, followed by pyrexia, influenza, and other device-related complications. Patients in the TED/NTT arm reported

more AEs ([redacted]AEs reported in 23 patients) compared with the TED/TED arm ([redacted]in four patients); a similar pattern was observed for SAEs (127 SAEs in 20 TED/NTT patients versus 21 SAEs in four TED/TED patients). During the prospective period in Study 303, [redacted]reported AEs ([redacted]). [redacted] was observed for SAEs ([redacted]). Common AEs in both arms included [redacted] during Study 303.

In Study 304, AEs were reported in 41 patients in the TED/TED group, [redacted]in the NTT/NTT (defined as "patients who did not receive teduglutide in either the core or extension study") group, [redacted]in the NTT/TED group and[redacted]in the TED/NTT group. [redacted]for SAEs ([redacted]in the TED/TED arm, [redacted]in the NTT/NTT arm, and [redacted] in the TED/NTT group). Of these, two SAEs in the TED/TED arm resulted in study discontinuation. The most frequent AEs in Study 304 included vomiting, pyrexia, abdominal pain, increased alanine aminotransferase, URTI, and product issues. All device-related events were related to central venous catheters used to administer PS, not to the teduglutide injection device. A cecal polyp was identified in one patient during a colonoscopy, but this was not related to teduglutide as determined by the investigator. The polyp was not biopsied or resected. No actions were taken with the study drug or other treatments and the patient continued in the study. Follow-up colonoscopy later did not identify any colonic polyps. One patient in the TED/TED arm died during the study.

Critical appraisal

The studies included a small number of patients. Given the small and imbalanced sample size between the treatment arms and the lack of any formal statistical analyses, no conclusion with respect to the comparative benefits and harms between teduglutide and no teduglutide can be made. The duration of the prospective follow-up was relatively short in both trials. Furthermore, fewer patients were available beyond the first cycle in either treatment period. The duration of teduglutide exposure during the retrospective period in Study 303 was also short, and the dosage was not specified in the Clinical Study Report. Together, these factors present a challenge in assessing the continued efficacy of the treatment. Another result of the short prospective follow-up duration is that rare AEs, including the SAEs of greatest interest, e.g., intestinal metaplasia, polyp formation and cancer, are unlikely to be captured during this period. Patients were allowed to switch between periods of teduglutide and no teduglutide cycles; however, there was no information on washouts between treatment cycles or exposure at each time interval. Therefore, it is unclear whether, and to what extent, the treatment effects were biased due to carryover effects. The outcomes assessed in the trial were clinically relevant, objective, and measured using standard equipment and procedures. The clinical experts reached a consensus that the primary outcome – a greater than and equal to 20% reduction in PS volume – was a clinically meaningful change. However, the experts agreed that the magnitude of change in PS volume was not translated to clinically observable end points like changes to hours per day or days per week of PS infusion time. Health-related quality of life (HRQoL) measures targeted at specific aspects of the treatment such as daily needle use as well as overall quality of life were not assessed for this interim analysis. Of the clinical end points, PS was measured using intake diaries and investigator-prescribed data. The sponsor mentioned that the diary data were more representative of patients' parenteral

nutrition intake, a statement not shared by the clinical experts consulted for this review. However, results using both methods were consistent; therefore, any bias introduced from subjective reporting of parenteral nutrition intake by the patients is likely minimal.

Conclusions

Two phase III studies (one double-blind, 24-week, randomized controlled trial and one open-label, 12-week, non-randomized controlled trial) were included in this review. The main limitations of the included studies were the small size, non-randomized comparison of teduglutide with SOC, extensive exclusion criteria, and no statistical testing between treatment groups. Teduglutide administered according to the Health Canada–approved dosage (0.05 mg/kg/day) was associated with better response rates than SOC in reducing parenteral nutrition volume and time. Treatment with teduglutide was also related to increased enteral feeding and complete weaning off parenteral nutrition for some patients. The studies did not demonstrate clinically meaningful improvement in nutritional status as measured by weight and height. Almost all study participants reported TEAEs, and the use of teduglutide was related to higher risk of some AEs. The majority of the reported AEs were mild to moderate in intensity. There were no deaths during the study, and no patients withdrew due to AEs. Results of the extension studies suggest that the treatment with teduglutide may be associated with clinical benefit in reducing parenteral nutrition requirement in some patients and suggest that there are no new safety signals in the study population, but follow-up is continuing.

Introduction

Disease Background

Short bowel syndrome (SBS) is a rare but serious condition that results from extensive resection of the small intestine, congenital abnormalities, or disease-associated loss of absorption.[3,4] In addition, SBS is the most common cause of intestinal failure, which is the state that arises when a patient's gastrointestinal function is inadequate to maintain nutrient, growth, and hydration status without intravenous or enteral supplementation.[3] In children, the most common causes of SBS include necrotizing enterocolitis (NEC), congenital intestinal atresia, gastroschisis, volvulus, extensive Hirschsprung disease, and inflammatory bowel disease.[3] Depending on the patient's age, underlying causes of SBS, and the quantity and location of affected bowel, clinical manifestations of SBS in children may include excessive fluid and electrolyte loss, inability to absorb adequate energy and nutrients (e.g., protein, carbohydrates, fats, necessary vitamins, and minerals), poor weight gain, and growth failure.[3,4] Patients' and caregivers' quality of life is subsequently impaired, according to the patient group input. In those with moderate to severe disease, their lifespan could be shortened due to the underlying condition, severe clinical manifestations of malabsorption, and treatment-related life-threatening complications.[5] Survival of children with SBS has been substantially improved since the introduction in the 1960s of parenteral support (PS) in the form of parenteral nutrition (the intravenous feeding of nutrients) and intravenous hydration,[6] also known as PN/IV (parenteral nutrition/intravenous fluid); however, prolonged PS is related to severe complications such as intestinal failure-associated liver disease, sepsis, and hemorrhage.[3,7,8] Estimated mortality rates for infants and children with SBS vary substantially both between institutions and over time. Mortality of pediatric patients has decreased in recent years from between 20% to 40%, to 10% or less, due to advances in nutritional support, neonatal intensive care, anesthesia, surgical techniques, and adoption of the intestinal rehabilitation program.[3,6]

Intestinal adaptation is a natural compensatory process that occurs when the gastrointestinal tract responds to the extensive resection of small intestine. It allows for an increase in the absorptive capacity of the remaining bowel by progressive anatomic and physiologic changes that improve fluid, electrolyte, and nutrient absorption, and allows progress toward normal growth, body composition, and enteral autonomy.[3,6,7] These changes usually occur within five years following the resection.[9]

In Canada, the number of pediatric patients with SBS who are dependent on PS was estimated to be [redacted].[10]

Standards of Therapy

The main treatment goals for SBS are to support adequate nutrition, reduce dependence on PS (and thus subsequently reduce PS-related complications), and to reach enteral autonomy.[7] Important factors that affect the chances of achieving enteral autonomy include longer residual small bowel, younger age at the time of intestinal resection, preservation of the ileocecal valve, diagnosis of NEC, absence of severe liver disease, and normal gastrointestinal motility.[7] The adoption of a multidisciplinary team consisting of pediatric gastroenterologists, surgeons, neonatologists, dietitians, nurses, pharmacists, speech/feeding therapists, social workers, and other ancillary health professionals is

considered crucial in the management of SBS in children, and is associated with better survival.[11,12]

The clinical management of SBS in children includes close monitoring of nutritional status and growth; steady and early introduction of enteral nutrition (EN); identification of patients at risk for long-term PS dependency; and prevention, diagnosis, and treatment of long-term PS-related complications such as central venous catheter sepsis and bacterial overgrowth.[12] During the first few months after intestinal resection, PS is provided to the patients to meet energy needs and promote growth. Continued PS is required for patients with poor weight gain or fluid and electrolyte losses that are too extensive to be replaced enterally. Although PS can meet basic nutrition and fluid requirements, it does not improve the body's ability to absorb nutrients. In addition, PS is associated with reduced lifespan, life-threatening complications (e.g., sepsis, blood clots, or liver damage), as well as compromised quality of life of patients and caregivers.[13-17] The development of PS-associated liver disease predisposes patients to an increased incidence of sepsis, increased mortality rates, and the potential to develop irreversible liver damage.[18] Following fluid and electrolyte stability and demonstrated growth on PS, enteral feeding is initiated to promote intestinal adaptation. As enteral feeds are increased, PS can be decreased gradually, therefore potentially lowering the risk for some of the complications of long-term PS.[19] The volume and composition of PS infusion should be adjusted frequently. Age-appropriate solid foods can be introduced to further promote intestinal adaptation and oral-motor skills.[3,20]

Medications may be required during the nutritional management of SBS to address specific symptoms and complications. These may include histamine-2 receptor antagonists and proton pump inhibitors for excessive gastric secretion, bile acid sequestrants for bile acid diarrhea, octreotide for diarrhea and fluid losses, clonidine for problematic diarrhea despite optimization of other antisecretory and antidiarrheal therapies, loperamide for chronic diarrhea, and promotility drugs for delayed gastric emptying. Glutamine and growth hormone are also used in order to enhance intestinal adaptation or weaning PS; however, there is to date no sufficient evidence to support their clinical benefit.[3]

Surgical therapies such as intestinal lengthening procedures may be considered for selected patients with the purpose of helping promote intestinal adaptation and enteral autonomy. Patients who fail medical and surgical therapy, those with little potential for intestinal rehabilitation, or those who develop intractable complications are potential candidates for intestinal transplantation. However, surgeries are associated with significant morbidity and mortality, and patients must receive lifelong immune suppression.[6,12]

Drug

Teduglutide was approved by Health Canada for the treatment of adult patients with SBS who are dependent on PS in 2015.[21] It was reviewed by CADTH Common Drug Review (CDR) in 2016, and was recommended to be reimbursed for adult patients who have SBS and are dependent on PS. Teduglutide is a 33-amino acid recombinant analogue of human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. Teduglutide binds to the glucagon-like peptide-2 receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts, and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of multiple mediators including insulin-like growth factor-1, vasoactive intestinal polypeptide, nitric oxide, and keratinocyte growth factor. These mediators are expected to

produce histological effects in crypts and villi, manifested as increases in absolute and relative absorption of fat, nitrogen, sodium, potassium, calories, and gastrointestinal fluid; and consequent decreases in fecal or stomal output of fat, nitrogen, sodium, potassium, calories, and gastrointestinal fluid.[21]

Teduglutide was approved for the treatment of pediatric patients one year of age and above with SBS who are dependent on PS by Health Canada on August 13, 2019.[22] It is available as powder for solution for injection, 5 mg per vial. The recommended daily dosage of teduglutide for children with SBS who are dependent on PS is 0.05 mg/kg body weight administered by subcutaneous injection once daily.[21]

Stakeholder Engagement

Patient Group Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, the Gastrointestinal (GI) Society, submitted the input for this review. The GI Society acts as a liaison between patients with GI and liver conditions and health care professionals, other patient groups, and governments at all levels. It is involved in providing evidence-based information on all areas of GI tract, supporting research, advocating for appropriate patient access to health care, responding to information requests, participating in community initiatives, and promoting GI and liver health.

The GI Society declared that they did not receive help from outside their group to collect and analyze data used in this submission, or to complete the submission. It received a total of $19,000 in funding from Shire Pharma Canada ULC in 2017 and 2018.

2. Condition-Related Information

Information for the submission was obtained from interviews, published information, and expert and patient opinion. The parent of a child involved in the Revestive® pediatric clinical trial and two health care professionals involved in the aforementioned trial or experienced working with children with SBS were interviewed by telephone or in person. Additionally, information was obtained from medical studies and expert opinion, and the 2015 Short Bowel Syndrome Oley Conference Roundtable in the US.

SBS is a potentially fatal condition in which patients are unable to absorb sufficient nutrients and fluids through the intestines, resulting from a birth defect, trauma, disease, or when too much intestine is surgically removed. The majority of infants presenting in Canada with SBS are born with inadequate bowel, and a smaller proportion have Hirschsprung's disease, mitochondrial disease, focal muscular atrophy syndrome, Crohn’s disease, NEC, traumatic injury, surgery, gastrointestinal cancer, perforated bowel, blocked or restricted blood flow to the bowel, or congenital abnormalities.

Common symptoms of SBS include vitamin and mineral deficiencies, frequent diarrhea, extreme fatigue, cramping, dehydration, failure to thrive, and weight loss. These symptoms can lead to further complications including peptic ulcer disease, kidney stones, gallstones, small bowel bacterial overgrowth, and metabolic bone disease. As different sections of the small intestine are responsible for different nutrient absorption, the symptoms and severity can vary depending on the missing intestinal part. Many patients may need an ostomy, a surgical procedure to change the way that urine or stool exits the body. With ostomy, bodily waste is rerouted from its usual path because of malfunctioning parts of the urinary or digestive system and waste material is collected in a pouch attached to the surface of the skin on the abdomen. The physiological symptoms impede patients from participating in social activities, such that they must plan accordingly for gatherings and holidays. The social consequences can be particularly dire for children, as the cumbersome feeding schedule and equipment, fatigue, and abdominal pain brought on directly or indirectly by malnourishment can negatively affect childhood activities such as play, school, self-care, and most social activities. In addition to being unable to eat normal foods and beverages, patients may overconsume to compensate for the poor absorption, which can lead to a voluminous ostomy output in patients who had an ostomy. Finally, living with SBS, restricted social interactions, and the ensuing isolation can lead to significant stress, anxiety, and depression.

3. Current Therapy Related Information

Current therapy for patients with SBS includes one or a combination of the following: dietary adjustments, parenteral nutrition, EN, enteral feeding, and surgery. Each treatment is associated with different drawbacks, and the choice of therapy is determined by the individual needs of the patients.

Dietary adjustments involve customized menus and eating plans managed by a dietitian, or adjustments in the intake of proteins, carbohydrates, and fluids. Specialized meals can be difficult and time-consuming to prepare. Ingesting frequent and large meals can be inconvenient. Nutritional supplements add expense to this form of treatment. PS is generally suitable for children without adequate bowel growth or functioning gut, given to prevent atrophy of the organs necessary for digestion. Concentrated forms of amino acids and lipids, carbohydrates, electrolytes, vitamins, and trace elements are administered intravenously via a central line. This solution can over-stress the relatively delicate digestive system in children, especially for infants. Children with SBS often receive very low amounts of water to satiate their thirst, which, in addition to detrimental physiological effects, can negatively affect their psychology by training them to ignore the normal bodily response to thirst.

Another treatment, EN, is often given to children in combination with PS; and it delivers nutrition and hydration directly to the stomach by the use of a gastrostomy tube (G-tube). This method is particularly cumbersome since children often vomit in response to forced feeding, requiring multiple daily treatments, which in turn leads to increased wastage and makes the preparations costly. Additionally, children suffer from increased fatigue, are at risk of serious infections, and require frequent hospitalization to receive nutrition. Moreover, they are required to have a partially functioning GI tract for this method to be effective. Enteral feeding frequently results in gastroesophageal reflux disease, abdominal bloating, cramps, nausea, diarrhea, constipation, and re-feeding syndrome; the latter can lead to a large increase in insulin levels which leads to increased oxygen consumption, and increased respiratory and cardiac demand. Blockages or bacterial contamination of the tube itself further limit its practicality.

Finally, a limited number of surgical treatments are available to increase the absorptive properties of the intestine. Artificially lengthening the intestine and small bowel transplantation were both referenced in the submission. However, severe and sometimes fatal post-surgical complications can arise from these surgeries, which may result in frequent hospitalizations due to infections; in addition, transplantation may cause serious damage to the liver or gallbladder.

Feedback for teduglutide was primarily provided by the parent of a child suffering from SBS resulting in the destruction of almost 90% of her intestine. The child had experienced great clinical benefits since starting the treatment; particularly a four- to six-hour decrease (approximately 30%) in PS, and increased oral hydration ability from a few drops of water to drinking small amounts. Additionally, she was able to consume a wide variety of oral foods and nutritional supplements, decreasing her G-tube feeding. As a consequence, she had more unencumbered play and socializing time. The family of the child also benefited significantly, as their entire schedule was centred around taking care of her. The family was able to have more sleep time, and generally less undisturbed time for other activities. There were reportedly financial benefits, due to reduced requirements for ostomy supplies, which are not covered by health insurance. Minimizing the use of PS may lower the risk of long-term complications such as the development of gallstones and liver damage to the point of needing transplant.

4. Expectations About the Drug Being Reviewed

Based on the input from patients and their families, two areas of unmet needs were identified. There currently is a shortage of effective treatments for the following groups of SBS patients: 1) adult patients who have failed other treatments, and 2) children at a higher risk of long-term complications from an early onset of SBS, and children whose inability to grow bowel may prevent any clinical improvements. Treatments that enable children to develop a functional bowel are of particular importance for their normal growth. In addition, a treatment option that can circumvent the need for PS or EN feeding apparatuses will enable children to live their day-to-day lives more comfortably, allowing for normal physical and social development.

5. Additional Information

The patient group acknowledged the high cost of teduglutide; however, the alternative treatments are also reported to be expensive, and there are many physical and psychological complications arising from both the disease and treatments, including poor quality of life, being confined to hospital, possible organ failure, lack of normal socialization, failure to thrive, and even childhood death. Based on the clinical benefits from Revestive, the patient group urges a positive recommendation for covering Revestive for children with SBS who are on PS.

Clinician Input Summary

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the teduglutide (Revestive) review, a panel of four clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented below.

Current Treatment Paradigm for Short Bowel Syndrome (SBS) in Pediatric Patients

There is no single directed medical therapy beyond supportive care available in the management of SBS in pediatric patients. In general, surgical care and non-surgical supportive care are available for the study population. The purpose of surgical therapy is to improve nutrient and fluid absorption. Non-surgical medical care, including PS, EN, treatment aimed at prevention of macro- and micro-nutrient deficiencies and prevention of long-term complications is provided to support the health of the patient with SBS to allow time for bowel growth and intestinal adaptation to occur. With the current standard of care (SOC) of surgical and non-surgical management by specialized multidisciplinary intestinal failure centres, approximately 50% to 80% of children with SBS are able to achieve enteral autonomy. To date, no medication is available to improve outcomes of children with SBS. Some medications, such as oral insulin, have been evaluated in clinical trials; however no successful trials have been conducted for SBS at this moment in the pediatric population.

There are no current evidence-based clinical practice guidelines for the treatment of children with SBS.

Treatment Goals

The most important goals for treatment in children with SBS are to improve survival, to achieve enteral autonomy from PS while maintaining optimal nutritional status and health, and to minimize the complications associated with the disease and treatments of intestinal failure.

Unmet Needs

Currently, no medication is available to stimulate intestinal differentiation and growth, or to address the main treatment goals such as elimination of PS, increase in oral and/or enteral feeding, and therefore lowering the risk of long-term complications, death, or need for intestine transplantation. Despite best practices, some patients may never achieve enteral autonomy. In addition, there are no treatments available to adequately treat the underlying physiologic basis of the disease. Treatments that are more effective and better tolerated are needed to manage the issues associated with SBS, especially related to feed tolerance, dysmotility, and small intestinal bacterial overgrowth.

The experts indicate that approximately 50% to 80% of the pediatric population would be able to achieve enteral autonomy after being treated in a multidisciplinary specialized centre with an intestinal rehabilitation program. Teduglutide may improve the rates of enteral autonomy and/or reduce PS usage in these patients. Unfortunately, clinical trials that have been conducted are not helpful in identifying a specific subgroup of patients who may have better response to the drug. The experts suggest the following criteria in defining patients who have the greatest unmet need:

- above one year of age; and/or
- have received at least one year of PS therapy, thus it is possible to find out whether the patients have intestinal adaptation); and/or
- stable PS requirements or no progression in EN for more than three months; and/or
- require PS that provides more than 30% of caloric and/or fluid/electrolyte needs; and/or
- patients with severe intestinal failure-associated complications such as PS-related liver disease, or central line-related complications like infections and venous thromboembolic events.

For the use of teduglutide in patients with severe intestinal failure-associated complications, practitioners will need to be cautious, because these patients are usually excluded from clinical trials, and there is a lack of safety data to support its use under these circumstances). In addition, once the treatment with teduglutide starts and is effective, it may require long-term therapy (months to years), because of the significant rebound after discontinuation of the treatment.

Place in Therapy

Teduglutide is not a first-line medication. It should only be provided to children who have already been treatment-optimized for their intestinal failure, and remain dependent on PS for fluid, electrolyte, or nutritional requirements.

The experts suggested that teduglutide should be prescribed only by physicians working in a specialized multidisciplinary intestinal rehabilitation program. Based on a position statement generated by the North American Society of Pediatric Gastroenterology Hepatology and Nutrition, the minimum requirements for an intestinal rehabilitation program are the inclusion of a pediatric gastroenterologist, pediatric surgeon, dietitian, pharmacist, and nurse with experience in intestinal rehabilitation.[6] After the initiation of treatment and the conditions are stable, patients may also receive monitoring and treatment in a pediatric medical centre with appropriate expertise, with continued consultation care with their primary intestinal rehabilitation program.

Patient Population

The question of the optimal patient population for treatment with teduglutide remains unanswered. Unfortunately, there is insufficient data to allow the identification of patients who will respond optimally to treatment due to the small sample size in the current pediatric clinical trials. In addition, the baseline patient characteristics in the included studies for the current review did not allow prediction of who will be more responsive. Even in the adult patient studies, there were no clear predictors. In the current clinical trials for children, the study participants had received more than one year of parenteral nutrition and required persistent PS therapy. Children may not be suitable for teduglutide therapy if they receive PS for less than one year, unless serious complications associated with current treatment develop (see the details in “Unmet Needs”). Other subgroups that are not appropriate for teduglutide therapy include patients with inadequate remaining small intestinal length (although evidence is lacking to provide a clear intestinal length threshold); those with intestinal failure from non-SBS causes; and patients who do not require PS therapy and are achieving adequate growth and development using EN. There are no data for the appropriateness of using teduglutide in patients who have undergone intestinal transplantation.

Assessing Response to Treatment

Several outcome measures are presented, such as reduction in PS volume, reduction in infusion time for PS therapy, increase in EN (volume and calories) and achievement of normal growth while weaning off parenteral support. The experts indicate that these are all clinically relevant outcomes and are measurable in practice. The ability to reduce PS volume and infusion time is an important indicator of whether the treatment should continue. The threshold of a greater than and equal to 20% reduction in PS volume that was used in the clinical trials is considered a clinically meaningful change. A 20% reduction in PS volume can be translated in children to a decrease in days or hours of infusion compared with the baseline before initiation of therapy. While it is reasonable to assume that a reduction in PS volume is associated with a decrease in some but not all PS-related complications, the data are not available to support this assumption.

Patients receiving teduglutide therapy initially require at least monthly follow-up visits at a specialized centre for intestinal rehabilitation to allow for adjustment of PS and EN volume and rates, and to assess response to therapy. At month six of treatment, comprehensive assessment is required to evaluate the patient’s response to treatment and to determine if teduglutide should be continued or discontinued if there has been inadequate response as defined above, or circumstances listed below. After six months, some experts suggest follow-up every two to three months in practice if stable and continuing therapy, while others suggest monthly follow-up for the next three months, especially for patients who

discontinue teduglutide at month six, since the patient's condition could deteriorate due to a rebound effect.

Discontinuing Treatment

Treatment with teduglutide needs to be discontinued if any of the following occurs:

- Lack of efficacy (experts suggest using a less than 20% reduction in PS volume [minimal clinically important improvement] at month six to define lack of efficacy)
- Allergic reaction to teduglutide
- Intolerable side effects of treatment.

Re-assessment should be conducted every two to three months to evaluate the treatment effect, side effects, and complications. Experience from adult patients suggests that if patients discontinue treatment with teduglutide after achieving PS independence, rebound may occur and these patients may need to re-start parenteral support or need an increase in their PS requirements. There is no data in children on the long-term effect of teduglutide and the needed length of therapy after weaning off parenteral support or reduction in PS calories. Initial experience in adults suggests a need for prolonged periods of therapy due to a rebound effect once the drug is discontinued. Discontinuation of treatment after the achievement of enteral autonomy at this stage is at the discretion of the treating team and requires careful monitoring if attempted.

Prescribing Conditions

It is strongly recommended that children with SBS undergo consultation in a recognized multidisciplinary specialized intestinal rehabilitation program with assessment by members of a team that includes a pediatric gastroenterologist or pediatric surgeon with expertise in SBS management for disease diagnosis, treatment, and follow-up, before teduglutide being prescribed. Furthermore, it is highly recommended that ongoing prescription of the medication should be done either directly by physicians in such units or by physicians with expertise in children that includes ongoing consultation with the intestinal rehabilitation program.

Additional Considerations

Experts indicate the following evidence gaps: 1) lack of long-term efficacy, effectiveness, and safety of teduglutide therapy in the trial populations and the real world; 2) the clinical benefits associated with a greater than and equal to 20% reduction in PS volume; and 3) the unknown clinical and patient characteristics that predict response to teduglutide; and 4) the impact of teduglutide discontinuation on children who adapted and weaned off PS.

Clinical Evidence

The clinical evidence included in the review of teduglutide is presented in two sections. Section 1 (Systematic Review) includes pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes manufacturer-submitted long-term extension studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of teduglutide (5 mg/vial) for subcutaneous injection for the treatment of pediatric patients one year of age and above with SBS who are dependent on PS.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR, as well as those meeting the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient Population	Children 1 year of age and above with SBS who are dependent on PS. Potential subgroups: • Age • Early onset vs. late onset • Etiology of SBS • Segments of remaining intestine • Length of residual intestine
Intervention	Teduglutide subcutaneous injection 0.05 mg/kg/day + standard of care
Comparators	Standard of care
Outcomes	**Efficacy outcomes:** • Survival • Change in parenteral feeding and fluid requirements[a] • Change in oral feeding and enteral feeding[a] • Need for dietary adjustment • Proportion of patients weaning from parenteral nutrition[a] • Change in SBS-related symptoms • Urinary/fecal output • Intestinal failure-associated liver disease • Health-related quality of life[a] • Growth delay measured with weight and/or height • Neurodevelopmental delay • Need for intestinal transplantation • Need for bowel lengthening procedure • Health care resource utilization

	Harms outcomes: AEs, SAEs, WDAEs, mortality **Notable harms:** Bowel obstruction, GI tract polyps, GI cancer, cholestasis, gallbladder disorders (e.g., obstruction, perforation, and infection), biliary disease, pancreatic disease (e.g., pancreatitis, pancreatic duct stenosis, and elevated serum amylase), infection/sepsis, heart failure, allergic reaction, and injection site reaction
Study Design	Published and unpublished phase III or IV RCTs

AE = adverse event; GI = gastrointestinal; PS = parenteral support; RCT = randomized controlled trial; SAE = serious adverse event; SBS = short bowel syndrome; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[23]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was teduglutide. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on June 29, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on October 16, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[24] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional Internet-based materials. These searches were supplemented by reviewing bibliographies of key papers. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings from the Literature

No studies were identified from the literature for inclusion in the systematic review (Figure 1). The manufacturer submitted two pivotal studies which are included in the systematic review. The included studies are summarized in Table 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

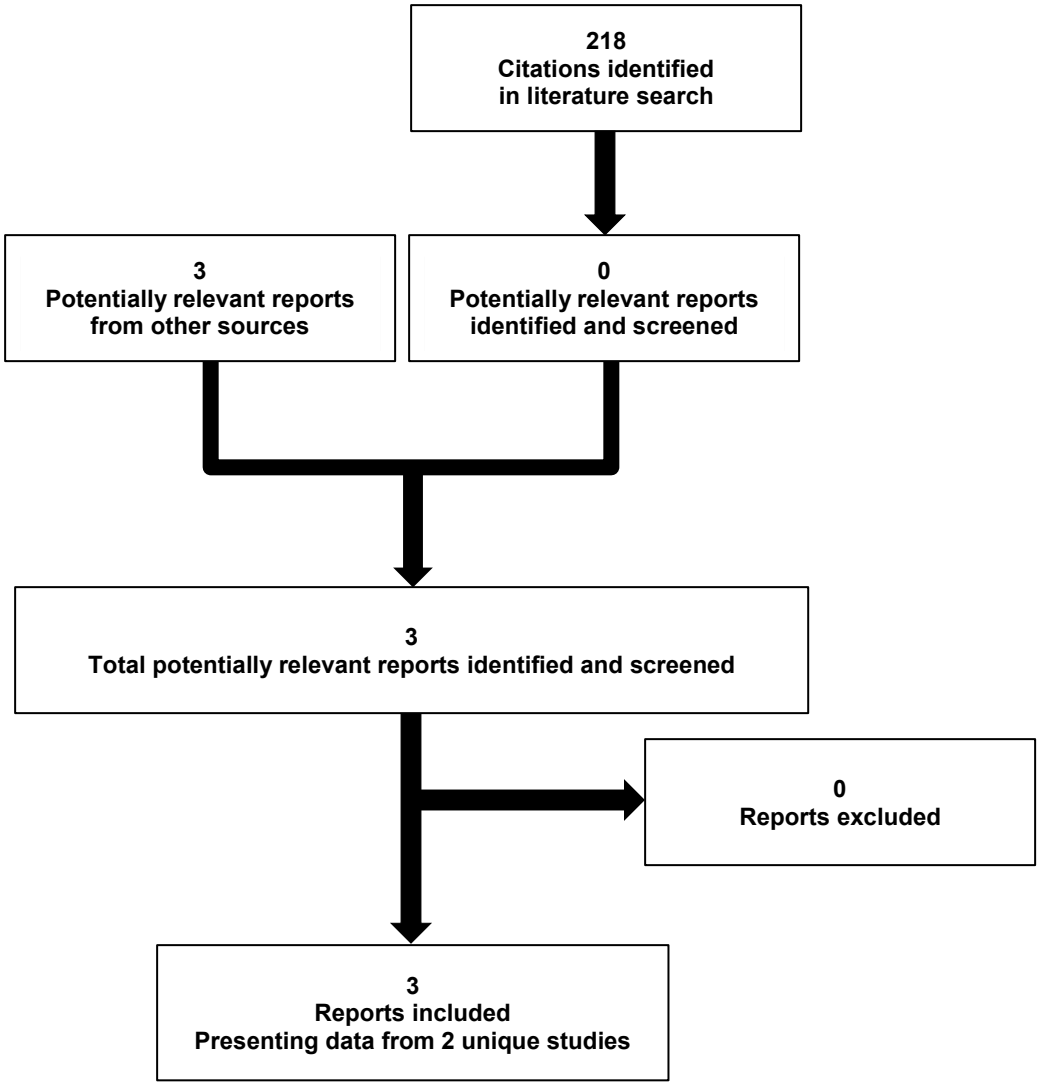


Table 3: Details of Included Studies

		TED-C14-006	TED-C13-003
Designs and Populations	**Study Design**	Phase III DB RCT	Phase III, OL, non-randomized, 4-cohort study
	Locations	27 sites in the US, Canada, & Europe	17 sites in the US & UK
	Randomized (N)	59	42 (non-randomized)
	Inclusion Criteria	Pediatric patients aged 1 year through 17 years with SBS as a result of major intestinal resection that required PN/IV support that provided ≥ 30% of caloric, fluid and/or electrolyte needs for ≥ 3 months prior to screening; stable PN/IV support for ≥ 3 months prior to and during screening.	
	Exclusion Criteria	• Known clinically significant untreated intestinal obstruction • Severe, known dysmotility syndrome or persistent, severe, active gastroschisis-related dysmotility prior to screening • Obstruction on upper GI series done within 6 months • Major GI surgical intervention within 3 months • History of cancer or clinically significant lymphoproliferative disease • Previous use of TED or native/synthetic GLP-2 • Previous use of GLP-1 analogue, human growth hormone, octreotide, or DPP-4 inhibitors within 3 months • > 3 SBS-related or PN/IV-related hospital admissions within 3 months • Body weight < 10 kg at screening and baseline visits • Active, unstable and clinically significant hepatic/renal impairment or pancreatic or biliary disease • Any condition, disease, illness, or circumstance that would put the patient at any undue risk, prevented completion of the study, or interfered with analysis of the study results.	
Drugs	**Intervention**	TED 0.025 mg/kg/day[a] TED 0.05 mg/kg/day + SOC	TED 0.0125 mg/kg/day[a] TED 0.025 mg/kg/day[a] TED 0.05 mg/kg/day + SOC
	Comparator(s)	SOC	SOC
Duration	**Phase**		
	Screening	2 weeks	
	Treatment	24 weeks	12 weeks
	Follow-up	4 weeks	
Outcomes	**Primary End Point**	• Number of patients with ≥ 20% reduction in average daily PS volume at EOT	• Number of patients with ≥ 20% reduction in weekly PS volume by scheduled visits and EOT • Per cent change in PS volume at EOT/week 12 • Absolute change in PS volume at week 12 or EOT • Number of patients who were completely weaned off PS at week 12 • Safety
	Secondary and Exploratory End Points	• Number of patients with TEAEs; • Number of patients who were completely weaned off PS at week 24;	

		TED-C14-006	TED-C13-003
		• Change from baseline in PS volume at week 24; • Change from baseline in PS caloric intake at week 24.	
NOTES	**Publications**	Posters[25,26]	Carter 2017[27]

DB = double-blind; DPP-4 = dipeptidyl peptidase-4; EOT = end of treatment; GI = gastrointestinal; GLP = glucagon-like peptide; IV = intravenous; OL = open label; PN/IV = parenteral nutrition/intravenous fluids; PS = parenteral support; RCT = randomized controlled trial; SOC = standard of care; TEAE = treatment-emergent adverse event; TED = teduglutide.

Note: One additional report was included (CDR Submission[10]).

[a] Not Health Canada–approved dosages.

Source: Clinical Study Reports of Studies 006[1] and 003.[2]

Description of Studies

Two studies provided by the manufacturer, TED-C14-006[1] and TED-C13-003[2] (herein referred to as Studies 006 and 003, respectively), were included in this systematic review.

The objective of Study 006 was to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy/pharmacodynamics (PD) of teduglutide in pediatric patients (aged one year through 17 years) with SBS who were dependent on PS. The study design of 006 is shown in Figure 2. The study participants were screened for a minimum of two weeks prior to the treatment to verify the requirements for nutritional support for each patient and to ensure adherence to eligibility parameters. To maintain consistency across all participating centres, sites and patients were required to follow the nutritional support adjustment guidelines (developed with input from the SBS experts) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, and urine and stool output in the setting of clinical stability. During the two-week screening period, the patient or patient's parent/guardian decided whether to participate in the teduglutide treatment groups or the SOC group. After screening, eligible patients who elected to receive teduglutide therapy were randomized in 1:1 ratio to receive either 0.025 mg/kg/day or 0.05 mg/kg/day of subcutaneous teduglutide injection for 24 weeks. Randomization was centrally carried out using an interactive voice response system and was stratified by age (less than one year, one year to less than 12 years, 12 to less than 17 years, and 17 to less than 18 years). Both investigators and patients were blinded to the two teduglutide dosages, while they were not blinded to whether the patient received active drug or SOC. Patients receiving SOC were enrolled to a separate SOC cohort, which served as an observational cohort for the 24-week treatment period. Safety and tolerability results were evaluated by a Data Monitoring Committee that convened approximately every three months during the treatment period.

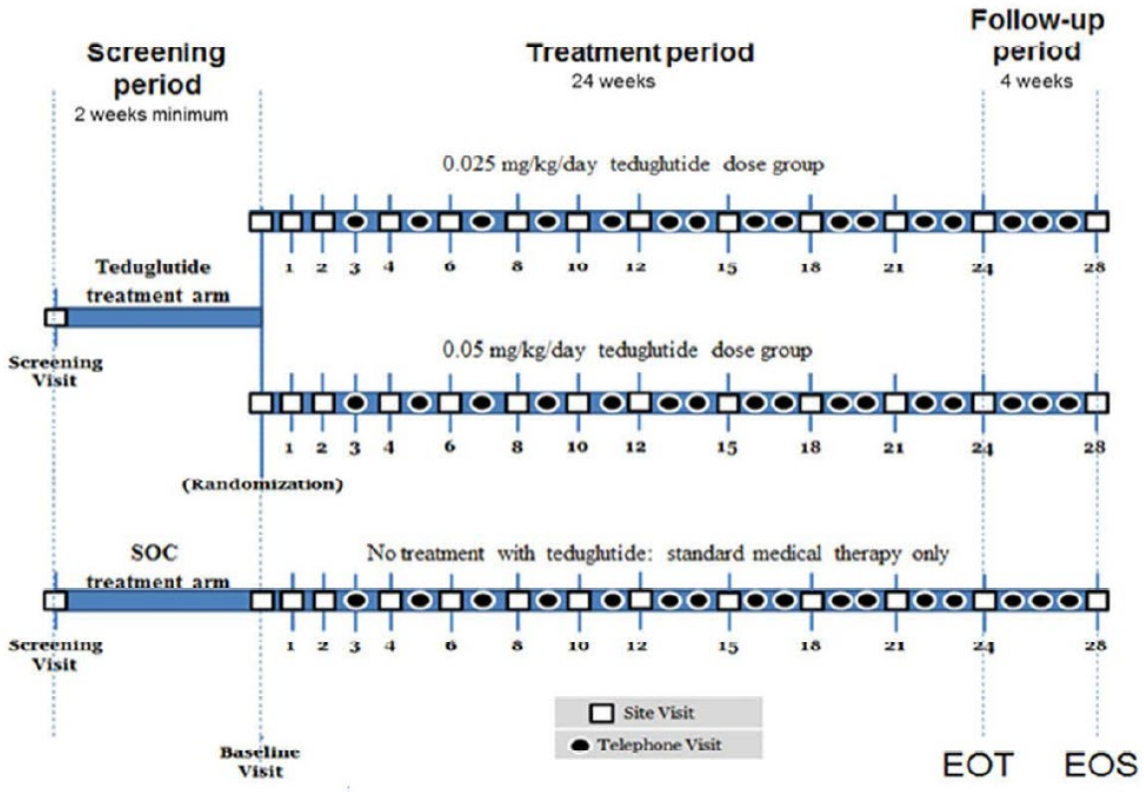
The objective of Study 003 was to evaluate the PK profile, PD effects, and safety and tolerability of teduglutide compared with SOC in pediatric patients with SBS who were dependent on PS. The study design is presented in

Figure 3. Approximately eight patients were to receive teduglutide in each of the three active cohorts (teduglutide 0.0125 mg/kg/day, 0.025 mg/kg/day, and 0.05 mg/kg/day). Another 12 patients were to be enrolled into an observational cohort which received SOC.

During the two-week screening period, the patient or patient's parent/guardian decided whether to participate in the teduglutide treatment groups or the SOC group. In this study, the timing of the patient's screening period determined which dosage group they would enter. The three dosages of teduglutide were investigated for 12 weeks in a staggered approach, starting with the lowest dosage. Safety and tolerability results were evaluated by Data Safety Monitoring Board (DSMB) at week 4 (approximately 28 days following the introduction of the 0.0125 mg/kg/day teduglutide dosage) and again at week 4 of the higher dosage cohorts. The DSMB review had to conclude that there were no untoward safety signals in at least six patients in order for the next cohort to proceed. Patients remained on treatment at their assigned dosage throughout the 12-week treatment period unless a safety issue was identified that indicated treatment should be discontinued or modified, for any or all patients. Patients in the SOC cohort could crossover to the last active drug cohort that had not been initiated, if they continued to meet eligibility criteria and the active recruitment of a dosage cohort was ongoing.

All patients were allowed to withdraw from the study at any time, for any reason, in either of the two studies. Patients who completed Studies 006 and 003, including those in the SOC treatment arm, were eligible to participate in the long-term extension phase (SHP633-304 and SHP633-303, respectively) in which patients could receive teduglutide if clinically indicated.

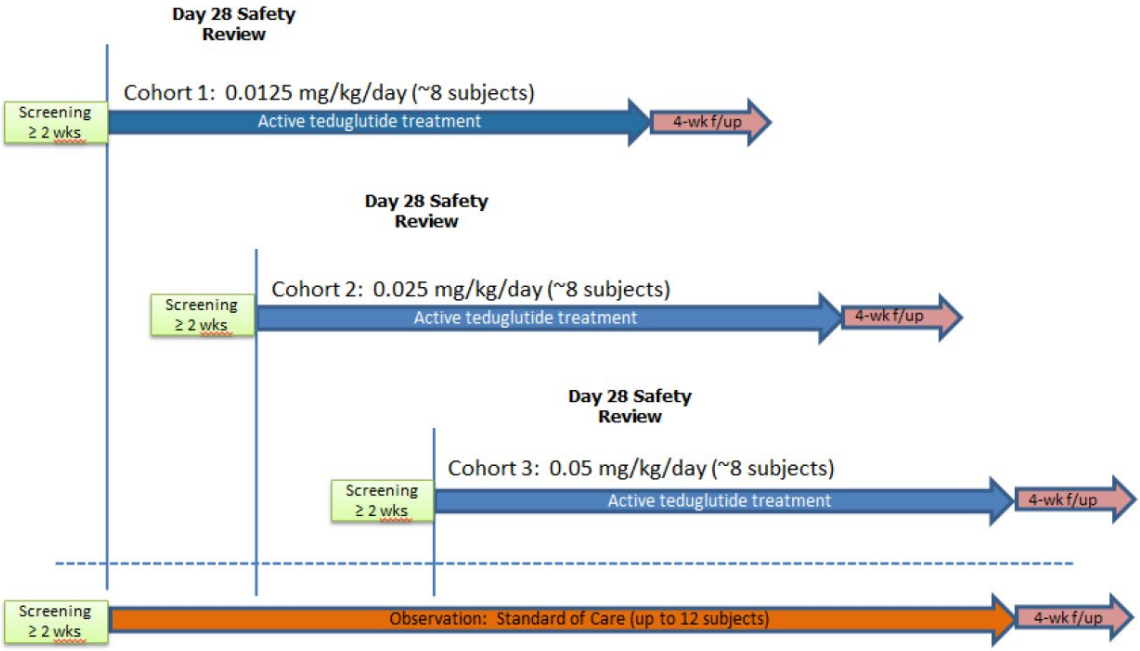
Figure 2: Study Design for Study 006



EOS = end of study; EOT = end of treatment; SOC = standard of care.

Source: Clinical Study Report of Study 006.[1]

Figure 3: Study Design for Study 003



f/up = follow-up.

Source: Clinical Study Report of Study 003.[2]

Populations

Inclusion and exclusion criteria

Both Studies 006 and 003 used the same inclusion and exclusion criteria. Details of the inclusion and exclusion criteria are presented in Table 3.

Overall, pediatric patients one year to 17 years of age with SBS as a result of major intestinal resection (e.g., due to NEC, midgut volvulus, intestinal atresia, or gastroschisis) who required PS that provided at least 30% of caloric and/or fluid/electrolyte needs for more than three months prior to screening were eligible for enrolment. Stable PS was defined as inability to significantly reduce PS, usually associated with minimal or no advance in enteral feeds (e.g., 10% or less change in PS volume or advance in feeds) for at least three months prior to and during screening, as assessed by the investigator. In total, 59 patients and 42 patients were enrolled in Studies 006 and 003, respectively. The key exclusion criteria include patients with: known clinically significant untreated intestinal obstruction; severe, known dysmotility syndrome or persistent, severe, active gastroschisis-related dysmotility prior to screening; major gastrointestinal surgical intervention within three months prior to screening; body weight less than 10 kg at screening and baseline visit; any condition, disease, or circumstance that would put the patient at any undue risk, prevent completion of the study or interfere with analysis of the study results; or previous use of teduglutide or certain medications.

Baseline characteristics

At baseline, patient demographic characteristics were similar between different teduglutide dosage groups. The mean age of the patients who received treatment with teduglutide ranged from 6.2 years to 6.6 years in Study 006 and from 4.5 years to 5.1 years in Study 003. The vast majority of these patients were in the one year to less than 12 years age group in both studies: 46 patients (92%) in Study 006, and 34 patients (92%) in Study 003. Most of the patients treated with teduglutide were white (67% to 81% in Study 006; 75% to 87% in Study 003) and male (67% to 73% in Study 006; 53% to 79% in Study 003). Below-average weight and height measured with respective z scores were observed for patients in the teduglutide treatment groups, except for the weight for those assigned to teduglutide 0.025 mg/kg/day and 0.05 mg/kg/day in Study 003, where near-normal weights were recorded at baseline. In both studies, compared with patients who received teduglutide, patients treated with SOC were younger (mean age: 5.7 years in Study 006; 2.2 years in Study 003), with near-normal average weight and height for age, and fewer were white (22% in Study 006; 60% in Study 003).

The baseline disease characteristics varied across treatment arms in the two studies. The primary underlying causes for SBS were NEC (12% to 22% in Study 006; 13% to 40% in Study 003), midgut volvulus (23% to 42% in Study 006; 25% to 47% in Study 003), intestinal atresia (4% to 8% in Study 006; 13% to 29% in Study 003) and gastroschisis (22% to 54% in Study 006; 20% to 50% in Study 003). Stoma was present in 19% to 33% of the patients in Study 006 and 7% to 13% of patients in Study 003. Colon was preserved in most of the patients: 67% to 96% in Study 006 and 88% to 100% in Study 003. The estimated percentage of remaining colon was 60% to 69% in Study 006 and 67% to 75% in Study 003. The mean length of the remaining small intestine was 38 cm to 47 cm in Study 006, and 28 cm to 66 cm in Study 003. The history of prior PS therapy was not reported in Study 006. [redacted]

Details of the demographic and disease characteristics at baseline are provided in Table 4.

Table 4: Summary of Baseline Characteristics — ITT Set

Title	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)[a]	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)[a]	TED 0.025 mg/kg/d (N = 14)[a]	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Age in years, mean (SD)	6.6 (3.61)	6.2 (3.67)	5.7 (4.72)	5.1 (4.55)	4.6 (3.43)	4.5 (3.16)	2.2 (0.45)
Sex, n (%)							
Male	16 (66.7)	19 (73.1)	6 (66.7)	6 (75.0)	11 (78.6)	8 (53.3)	3 (60.0)
Female	8 (33.3)	7 (26.9)	3 (33.3)	2 (25.0)	3 (21.4)	7 (46.7)	2 (40.0)
Race, n (%)							
White	16 (66.7)	21 (80.8)	2 (22.2)	6 (75.0)	11 (78.6)	13 (86.7)	3 (60.0)
Black or African American	3 (12.5)	3 (11.5)	1 (11.1)	2 (25.0)	1 (7.1)	1 (6.7)	1 (20.0)
Asian	1 (4.2)	1 (3.8)	1 (11.1)	0	0	1 (6.7)	1 (20.0)
Other	4 (16.7)	1 (3.8)	4 (55.5)	0	2 (14.2)	0	0
Weight, z score, mean (SD)	–0.85 (1.08)	–0.88 (1.11)	–0.22 (0.81)	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg, mean (SD)	NR			[redacted]	[redacted]	[redacted]	[redacted]
Height, z score, mean (SD)	–1.28 (1.22)	–1.31 (1.18)	–0.39 (1.59)	NR			
Height, cm, mean (SD)	NR			[redacted]	[redacted]	[redacted]	[redacted]
Head circumference, z score, mean (SD)[b]	–1.79 (0.50)	–0.13 (0.49)	–0.97 (–)	NR			
Primary reason for SBS, n (%)							
Necrotizing enterocolitis	5 (20.8)	3 (11.5)	2 (22.2)	1 (12.5)	2 (14.3)	3 (20.0)	2 (40.0)
Midgut volvulus	10 (41.7)	6 (23.1)	3 (33.3)	2 (25.0)	4 (28.6)	7 (46.7)	2 (40.0)
Intestinal atresia	2 (8.3)	1 (3.8)	0	1 (12.5)	4 (28.6)	2 (13.3)	1 (20.0)
Gastroschisis	6 (25.0)	14 (53.8)	2 (22.2)	2 (25.0)	7 (50.0)	3 (20.0)	0
Long-segment Hirschsprung disease	1 (4.2)	1 (3.8)	2 (22.2)	NR			
Other	0	1 (3.8)	0	2 (25.0)	0	1 (6.7)	0
Patients with stoma, n (%)	5 (20.8)	5 (19.2)	3 (33.3)	1 (12.5)	1 (7.1)	1 (6.7)	0
Jejunostomy[c]	3 (60.0)	4 (80.0)	2 (66.7)	0	0	0	0
Ileostomy[c]	0	1 (20.0)	1 (33.3)	1 (100)	1 (100)	1 (100)	0
Colostomy[c]	2 (40.0)	0	0	0	0	0	0
Patients with any remaining colon, n (%)	22 (91.7)	25 (96.2)	6 (66.7)	7 (87.5)	14 (100.0)	14 (93.3)	5 (100.0)

Title	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)[a]	**TED 0.05 mg/kg/d (N = 26)**	**SOC (N = 9)**	**TED 0.0125 mg/kg/d (N = 8)[a]**	**TED 0.025 mg/kg/d (N = 14)[a]**	**TED 0.05 mg/kg/d (N = 15)**	**SOC (N = 5)**
Estimated % of colon remaining, mean (SD)	60.9 (36.10)	68.8 (30.72)	60.3 (33.45)	75.0 (30.17)	67.1 (34.64)	75.4 (29.77)	66.6 (31.27)
Colon in continuity, n (%) [c]	22 (100)	22 (88.0)	6 (100)	7 (100.0)	12 (85.7)	14 (100.0)	5 (100.0)
Total estimated remaining small intestinal length (cm), mean (SD)	38.20 (38.76)	46.75 (27.90)	45.28 (31.05)	28.1 (25.89)	66.3 (37.19)	32.8 (21.74)	37.4 (25.89)
Distal/terminal ileum present, n (%)	9 (37.5)	9 (34.6)	3 (33.3)	2 (25.0)	1 (7.1)	4 (26.7)	1 (20.0)
Ileocecal valve present, n (%)[e]	6 (66.7)	7 (77.8)	3 (100.0)	2 (100.0)	1 (100.0)	4 (100.0)	1 (100.0)
Length of PS dependence, years, mean (SD)	NR			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intention-to-treat; NR = not reported; PS = parenteral support; SBS = short bowel syndrome; SD = standard deviation; SOC = standard of care; TED = teduglutide.

[a] Not a Health Canada–approved teduglutide dosage.

[b] Head circumference was scheduled to be collected only for patients ≤ 36 months of age at the time of measurement.

[c] Percentages were based on the number of patients with a stoma in each treatment group.

[d] Percentages were based on the number of patients who had remaining colon in each treatment group.

[e] Percentages were based on the number of patients with distal/terminal ileum present in each treatment group.

Source: Clinical Study Reports of Studies 006[1] and 003.[2]

Interventions

In both studies, patients or their parent/guardian decided whether to participate in the teduglutide treatment group or SOC. All patients assigned to teduglutide therapy received SOC. A description of SOC was not provided in either study.

In Study 006, the efficacy and safety of treatment with two dosages of teduglutide were examined. Those who elected to receive teduglutide were randomized into treatment with teduglutide 0.025 mg/kg/day or 0.05 mg/kg/day group for 24 weeks, in a double-blind manner. The actual received dose was calculated based on patient's body weight measured at baseline, and the dose was adjusted as needed based on measurements made at week 12. Adjustment on nutritional support (including PS and EN) were made after review of the intake and output diaries and safety laboratory data.

In Study 003, treatment effect was evaluated for three different dosages of teduglutide: 0.0125 mg/kg/day, 0.025 mg/kg/day, and 0.05 mg/kg/day. The actual received dose was calculated based on patient's body weight measured at baseline. The study drug was administered in an open-label fashion. Patients remained on treatment at their specified dosage throughout the 12-week treatment period unless a safety issue was identified indicating that treatment should be discontinued or modified for any or all patients. No adjustment to dosage was made during the 12-week treatment period. Patients in the SOC cohort could crossover to the last active drug cohort that had not been initiated, if they continued to meet eligibility criteria and the active recruitment of a drug cohort was ongoing. PS adjustments could be made after review of the previous 72 hours' oral fluid intake and urine output data and the patient's safety laboratory data.

Teduglutide 0.05 mg/kg/day is the only Health Canada–approved dosage for children with SBS; however, all available dosages for teduglutide, e.g., 0.0125 mg/kg/day and 0.025 mg/kg/day are included in this CDR review. [redacted]

Outcomes

Change in parenteral feeding and fluid requirements

In Study 006, the primary efficacy end point was weight-normalized reduction from baseline in PS volume of at least 20% at end of treatment (EOT). Responders were defined as patients who achieved a greater than and equal to 20% reduction in PS volume at EOT. [redacted]

[redacted]

In Study 003, the number and percentage of patients who achieved at least a 20% reduction from baseline in weekly PS volume and calories by scheduled visit and at EOT were used to measure the change in parenteral feeding. [redacted]

No information was found for the validity and reliability of the 20% threshold used in the included studies. Similarly, what constitutes minimally clinical important differences in reduction of PS volume is unknown. In the literature, a decrease of at least 20% in parenteral fluid was considered to result in a clinical benefit to adult patients with a history of SBS due to intestinal resection and dependent on PS.[28] [redacted]

In both studies, the analyses on change in parenteral feeding were performed based on two data sources: patient's diary as well as the investigator-prescribed data.

Change in oral feeding and enteral feeding

In both studies, change and per cent change from baseline in average daily weight-normalized actual and prescribed EN volume and calories at each post-baseline visit during the 24-week or 12-week treatment period was calculated. Two sets of results were reported based on two data sources: patient diary data and the investigator-prescribed data.

Proportion of patients weaning from parenteral nutrition

In Study 006, a patient was considered to have achieved independence from PS (completely weaned off PS) at EOT if the investigator prescribed no PS at that visit and there was no use of PS recorded in the patient diary during the week prior to EOT. Enteral autonomy was defined as complete weaning off PS at the EOT, which was at week 24.

In Study 003, completely weaning off parenteral support was determined when there was no PS consumption at the visit before EOT, based on investigator-prescribed data and no PS consumption at EOT based on patient diary data, or no PS consumption at EOT based on investigator-prescribed data.

Urinary/fecal output

This outcome was measured in Study 003; however, details were not provided with regard to the methods used for data collection.

Growth delay

This outcome was measured with change from baseline in actual value of weight and/or height, or weight z score.

Safety

In both studies, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and adverse events (AEs) of special interest were reported. AEs of special interest were pre-specified in the study protocol. TEAEs were defined as AEs that started or worsened on or after the date of first dose for treatment arms and AEs that started or worsened on or after the baseline visit for SOC group.

Statistical Analysis

According to the Clinical Study Reports of Studies 006 and 003, a power calculation was not conducted. The sample size of the two studies was determined based on the small patient population and the feasibility of the study. Due to the limited sample size of the study population, descriptive statistics were used to summarize the sample. For continuous variables, the mean, median, standard deviation (SD), maximum, and minimum values were reported. For categorical variables, the number of patients and relevant percentages were reported. Statistical inference was not made between treatment groups comparisons, and no adjustments for covariates are planned in the statistical analyses. In addition, no adjustment for multiple comparisons was made. There was no interim analysis in these two studies.

Primary Outcome(s) of the Studies

In Study 006, the primary efficacy outcome was weight-normalized reduction in PS volume of at least 20% at EOT compared with baseline. This outcome was analyzed based on patient diary data as well as the investigator-prescribed data.

In Study 006, approximately 26 patients were planned for each of the teduglutide treatment arms and at least eight patients were planned for the SOC treatment arm. At least one patient younger than one year and at least two patients aged 12 years to less than 17 years were planned in each teduglutide dosage group. Sensitivity analyses were conducted for the primary efficacy end point using the per-protocol (PP) set. Both patient diary data and

investigator-prescribed data were used for sensitivity analyses. [redacted]

In Study 003, change in parenteral feeding and fluid requirement was assessed. This was not classified as primary efficacy outcome. It was anticipated that approximately 24 to 36 patients would be enrolled. The actual number of enrolled patients was 42 (eight in the 0.0125 mg/kg/day cohort, 14 in the 0.025 mg/kg/day cohort, 15 in the 0.05 mg/kg/day cohort, and five in the SOC cohort). There was no subgroup analysis in Study 003. Sensitivity analyses were not performed.

In both studies, missing daily PS volume, PS hours per day, and EN volume were not imputed. If there were more than two days of missing diary data within an interval (e.g., a week in Study 006), the interval was classified as missing actual volume information.

Other outcomes of the studies

Change in oral feeding and enteral feeding was measured in the two studies, using both patient diary data and investigator-prescribed data. Proportion of patients weaning off PS was also examined. In addition, growth delay was measured using change in actual height, weight, and weight z score.

Similar to the primary efficacy outcome, these efficacy outcomes were analyzed using descriptive statistics. No missing data imputation was conducted for these outcomes.

Analysis Populations

Study 006

The intention-to-treat (ITT) set included all patients who provided informed consent for the study, satisfied all of the inclusion criteria and none of the exclusion criteria defined in the protocol, and made the choice of treatment arm (e.g., teduglutide or SOC) at the baseline visit. This was the primary population analyzed for efficacy.

The PP set included all patients who completed the study treatment period without protocol violations or other situations that could potentially affect the efficacy conclusions of the study. An efficacy analysis was conducted in the PP set. Sensitivity analysis of the primary efficacy outcome was also performed in the PP set.

The safety set included patients in the teduglutide arm who received at least one dose of teduglutide and had at least one post-baseline safety assessment, as well as patients in the SOC arm who had at least one post-baseline safety assessment.

Study 003

The ITT population included all patients who were enrolled in the trial. This was the primary analysis population analyzed for PK/PD end points.

The PP population included all patients in the ITT population who completed the study without major protocol deviations. This was the secondary analysis population analyzed for PD end points.

The safety population included all patients in the ITT population who received at least one dose of study medication or SOC.

Results

Patient Disposition

In Study 006, a total of 71 patients were screened and 59 were enrolled. Fifty patients were enrolled in the teduglutide treatment arms. Randomization was conducted between the two teduglutide dosage groups (24 with 0.025 mg/kg/day, 26 with 0.05 mg/kg/day). All 50 patients in the teduglutide treatment arm were treated with the assigned dosage. Nine patients enrolled in an SOC arm. In the ITT population, 50 patients were enrolled in the teduglutide treatment arms (24 in the 0.025 mg/kg/day group and 26 in the 0.05 mg/kg/day group), and nine patients in the SOC group. [redacted] All 59 patients completed treatment at week 24 and completed the study. All 59 (100%) enrolled patients were included in the safety set. The safety set included the same patients who were included in the ITT set.

In Study 003, of the 42 patients who entered the study, 37 were treated with teduglutide (eight with 0.0125 mg/kg/day, 14 with 0.025 mg/kg/day, and 15 with 0.05 mg/kg/day) and five received SOC treatment. Of these patients, one in the teduglutide 0.0125 mg group and one in the teduglutide 0.05 mg group did not complete the treatment and were discontinued from the study.

Details of patient disposition for Studies 006 and 003 are provided in Table 5.

Table 5: Patient Disposition

	Study 006			Study 003			
	TED 0.025 mg/kg/d	TED 0.05 mg/kg/d	SOC	TED 0.0125 mg/kg/d	TED 0.025 mg/kg/d	TED 0.05 mg/kg/d	SOC
Screened, N	71			42			
Enrolled	24	26	9	8	14	15	5
Completed treatment, n (%)	24 (100)	26 (100)	9 (100)	7 (87.5)	14 (100)	14 (93.3)	5 (100)
Discontinued, n (%)	0	0	0	1 (12.5)	0	1 (6.7)	0
Reason for discontinuation, n (%)							
Adverse events	0			0	0	0	0
Lost to follow-up				0	0	0	0
Protocol non-compliance				1 (12.5)	0	0	0
Withdrawal of consent				0	0	1 (6.7)	0
ITT, n (%)	24 (100)	26 (100)	9 (100)	8 (100)	14 (100)	15 (100)	5 (100)
PP, n (%)	[redacted]	[redacted]	[redacted]	7 (87.5)	13 (92.9)	14 (93.3)	5 (100)
Safety, n (%)	24 (100)	26 (100)	9 (100)	8 (100)	14 (100)	15 (100)	5 (100)

ITT = intention-to-treat; PP = per-protocol; SOC = standard of care; TED = teduglutide.

Source: Clinical Study Reports of Studies 006[1] and 003.[2]

Exposure to Study Treatments

In Study 006, the number of days exposed to the assigned teduglutide groups was 169 days and 168 days in the 0.025 mg group and 0.05 mg group, respectively.

In Study 003, the number of days exposed to the assigned teduglutide groups was [redacted], [redacted], and [redacted] in the [redacted].

Details of exposure to study treatments are presented in Table 6.

Table 6: Extent of Exposure

	Study 006			Study 003	
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	TED 0.0125 mg/kg/d (N = 5)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)
Extent of exposure, days					
Mean (SD)	169.0 (2.7)	167.8 (1.3)	[redacted]	[redacted]	[redacted]
Median (range)	169.0 (165 to 178)	168.0 (165 to 171)	[redacted]	[redacted]	[redacted]

SD = standard deviation; TED = teduglutide.

Sources: Clinical Study Reports of Studies 006[1] and 003.[2]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. All outcome measures in Studies 006 and 003 were descriptively summarized without statistical tests.

Survival

There were no deaths reported in Studies 006 and 003.

Change in parenteral feeding and fluid requirements

In Studies 006 and 003, parenteral feeding was evaluated using the following measures:

- The percentage of patients with a greater than and equal to 20% reduction in PS volume at EOT (week 24 in Study 006 and week 12 in Study 003) from baseline. This was a primary efficacy outcome in Study 006
- Change from baseline in PS volume to EOT
- Change from baseline in PS days per week or hours per day to EOT

Study 006

In the ITT set, 13 patients (54.2%) in the teduglutide 0.025 mg group, 18 patients (69.2%) in the teduglutide 0.05 mg group, and one patient (11.1%) in the SOC group achieved the primary end point at EOT based on patient diary data. Results of the subgroup analysis based on age (one year to less than 12 years versus 12 years to 17 years) suggested that in the subgroup of patients aged one year to less than 12 years of age, more patients achieved a greater than and equal to 20% reduction in PS volume at EOT, compared with those who received SOC only. When analyzed using the investigator-prescribed data, the percentage

of patients achieving a greater than and equal to 20% reduction in PS volume at the EOT was higher in the two teduglutide dosage groups

compared with SOC, 54.2% versus 69.2% versus 22.2%, respectively. Sensitivity analyses with a PP set showed similar results on the proportion of patients with a greater than and equal to 20% reduction in PS volume at EOT, using both patient diary data and investigator-prescribed data (data not shown).

Both teduglutide groups reported greater reductions in PS volume from baseline to EOT compared with the SOC group. The change (mean ± SD) from baseline in PS volume to EOT was –16.16 ± 10.52 mL/kg/day; –23.30 ± 17.50 mL/kg/day; and –6.03 ± 4.55 mL/kg/day for the teduglutide 0.025 mg group, teduglutide 0.05 mg group, and SOC group, respectively. These results correspond to a per cent change of –36.17%, –41.57%, and –10.21%, respectively.

In addition, patients in the teduglutide groups experienced fewer PS days per week compared with the SOC group, based on patient diary data as well as the investigator-prescribed data. Similarly, patients in the teduglutide groups experienced fewer PS hours per day compared with the SOC group.

Study 003

In the ITT set, one patient (12.5%) in the teduglutide 0.0125 mg group, 10 patients (71.4%) in the teduglutide 0.025 mg group, seven patients (46.7%) in the teduglutide 0.05 mg group, and no patient in the SOC group achieved a greater than and equal to 20% reduction in PS volume at week 12, based on patient diary data. When analyzed using the investigator-prescribed data, the percentage of patients achieving a greater than and equal to 20% reduction in PS volume at week 12 [redacted].

All teduglutide dosage groups experienced greater reductions in PS volume from baseline to week 12 compared with the SOC group. Subgroup analyses of PS volume change from baseline was evaluated in the ITT population by etiology of SBS, remaining length of small intestine, presence of a stoma, and presence of a colon. Due to the small sample size, results of these subset analyses are considered inconclusive (data not shown).

In addition, patients in the teduglutide dosage groups (0.025 mg and 0.05 mg groups) experienced [redacted] at week 12, based on patient diary data as well as the investigator-prescribed data. Patients in the teduglutide dosage groups (0.025 mg and 0.05 mg groups) [redacted], based on patient diary data. Details of change in parenteral feedings are provided in Table 7.

Table 7: Results of Change in Parenteral Feeding/Fluid Requirement — ITT Set

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Patients with ≥ 20% reduction in PS volume							
From patient diary data							
Number of patients analyzed, n	20	25	9	7	14	14	5
Patients with ≥ 20% reduction in PS volume at EOT from baseline, n (%)	13 (54.2)	18 (69.2)	1 (11.1)	1 (12.5)	10 (71.4)	7 (46.7)	0
Patients with < 20% reduction in PS volume at EOT from baseline, n (%)	7 (29.2)	7 (26.9)	8 (88.9)	6 (75.0)	4 (28.6)	[redacted]	5 (100.0)
Missing, n (%)	4 (16.7)	1 (3.8)	0	1 (12.5)	0	[redacted]	0
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]				
From investigator-prescribed data							
Number of patients analyzed, n	24	26	9	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 20% reduction in PS volume at EOT from baseline, n (%)	13 (54.2)	18 (69.2)	2 (22.2)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in PS volume							
From patient diary data							
Number of patients analyzed, n	24	26	9	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD) 006: mL/kg/day 003: L/week	56.84 (25.24)	60.09 (29.19)	79.59 (31.12)	[redacted]	[redacted]	[redacted]	[redacted]
EOT, mean (SD) 006: mL/kg/day 003: L/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	–16.16 (10.52)	–23.30 (17.50)	–6.026 (4.55)	[redacted]	[redacted]	[redacted]	[redacted]

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Per cent change, mean (%)	–36.17 (30.65)	–41.57 (28.90)	–10.21 (13.59)	[redacted]	[redacted]	[redacted]	[redacted]
From investigator-prescribed data							
Number of patients analyzed, n	24	26	9	8	14	15	5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)[b]	–11.28 (15.51)	–22.13 (17.92)	–5.84 (9.80)	–0.43 (0.86)	–2.73 (1.92)	–2.40 (3.50)	0.43 (0.75)
Per cent change, mean (%)[b]	[redacted]	[redacted]	[redacted]	–8.60 (20.38)	–35.61 (26.20)	–36.50 (40.59)	7.38 (12.76)
Change from baseline in PS days per week							
From patient diary data							
Number of patients analyzed, n	24	26	9	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, days/week, mean (SD)	6.5 (1.10)	6.6 (0.79)	6.6 (1.33)	[redacted]	[redacted]	[redacted]	[redacted]
EOT, days/week, mean (SD)	5.8 (2.25)	5.2 (2.47)	6.6 (1.33)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	–0.88 (1.78)	–1.34 (2.24)	0 (0)	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change, mean (%)	–16.03 (31.34)	–21.33 (34.09)	0 (0)	[redacted]	[redacted]	[redacted]	[redacted]
From investigator-prescribed data							
Number of patients analyzed, n	24	26	9	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	–0.79 (1.62)	–1.42 (2.32)	0 (0)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in PS hours per day							
From patient diary data							
Number of patients analyzed, n	24	26	9	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, hours/day, mean (SD)	11.7 (3.03)	11.2 (2.99)	12.6 (5.50)	[redacted]	[redacted]	[redacted]	[redacted]
EOT, hours/day, mean (SD)	9.7 (4.88)	8.1 (4.02)	12.4 (5.42)	[redacted]	[redacted]	[redacted]	[redacted]

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Change from baseline, mean (SD)	–2.47 (2.73)	–3.03 (3.84)	–0.21 (0.69)	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change, mean (%)	–26.04 (31.56)	–26.09 (36.14)	–1.75 (5.89)	[redacted]	[redacted]	[redacted]	[redacted]
From investigator-prescribed data							
Number of patients analyzed, n	24	26	9	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]				
Change from baseline, mean (SD)	–1.48 (3.59)	–1.79 (3.52)	0.11 (0.33)				
[redacted]	[redacted]	[redacted]	[redacted]				

EOT = end of treatment; ITT = intention-to-treat; IV = intravenous; NR = not reported; PS = parenteral support; SD = standard deviation; SOC = standard of care; TED = teduglutide.

Sources: Clinical Study Reports of Studies 006[1] and 003.[2]

Change in oral feeding and enteral feeding

In both studies, enteral feeding was evaluated using the following measure:

- Change from baseline in EN volume

Based on patient diary data, in Study 006, both teduglutide groups experienced greater increase in EN volume from baseline to EOT compared with the SOC group. The mean ± SD change from baseline in EN volume to the EOT was 7.69 ± 13.5 mL/kg/day, 10.96 ± 16.59 mL/kg/day, and 0.74 ± 5.91 mL/kg/day for the teduglutide 0.025 mg group, the teduglutide 0.05 mg group, and the SOC group, respectively. This corresponds to a percentage change of 76.89%, 79.52%, and 2.50%, respectively.

[redacted]

[redacted]

Details of improvement in enteral feeding are shown in Table 8.

Table 8: Results of Change in Enteral Feeding — ITT Set

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Change from baseline in EN volume							
From patient diary data							
Number of patients analyzed, n	23	26	9	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD) 006: mL/kg/day 003: L/week	17.80 (24.45)	27.64 (29.47)	14.04 (18.19)	[redacted]	[redacted]	[redacted]	[redacted]
EOT, mean (SD) 006: mL/kg/day 003: L/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	7.69 (13.46)	10.96 (16.59)	0.74 (5.91)	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change, mean (%)	76.89 (117.19)	79.52 (134.49)	2.50 (33.87)	[redacted]	[redacted]	[redacted]	[redacted]
From investigator-prescribed data							
Number of patients analyzed, n	18	22	5	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	7.67 (17.77)	8.17 (17.87)	0.33 (0.90)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EOT = end of treatment; ITT = intention-to-treat; SD = standard deviation; SOC = standard of care; TED = teduglutide.

Sources: Clinical Study Reports of Studies 006[1] and 003.[2]

Need for dietary adjustment

This outcome was not assessed in the included studies.

Proportion of patients weaning off parenteral support

In Study 006, two patients (8.3%) in the teduglutide 0.025 mg group and three patients (11.5%) in the teduglutide 0.05 mg group achieved enteral autonomy, which was defined as complete weaning off PS at EOT. No patients from the SOC group achieved complete weaning off PS infusion.

In Study 003, one patient (7.1%) in the teduglutide 0.025 mg group and [redacted] in the teduglutide 0.05 mg group achieved complete weaning off PS infusion at week 12.

Table 9: Results of Complete Weaning Off Parenteral Support – ITT Set

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Number of patients analyzed, n	24	26	9	8	14	15	5
Patients with 100% reduction in PS volume at EOT from baseline, n (%)	2 (8.3)	3 (11.5)	0	0	1 (7.1)	[redacted]	0
Patients with < 100% reduction in PS volume at EOT from baseline, n (%)	[redacted]	[redacted]	[redacted]	7 (87.5)	13 (92.9)	14 (93.3)	5 (100)
Missing, n (%)	4 (16.7)	1 (3.8)	0	1 (12.5)	0	0	0

EOT = end of treatment; ITT = intention-to-treat; PS = parenteral support; SD = standard deviation; SOC = standard of care; TED = teduglutide.

Note: A patient was considered to completely wean off PS if the investigator prescribed no PS and there was no use of PS recorded in the patient diary at the scheduled site visit (weaning was evaluated based on physician-prescribed data combined with patient diary data in both studies).

Sources: Clinical Study Reports of Studies 006[1] and 003.[2]

Change in SBS-related symptoms

This outcome was not measured in the included studies.

Urinary/fecal output

This outcome was not measured in Study 006.

[redacted]

Intestinal failure-associated liver disease

This outcome was not measured in the included studies.

Health-related quality of life

This outcome was not measured in the included studies.

Growth delay measured with weight and/or height

This outcome was not measured in Study 006.

In Study 003, change in nutritional status was assessed using weight, weight z score, and height at the EOT. Overall, improvements in weight and height were observed after 12 weeks' treatment with teduglutide or SOC, compared with baseline. However, the weight z score decreased in the teduglutide 0.05 mg group.

Details in changes in weight and height are provided in Table 10.

Table 10: Results of Change in Height and Weight at End of Treatment — ITT Set

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Weight, kg, mean (SD)							
Number of patients analyzed, n	NR			[redacted]	[redacted]	[redacted]	[redacted]
Baseline				[redacted]	[redacted]	[redacted]	[redacted]
EOT				[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				[redacted]	[redacted]	[redacted]	[redacted]
Per cent change				[redacted]	[redacted]	[redacted]	[redacted]
Weight, z score, mean (SD)							
Number of patients analyzed, n	NR			[redacted]	[redacted]	[redacted]	[redacted]
Baseline				[redacted]	[redacted]	[redacted]	[redacted]
EOT				[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				[redacted]	[redacted]	[redacted]	[redacted]
Per cent change				NR			
Height, cm, mean (SD)							
Number of patients analyzed, n	NR			[redacted]	[redacted]	[redacted]	[redacted]
Baseline				[redacted]	[redacted]	[redacted]	[redacted]
EOT				[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				[redacted]	[redacted]	[redacted]	[redacted]
Per cent change				[redacted]	[redacted]	[redacted]	[redacted]

EOT = end of treatment; ITT = intention-to-treat; NR = not reported; SD = standard deviation; SOC = standard of care; TED = teduglutide.

Note: Change in height z score was not reported at the study end point in Study 003.

Sources: Clinical Study Reports of Studies 006[1] and 003.[2]

Neurodevelopmental delay

This outcome was not measured in the included studies.

Need for intestinal transplantation

This outcome was not measured in the included studies.

Need for bowel lengthening procedure

This outcome was not measured in the included studies.

Health care resource utilization

This outcome was not measure in the included studies.

Harms

Only those harms identified in the review protocol are reported below. See Table 11 for detailed harms data.

Adverse events

During the treatment, almost all patients reported AEs in the two studies. The majority of the AEs were mild or moderate in severity. The common AEs were vomiting (31% to 56% in Study 006; 36% to 47% in Study 003); diarrhea (11% to 33% in Study 006; 7% to 20% in Study 003); abdominal pain (17% to 23% in Study 006; 7% to 27% in Study 003); pyrexia (33% to 44% in Study 006; 14% to 47% in Study 003); upper respiratory tract infection (URTI) (29% to 44% in Study 006; 25% to 40% in Study 003); nasopharyngitis (17% to 23% in Study 006; 7% to 25% in Study 003); dehydration (4% to 33% in Study 006; 7% to 20% in Study 003); headache (11% to 19% in Study 006; 13% to 14% in Study 003); and cough (33% to 39% in Study 006; 13% to 27% in Study 003). The most common AEs reported in Study 006 by the pediatric patients treated with 0.05 mg/kg teduglutide were pyrexia (42%), cough (39%), vomiting (31%), URTI (31%), abdominal pain (23%), and nasopharyngitis (23%).[26] Although the majority of the AEs were reported by patients treated with teduglutide, the risk of certain AEs was higher in the SOC group, such as vomiting, pyrexia, and URTI.

Serious adverse events

In Study 006, the incidence of SAEs were higher in teduglutide-treated groups (63% to 77%) than in the SOC group (44%), while in Study 003, treatment with a higher dosage of teduglutide (0.05 mg/kg/day) or SOC was associated with more SAEs. The common SAEs in the included studies were pyrexia, dehydration, and central line-related breakage and infection.

Withdrawal due to adverse events

No patients withdrew due to AEs in either study.

Mortality

No deaths were reported in either study.

Notable harms

During the study, there were no reports of gastrointestinal tract polyp formation, biliary complications, neoplasia, or intestinal obstruction in either study. At the end of the study, antibody development was found in eight patients in Study 006 (three patients in the teduglutide 0.025 mg group, five patients in the teduglutide 0.05 mg group) and one patient (in the teduglutide 0.025 mg group) in Study 003.

Table 11: Summary of Harm Outcomes — Safety Set

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Patients with ≥ 1 AE, n (%)							
	24 (100)	25 (96.2)	9 (100)	8 (100)	14 (100)	15 (100)	5 (100)
Most common events[a]							
Vomiting	10 (41.7)	8 (30.8)	5 (55.6)	0	5 (35.7)	7 (46.7)	0
Diarrhea	8 (33.3)	3 (11.5)	1 (11.1)	0	1 (7.1)	3 (20.0)	1 (20.0)
Abdominal pain	4 (16.7)	6 (23.1)	0	1 (12.5)	1 (7.1)	4 (26.7)	1 (20.0)
Abdominal pain upper	3 (12.5)	3 (11.5)	1 (11.1)	NR			
Nausea	3 (12.5)	3 (11.5)	1 (11.1)	1 (12.5)	2 (14.3)	2 (13.3)	0
Pyrexia	8 (33.3)	11 (42.3)	4 (44.4)	0	2 (14.3)	7 (46.7)	2 (40.0)
Injection site bruising	3 (12.5)	1 (3.8)	0	0	0	3 (20.0)	0
URTI	7 (29.2)	8 (30.8)	4 (44.4)	2 (25.0)	4 (28.6)	4 (26.7)	2 (40.0)
Nasopharyngitis	4 (16.7)	6 (23.1)	2 (22.2)	2 (25.0)	0	1 (6.7)	0
Device-related infection	1 (4.2)	5 (19.2)	0	NR			
Rhinitis	1 (4.2)	5 (19.2)	0	NR			
Viral infection	3 (12.5)	3 (11.5)	1 (11.1)	NR			
Gastric viral	3 (12.5)	0	0	1 (12.5)	0	2 (13.3)	1 (20.0)
Elevated ALT	7 (29.2)	2 (7.7)	0	0	1 (7.1)	1 (6.7)	0
Dehydration	8 (33.3)	1 (3.8)	0	1 (12.5)	0	1 (6.7)	1 (20.0)
Headache	3 (12.5)	5 (19.2)	1 (11.1)	1 (12.5)	2 (14.3)	2 (13.3)	0
Catheter-related complication	NR			3 (37.5)	4 (28.6)	2 (13.3)	1 (20.0)
Cough	2 (8.3)	10 (38.5)	3 (33.3)	1 (12.5)	2 (14.3)	4 (26.7)	1 (20.0)
Constipation	1 (4.2)	1 (3.8)	0	0	0	2 (13.3)	1 (20.0)
Fatigue	0	1 (3.8)	0	0	1 (7.1)	4 (26.7)	0
Patients with ≥ 1 SAE, n (%)							
	15 (62.5)	20 (76.9)	4 (44.4)	3 (37.5)	6 (42.9)	8 (53.3)	3 (60.0)
Most common events[a]							
Pyrexia	4 (16.7)	7 (26.9)	1 (11.1)	0	1 (7.1)	3 (20.0)	2 (40.0)
Dehydration	4 (16.7)	0	0	NR			
Catheter-related complication	NR			0	2 (14.3)	1 (6.7)	1 (20.0)
Central line infection	NR			0	3 (21.4)	1 (6.7)	0
Patients who stopped treatment due to adverse events, n (%)							
	0	0	0	0	0	0	0
Deaths, n (%)	0	0	0	0	0	0	0
Notable harm, n (%)							
GI polyps	0	0	0	0	0	0	0
Neoplasia	0	0	0	NR			
Intestinal obstruction	NR			0	0	0	0

	Study 006			Study 003			
	TED 0.025 mg/kg/d (N = 24)	TED 0.05 mg/kg/d (N = 26)	SOC (N = 9)	TED 0.0125 mg/kg/d (N = 8)	TED 0.025 mg/kg/d (N = 14)	TED 0.05 mg/kg/d (N = 15)	SOC (N = 5)
Biliary complications	NR			0	0	0	0
Antibody development	Positive at baseline: 1 (4.2) Positive at week 24: 3 (12.5)	Positive at baseline: 0 Positive at week 24: 5 (19.2)	n/a	Positive at week 16: 0	Positive at week 16: 1 (7.1)	Positive at week 16: 0	n/a

AE = adverse event; ALT = alanine aminotransferase; GI = gastrointestinal; n/a = not applicable; NR = not reported; SAE = serious adverse events; SOC = standard of care; TED = teduglutide; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

[a] Frequency of greater than 10%.

Source: Clinical Study Reports of Studies 006[1] and 003.[2]

Critical Appraisal

Internal validity

Both included studies were labelled as phase III trials by the investigator, although one trial had a dose ranging design (Study 003). Neither included a randomized comparison of teduglutide with SOC. Patients or their parents determined whether they would receive treatment with teduglutide or SOC. A randomized study design may not be feasible for clinical trials of a rare disease. In Study 006, randomization was conducted between low and high teduglutide dosage. Appropriate methods of randomization (using a central interactive voice response system) and blinding (investigators and patients) were reported. Study 003 was an open-label non-randomized trial, with staggered entry of three dosage cohorts. Systematic differences with respect to patients' baseline characteristics between the teduglutide treatment groups and the SOC group, e.g., age, race, nutritional status, underlying causes for SBS, and remaining small intestinal length, were observed. The imbalanced baseline characteristics may have an impact on data interpretation and bias the results. Patients in the teduglutide groups tended to be older and have more severe conditions. Compared with younger patients with milder disease, it may be challenging for them to grow adequate bowel length and achieve enteral autonomy. Therefore, this may conservatively bias the results toward the non-teduglutide treatment, however, it is uncertain to what extent the imbalances in the patient's baseline characteristics would influence the relative treatment effect between teduglutide and SOC. Almost all patients completed the assigned treatment and the dropout was very low. This was expected given the relative lack of treatment options for these patients and the manageable side effects.

SBS is a rare condition, thus it is challenging to recruit a large number of patients to clinical trials. The small number of study participants makes data interpretation difficult when the observed treatment effect could be due to chance, or alternatively, a true effect may not be detected due to insufficient power of the trial. In addition, sensitivity analyses and subgroup analyses are not easy to perform in these small trials. For example, in Study 006, there were only four patients (6.8%) in the subgroup of 12 years to 17 years of age. Therefore, treatment effect of the study drug in the interested subgroups cannot be fully explored. Data in both studies were descriptively reported without performing statistical testing; no adjustments on covariates were planned and there was no adjustment on multiple comparisons.

SOC was the comparator in Studies 006 and 003, however it was not described in detail. It is unknown whether the SOC treatments in different countries or regions were similar. In addition, the baseline characteristics of the study participants suggested that white patients may prefer teduglutide therapy to SOC. By-country or by-region effect could also impact the results. Interpretation of the results of between-group comparisons should be with caution.

Several of the end points concerned the amount of PS given. In both studies, a protocol-specified dose adjustment regimen for PS was adopted. It is reasonable to assume that treatment compliance was high in the study population, when there was no dropout during the 24-week treatment in Study 006 and only two patients discontinued the 12-week treatment in Study 003. Effect of teduglutide on reducing PS volume and increasing EN volume was examined using two data sets: patient-recorded diary data as well as investigator-prescribed data. Comparable results were reported between the two data sets with respect to change in PS volume or the proportion of responders at EOT. Sensitivity analysis using PP set was conducted in Study 006. The number of patients in the PP set was close to the ITT set, and results of the sensitivity analysis were also similar to the primary efficacy analysis using an ITT set.

The primary end points depended on patient/caregiver records. However, there was no detail provided with respect to data verification in the patient's diaries. It is also unclear how patients or caregivers received training in drug administration in the included studies.

A reduction of greater than and equal to 20% in PS volume was the main efficacy outcome measure in both studies. Although this is commonly used in clinical trials as well as in practice, there is a lack of underlying scientific basis for the use of 20% as a threshold at present.

The control group (SOC) was very small in both cases. There were nine and five patients in the SOC arm in Study 006 and Study 003, respectively. This may lead to highly imprecise measures of the study end points. In Study 003, patients initially treated with SOC had an opportunity to switch to teduglutide therapy, which made data analysis more complicated. Furthermore, there was no information provided regarding the crossover. The number of patients who switched was unknown. The methods used for data analysis in these patients were also not described.

Some of the important clinical outcomes for patients with SBS were not measured in the included studies, such as health-related quality of life, change in SBS-related symptoms and intestinal failure-associated liver disease.

Missing data were reported for most of the outcome measures in the two studies; however, it is unclear whether the patient data were missing at random or not.

External validity

According to the clinical experts involved in the review, the two studies used more stringent exclusion criteria for patient recruitment than are usually observed in clinical practice. In addition, the study population was older and is representative of more severe disease, compared with what can be usually seen in Canadian practice, based on the patients' baseline characteristics. However, according to the experts, the study results are likely generalizable to the Canadian patient population.

Three dosages of teduglutide were evaluated in the included studies, however, only the dosage of 0.05 mg/kg/day is approved by Health Canada for children with SBS at present.

Due to the relatively short duration (12 weeks to 24 weeks) of the included studies, some important clinical outcomes cannot be sufficiently examined, such as survival, growth failure, need for intestinal transplantation, and certain harm outcomes (e.g., colon polyps, neoplasia) that may be related to the use of the study drug.

Indirect Evidence

There is no indirect comparison analysis submitted for this review.

Other Relevant Studies

Long-term Extension Studies

The following section provides a summary and critical appraisal of Study SHP633-303 and Study SHP633-304 (herein referred to as Studies 303[29] and 304,[30] respectively), which were phase III, open-label extension trials designed to assess the safety and long-term efficacy of teduglutide treatment in pediatric patients with SBS who completed Study 003 and Study 006, respectively. The studies did not meet the inclusion criteria listed in

Table 2 due to their non-randomized design. Results for the studies are summarized below.

Study Design

Studies 303 and 304 were extension periods of Studies 003 and 006 (the core studies), respectively; and were designed to evaluate the safety and long-term efficacy of teduglutide in pediatric patients with SBS. Both studies were phase III, open-label, and currently ongoing. Study 303 consisted of a retrospective and a prospective period. Once patients (or caregivers) provided informed consent and entered the open-label study, data were retrospectively collected for the period between the end of study 003 and the beginning of study 303 using medical reports (2.4 years to 3.3 years; N = 29). Patients were then followed up prospectively for a period of at least six months (greater than and equal to six months or 24 weeks for [redacted] and greater than and equal to 22 weeks for [redacted]), during which data were collected using intake diaries and PS prescription. Patients had the opportunity to consent to retrospective data collection only, without enrolling in the prospective study. Study 304 (greater than and equal to six months or 24 weeks of follow-up for [redacted] and greater than and equal to four months or 16 weeks of follow-up for [redacted]) consisted of a prospective period, designed and conducted identically to the prospective period of Study 303; patients entered immediately after completing Study 006. For both studies, only interim results were reported, consisting of all data from the retrospective period of the study (Study 303) and at least six months (24 weeks) of prospective data (both studies). The maximum duration of participation in both studies was approximately three years.

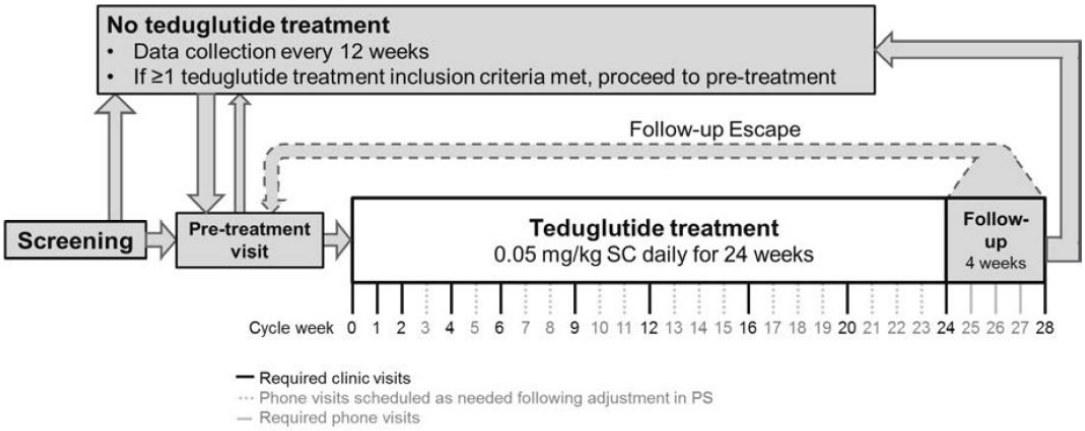
The main criteria for inclusion in the core studies were children and adolescents aged one year to 17 years with SBS who had stable PS requirements (unable to reduce PS or advance enteral feeds) for at least three months prior to screening. All patients who completed the core studies were eligible to continue in the extension period, regardless of their treatment assignment in the core study.

Treatment during the extension period consisted of multiple recurring teduglutide treatment or no teduglutide cycles, with crossover allowed depending on the disease course. Each teduglutide cycle consisted of a 24-week block of teduglutide treatment, followed by 4-week

follow-up period to evaluate whether continued teduglutide was needed. The duration of the no teduglutide cycles was not pre-specified, although patients were assessed every 12 weeks during a no teduglutide period. At any point during the study, including during or after a no teduglutide period or follow-up period, patients could be assessed for treatment with teduglutide. Patients were eligible for teduglutide treatment if they were unable to reduce PS burden significantly (among teduglutide-naive patients), or clinically deteriorated or stopped improving (PS burden increased) at any time after discontinuing teduglutide. It was not mentioned if the dose and treatment schedules between the retrospective and prospective period were similar or different in Study 303.

A schematic diagram of the prospective period of Studies 303 and 304 are given in Figure 4.

Figure 4: Schematic Design of Studies 303 (Prospective Period) and 304



SC = subcutaneous.

Sources: Study 303 CSR,[29] Study 304 CSR.[30]

Populations

Demographics and baseline characteristics

The demographics and clinical characteristics at baseline differed between the treatment arms in all studies, and between retrospective and prospective follow-up periods in Study 303. However, given the open-label and non-randomized design of the trials, coupled with small number of patients in any group, the varying distribution of baseline characteristics is expected. Overall, the majority of the patients were male, white, and showed below-average weight and height, particularly in the teduglutide-treated arms Table 12.

Study 303

[redacted]

[redacted]

[redacted]

Study 304

The mean age of patients was similar in all treatment arms (6.1 years across all arms). The most common primary causes of SBS were gastroschisis, midgut volvulus, and NEC. The mean small intestine length was 44.2 cm and 29.8 cm among patients receiving teduglutide [redacted]

Table 12: Demographics and Baseline Characteristics — Studies 303 and 304

Characteristic	Study 303				Study 304[b]			
	Retrospective Period[a]		Prospective Period[b]					
	TED/NTT (N = 24)	TED/TED (N = 5)	TED/NTT (N = 8)	TED/TED (N = 16)	NTT/NTT (N = 6)	NTT/TED (N = 2)	TED/NTT (N = 3)	TED/TED (N = 44)
Age at baseline (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.2 (3.55)
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29 (65.9)
Race, n (%) White Black Asian Other Not allowed based on local regulations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33 (75.0)
Weight z score at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–0.76 (0.99)
Height z score at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–1.24 (1.22)
BMI z score at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.03 (1.00)
Primary reason for diagnosis of SBS, n (%)								
Necrotizing enterocolitis			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (15.9)
Midgut volvulus			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15 (34.1)
Intestinal atresia			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2 (4.5)
Gastroschisis			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18 (40.9)

Characteristic	Study 303				Study 304[b]			
	Retrospective Period[a]		Prospective Period[b]					
	TED/NTT (N = 24)	TED/TED (N = 5)	TED/NTT (N = 8)	TED/TED (N = 16)	NTT/NTT (N = 6)	NTT/TED (N = 2)	TED/NTT (N = 3)	TED/TED (N = 44)
Long-segment Hirschsprung disease								1 (2.3)
Patients with a stoma, n (%)								9 (20.5)
Type of stoma, n (%)								
Jejunostomy								
Ileostomy/ Colostomy								
Patients with any remaining colon, n (%)								
Estimated % of colon remaining, Mean (SD)								
Colon in continuity, n (%)								
Total estimated remaining small intestinal length (cm), mean (SD)								43.5 (34.37)
Distal/terminal Ileum present, n (%)								
Ileocecal valve present, n (%)								

BMI = body mass index; NTT = no teduglutide treatment; SBS = short bowel syndrome; SD = standard deviation; TED = teduglutide.

Notes:

TED/NTT: Patients who received teduglutide in the core study but not during the extension study;

TED/TED: Patients who received teduglutide in both the core and extension study;

NTT/NTT: Patients who did not receive teduglutide in either the core or extension study;

NTT/TED: Patients who did not receive teduglutide in the core study but subsequently received teduglutide in the extension study.

Z score was calculated as (observed value – median value of the reference population) / standard deviation value of reference population. Z score calculation charts from Centers for Disease Control and Prevention (age ≥ 2 years old) and World Health Organization (age < 2 years old) were used for calculation.

Baseline was defined as the baseline value in the core study.

[a] All retrospective patients.

[b] Safety population.

Sources: Clinical Study Reports of Studies 303[29] and 304.[30]

Interventions

In both studies, teduglutide 0.05 mg/kg was administered by subcutaneous injection once daily into the abdomen, thigh, or arm. Dose was given at approximately the same time each day. During the extension period, patients underwent multiple no teduglutide periods and/or multiple 28-week teduglutide treatment cycles, depending on the disease course. If a patient discontinued a teduglutide cycle prematurely, he/she could enter a no teduglutide period and could have been evaluated for subsequent teduglutide eligibility as per above. Each teduglutide cycle consisted of a 24-week block of teduglutide treatment, followed by a 4-week follow-up period. The duration of the no teduglutide cycles was not pre-specified, although patients were assessed every 12 weeks during a no teduglutide period. Notably, the dose and treatment schedules used during the retrospective period in Study 303 were not given. Patients were classified into one of the following treatment groups depending on the treatment received during the core and extension study:

- TED (teduglutide)/NTT (no teduglutide treatment): Patients who received teduglutide in the core study but not during the extension study.
- TED/TED: Patients who received teduglutide in both the core and extension study.
- NTT/NTT: Patients who did not receive teduglutide in either the core or extension study.
- NTT/TED: Patients who did not receive teduglutide in the core study but subsequently received teduglutide in the extension study.

Studies 303 and 304 were open-label trials; therefore, treatment assignment was not concealed. Patients were assessed for teduglutide treatment eligibility at any point during the study, including during or after a no teduglutide period or follow-up period. [redacted]

Standard medical therapy for SBS was continued throughout the studies. Concomitant treatments included all non-study treatments (medications, herbal treatments, vitamins, invasive, and diagnostic procedures). Concomitant teduglutide, native/synthetic GLP-2 or GLP-1 analogues, octreotide or dipeptidyl peptidase-4 inhibitors, and biological therapy (e.g., antitumor necrosis factor) were prohibited during the study.

Outcomes

Clinical benefit was assessed by the proportion of patients achieving a greater than and equal to 20% reduction in PS volume from baseline in the core study. A number of PS parameters were collected, including volume (mL/kg/day), infusion time (hours per day and days per week of PS), and complete weaning off PS (defined as no PS at that visit and the visit prior). PS data were recorded using patient intake diary (completed by patient/parent/guardian) and investigator-prescribed data. Body weight and height were measured, and a z score was calculated by the sponsor using the site-provided data. A number of health-related quality of life (HRQoL) assessments were captured but are not included in the interim report.

The following safety end points assessed were relevant for this review: any AEs, SAEs, urine and stool output, and antibody to teduglutide.

Statistical Analysis

No formal statistical analyses were conducted due to the small sample size in both studies. Descriptive statistics was used instead to summarize the results of continuous and categorical variables and presented by study visit and time point. [redacted]

Efficacy end points were analyzed at the end of each teduglutide treatment period (week 24 or EOT), and at each study visit, relative to the baseline of the core study and/or first exposure to teduglutide.

Safety end points were also summarized descriptively. Analysis of HRQoL data was not performed for this interim analysis.

Disposition

A total of 40 patients completed Study 003, and 29 of these were screened and enrolled in Study 303. All 29 patients consented for the retrospective period, and 24 patients further consented for the subsequent prospective period. At the time of the data cut-off, none of the 24 patients had completed or been discontinued from the prospective follow-up. [redacted]

Fifty-nine patients completed Study 006, of whom 55 were screened and enrolled in Study 304. [redacted]

There was no mention in either study of how many patients switched from no teduglutide to teduglutide or vice versa, or how many times the crossover occurred in a given patient.

Table 13: Disposition in Studies 303 (Prospective Period) and 304

Category	Study 303		Study 304			
	TED/NTT (N = 8)	TED/TED (N = 16)	NTT/NTT (N = 6)	NTT/TED (N = 2)	TED/NTT (N = 3)	TED/TED (N = 44)
Screened patients	29		55			
Ongoing patients at interim analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early study discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by Parent/Guardian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician Decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol Deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of Efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; NTT = no teduglutide; TED = teduglutide.

Note: Listings were based on the All Subjects Screened Set (SRN), defined as all patients who provided signed informed consent for the study.

Sources: Clinical Study Reports of Studies 303[29] and 304.[30]

Analysis Populations

Unless specified otherwise, all efficacy and safety analyses were performed in the safety population, defined as all enrolled patients who provided informed consent for the prospective portion and met all the inclusion criteria of the respective study. All participating patients were included for the retrospective analyses in Study 303.

Exposure to Study Treatments

Exposure to teduglutide in both studies is presented in Table 14. For the five patients receiving teduglutide during the retrospective period in Study 303, the mean exposure to teduglutide was 42.9 weeks. [redacted] Notably, these patients started teduglutide treatment between week 78 and week 96 following the completion of the core study. During the prospective period, the mean exposure to teduglutide in the 16 patients in the TED/TED arm was 26.1 weeks. Of these, 13 patients had 24 weeks to less than 48 weeks exposure and three had less than 24 weeks of exposure. A total of 13 patients completed teduglutide C1 (out of 16), [redacted]

[redacted]

[redacted]

Table 14: Exposure to Study Drug

Parameter	Study 303		Study 304	
	Retrospective TED/TED (N = 5)	Prospective TED/TED (N = 16)	NTT/TED (N = 2)	TED/TED (N = 44)
Extent of exposure (weeks)				
Mean (SD)	42.9 (17.92)	[redacted]	[redacted]	[redacted]
Median (range)	40.29 (18.29 to 66.57)	[redacted]	[redacted]	[redacted]

NTT = no teduglutide; SD = standard deviation; TED = teduglutide.

Note: Extent of exposure was calculated as the sum of all the teduglutide prescription durations.

Sources: Clinical Study Reports of Studies 303[29] and 304.[30]

Efficacy

Overall, the small number of patients, imbalance between the treatment arms, and provision to crossover between treatments without any information on when or how many times crossover occurred prevent any conclusion from being drawn regarding comparative treatment efficacy. In Study 303, data for the retrospective period were collected using historical PS prescription, as patients did not complete diaries during this period. On the other hand, data for the prospective period in Study 303 as well as in Study 304 were based on the patient diary data and the investigator-prescribed data (captured in the eCRF). Although the diary and prescribed data were similar, the sponsor mentioned that the diary data were more representative of patients' parenteral nutrition intake. Therefore, only the diary data are presented for the prospective period.

Among the patients receiving teduglutide during the extension period in both studies, the summary of efficacy data at treatment C1 will be focused on primarily in this report. This is because the majority of the TED/TED patients completed teduglutide C1; none of the patients in either study completed C2 at the time of data cut-off date. Patients who received no teduglutide during the extension period had reached the third no teduglutide visit (NT3) at the data cut-off date, i.e., 36 weeks of follow-up. However, the summary of efficacy data for no teduglutide periods will be limited to no teduglutide period 1 (NT1), since patients receiving teduglutide in either study had a single no teduglutide visit.

Greater than and equal to 20% reduction in PS volume

Study 303

[redacted]

[redacted]

Table 15: Summary of ≥ 20% Reduction in PS Volume — Study 303 (Retrospective Period)

Visit Parameter, n (%)	TED/NTT (N = 24)	TED/TED (N = 5)
[redacted]		

Visit Parameter, n (%)	TED/NTT (N = 24)	TED/TED (N = 5)
[redacted]	[redacted]	[redacted]

NTT = no teduglutide treatment; PS = parenteral support; TED = teduglutide.

[redacted]

Source: Clinical Study Report of Study 303.[29]

During the prospective period of Study 303, the number of patients in the TED/TED arm achieving a greater than and equal to 20% reduction in PS volume [redacted]; [redacted] at C1 day 1 (C1D1) compared with [redacted] at teduglutide C1 EOT. [redacted]. In the TED/NTT arm, [redacted] achieving a greater than and equal to 20% reduction in PS volume at [redacted].

Study 304

In Study 304, the number of patients in the TED/TED arm who achieved a greater than and equal to 20% reduction in PS volume [redacted] C1D1 [redacted] at C1 EOT. [redacted]. For the no teduglutide period, [redacted] in the NTT/NTT arm achieved this end point at each no teduglutide visit. [redacted].

The number and percentage of patients who achieved a greater than and equal to 20% reductions in weight-normalized PS volume (mL/kg/day) from baseline in both the prospective period of Study 303 and Study 304 are presented by treatment cycle in Table 16.

Table 16: Summary of ≥ 20% Reduction in PS Volume — Studies 303 (Prospective Period) and 304

	Study 303		Study 304			
TED Treatment Periods		**TED/TED (N = 16)**		**NTT/TED (N = 2)**		**TED/TED (N = 44)**
Day 1, N		[redacted]		[redacted]		[redacted]
C1D1, n (%)		[redacted]		[redacted]		[redacted]
Missing, n (%)		[redacted]		[redacted]		[redacted]
C1 EOT, N		[redacted]		[redacted]		[redacted]
C1 EOT, n (%)		[redacted]		[redacted]		[redacted]
Missing, n (%)		[redacted]		[redacted]		[redacted]
Week 28, N		[redacted]		[redacted]		[redacted]
Week 28, n (%)		[redacted]		[redacted]		[redacted]
Missing, n (%)		[redacted]		[redacted]		[redacted]
C2D1, N		[redacted]		[redacted]		[redacted]
C2D1, n (%)		[redacted]		[redacted]		[redacted]
Missing, n (%)		[redacted]				[redacted]
C2 EOT, N		[redacted]		[redacted]		[redacted]
C2 EOT, n (%)		[redacted]				[redacted]
Missing, n (%)		[redacted]				[redacted]
No TED Treatment Periods	**TED/NTT (N = 8)**	**TED/TED (N = 16)**	**NTT/NTT (N = 6)**	**NTT/TED (N = 2)**	**TED/NTT (N = 3)**	**TED/TED (N = 44)**
NT1, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT2, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT3, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C1(2)D1 = cycle 1(2) day 1; EOT = end of treatment; PS = parenteral support; NT(T) = no teduglutide (treatment period); TED = teduglutide.

Note: Per cent reduction was calculated as (change from baseline at the week / baseline value) x 100. Baseline was defined as the baseline visit in the core study.

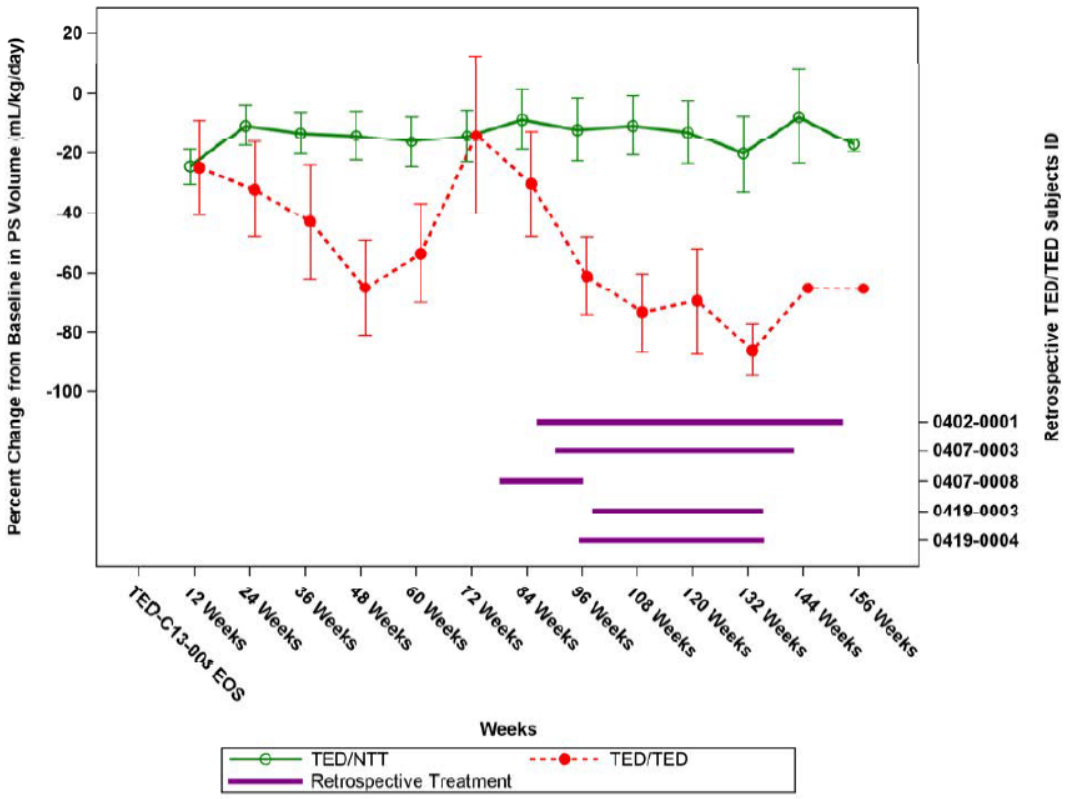
Source: Clinical Study Reports of Studies 303[29] and 304.[30]

Change in PS volume

Study 303

During the retrospective period, reductions in mean prescribed PS volume were [redacted] in the TED/TED arm [redacted]. In the TED/NTT arm [redacted], the mean prescribed PS volume [redacted]. Figure 5 shows the per cent change from baseline in retrospective prescribed PS volume (mL/kg/day) by 12-week intervals.

Figure 5: Per Cent Change From Baseline in Prescribed PS Volume in Retrospective Period of Study 303



PS = parenteral support; NTT = no teduglutide treatment; SE = standard error; TED = teduglutide.

Note: Per cent change was calculated as (change from baseline at the week / baseline value) x 100. Baseline was defined as the baseline visit in the core study.

Source: Clinical Study Report for Study 303.[29]

During the prospective period of Study 303, the mean PS volume [redacted]. Among patients in the TED/TED arm, the mean PS volume [redacted] at teduglutide C1 EOT from baseline. [redacted]. During the no teduglutide period, patients in both TED/NTT and TED/TED arms [redacted]. Among patients in the

TED/NTT arm, the mean PS volume [redacted]

Study 304

The mean PS volume [redacted]. Among patients who received teduglutide during the extension period, there was [redacted] and [redacted] in the NTT/TED and TED/TED arm, respectively. [redacted]. During the no teduglutide period, patients [redacted]. Of these, patients in NTT/NTT arm [redacted] in mean PS volume over time. [redacted]

Table 17 shows the change and per cent change from baseline in PS volume (mL/kg/day) for both the prospective period of Studies 303 and 304.

Table 17: Change From Baseline in PS Volume — Studies 303 (Prospective Period) and 304

	Study 303		Study 304			
TED Treatment Periods		**TED/TED (N = 16)**		**NTT/TED (N = 2)**		**TED/TED (N = 44)**
Baseline, n		15		[redacted]		39
Mean (SD)		61.35 (24.13)		[redacted]		61.33 (27.55)
C1 EOT, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
Week 28, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]				[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
C2 EOT, n		[redacted]				[redacted]
Mean (SD)		[redacted]				[redacted]
Change from baseline, mean (SD)		[redacted]				[redacted]
% change from baseline, mean (SD)		[redacted]				[redacted]

	Study 303		Study 304			
TED Treatment Periods		**TED/TED (N = 16)**		**NTT/TED (N = 2)**		**TED/TED (N = 44)**
No TED Treatment Periods	**TED/NTT (N = 8)**	**TED/TED (N = 16)**	**NTT/NTT (N = 6)**	**NTT/TED (N = 2)**	**TED/NTT (N = 3)**	**TED/TED (N = 44)**
Baseline, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT1, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT2, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]		[redacted]			
% change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT3, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]			
% change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C1(2)D1 = cycle 1(2) day 1; EOT = end of treatment; NT(T) = no teduglutide (treatment period); SD = standard deviation; TED = teduglutide.

[redacted]

Note: Based on patient diary data.

Sources: Clinical Study Reports of Studies 303[29] and 304.[30]

Change in days per week of PS /reduction in PS infusion time

Prescribed hours per day were summarized for observed values only; changes from baseline were not presented as no hours per day were collected in the core study. Prescribed hours per day of infusion time were averaged over the days in which PS if given, whereas actual hours per day were averaged over all days, even when no PS was given.

Study 303

During the retrospective period, teduglutide treatment was temporally associated with reductions in mean PS days per week and hours per day infusion time, as shown by the overall decrease in both parameters in the retrospective TED/TED arm over time. [redacted]

[redacted]

These findings are consistent with a greater than and equal to 20% reduction in PS volume as shown earlier. Patients in the retrospective TED/NTT arm showed relatively no change in mean hours per day or days per week of prescribed PS infusion time. Results for patients' changes from baseline in hours per day and days per week of PS infusion time during the retrospective period are summarized by 12-week intervals in Table 18.

Table 18: Hours per Day and Days per Week of Prescribed Parenteral Support — Study 303 (Retrospective Period)

Visit Parameters	Hours per Day		Days per Week	
	TED/NTT (N = 24)	TED/TED (N = 5)	TED/NTT (N = 24)	TED/TED (N = 5)
Baseline, n			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
12 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
24 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
36 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
48 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
60 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
72 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
84 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
96 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Visit Parameters	Hours per Day		Days per Week	
	TED/NTT (N = 24)	TED/TED (N = 5)	TED/NTT (N = 24)	TED/TED (N = 5)
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
108 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
120 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
132 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]
144 weeks, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)			[redacted]	[redacted]
% change from baseline, mean (SD)			[redacted]	[redacted]

NTT = no teduglutide treatment; SD = standard deviation; TED = teduglutide.

[redacted]

Source: Clinical Study Report of Study 303.[29]

During the prospective period of Study 303, the mean hours per day of PS infusion time generally decreased with both teduglutide and no teduglutide treatment. Among patients in the TED/TED arm, the mean hours per day of PS infusion time was [redacted]. The decreasing trend continued in subsequent weeks, although data were available for fewer patients. During the no teduglutide period, patients in the TED/TED arm showed a decrease in the mean hours per day of PS from baseline, although patients in this arm only received treatment at NT1. Among patients in the TED/NTT arm, the mean hours per day [redacted].

Among patients in the TED/TED arm, mean change in PS days per week of infusion time [redacted]. Among patients in the TED/NTT arm, the mean days per week [redacted]

Study 304

Overall, PS infusion hours per day and days per week [redacted] with teduglutide treatment, [redacted] in the NTT/NTT group. Among patients in the TED/TED arm, there was [redacted] in the mean PS hours per day and days per week [redacted]

[redacted]. During the no teduglutide period, patients in all treatment arms generally showed [redacted]. Patients in the NTT/NTT arm [redacted]; however, [redacted].

Table 19 and Table 20 show the change and per cent change from baseline in PS hours per day and days per week for both the prospective period of Studies 303 and 304.

Table 19: Change From Baseline in Hours per Day of Parenteral Support — Studies 303 (Prospective Period) and 304

	Study 303		Study 304			
TED Treatment Periods		**TED/TED (N = 16)**		**NTT/TED (N = 2)**		**TED/TED (N = 44)**
Baseline, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
C1 EOT, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
Week 28, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
C2 EOT, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
No TED Treatment Periods	**TED/NTT (N = 8)**	**TED/TED (N = 16)**	**NTT/NTT (N = 6)**	**NTT/TED (N = 2)**	**TED/NTT (N = 3)**	**TED/TED (N = 44)**
Baseline, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT1, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT2, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Study 303		Study 304			
Mean (SD)	[redacted]		[redacted]			
Change from baseline, mean (SD)	[redacted]		[redacted]			
% change from baseline, mean (SD)	[redacted]		[redacted]			
NT3, n						
Mean (SD)	[redacted]		[redacted]			
Change from baseline, mean (SD)	[redacted]		[redacted]			
% change from baseline, mean (SD)	[redacted]		[redacted]			

C1(2)D1 = cycle 1(2) day 1; EOT = end of treatment; NT(T) = no teduglutide (treatment period); TED = teduglutide.

[redacted]

Note: Based on patient diary data.

Sources: Clinical Study Reports of Studies 303[29] and 304.[30]

Table 20: Change From Baseline in Days per Week of Parenteral Support — Studies 303 (Prospective Period) and 304

	Study 303		Study 304			
TED Treatment Periods		**TED/TED (N = 16)**		**NTT/TED (N = 2)**		**TED/TED (N = 44)**
Baseline, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
C1 EOT, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
Week 28, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
C2 EOT, n		[redacted]		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]		[redacted]
Change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
% change from baseline, mean (SD)		[redacted]		[redacted]		[redacted]
No TED Treatment Periods	**TED/NTT (N = 8)**	**TED/TED (N = 16)**	**NTT/NTT (N = 6)**	**NTT/TED (N = 2)**	**TED/NTT (N = 3)**	**TED/TED (N = 44)**
Baseline, n						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Study 303		Study 304			
TED Treatment Periods		**TED/TED (N = 16)**		**NTT/TED (N = 2)**		**TED/TED (N = 44)**
NT1, n						
Mean (SD)						
Change from baseline, mean (SD)						
% change from baseline, mean (SD)						
NT2, n						
Mean (SD)						
Change from baseline, mean (SD)						
% change from baseline, mean (SD)						
NT3, n						
Mean (SD)						
Change from baseline, mean (SD)						
% change from baseline, mean (SD)						

C1(2)D1 = cycle 1(2) day 1; EOT = end of treatment; NT(T) = no teduglutide (treatment); TED = teduglutide.

Note: Based on patient diary data.

Sources: Clinical Study Reports of Studies 303 CSR[29] and 304.[30]

Complete weaning off PS

Study 303

By the end of the retrospective period, a total of achieved enteral autonomy according to PS prescription, in the TED/TED arm and in the TED/NTT arm.

Study 304

A total of seven patients in the TED/TED arm achieved enteral autonomy at C1 EOT,

Growth delay measured with weight and height

Study 303

During the retrospective period, patients in both TED/NTT and TED/TED arm had a stable body weight and height z score [redacted] The number of patients in subsequent weeks or in other treatment arms were too small to make any meaningful conclusion (data not presented).

Study 304

No clinically meaningful changes in weight or height z scores were noted. For patients in the TED/TED arm during teduglutide C1, the mean change in body weight and height z score from baseline to C1 EOT was [redacted] and [redacted], respectively. [redacted] (data not presented).

Fecal output

Overall, [redacted]. Stool output was measured using daily output and diaper weight (in patients who were not toilet trained and in diapers). Results for teduglutide C1 in patients in the TED/TED arm will be reported here. [redacted].

In Study 303, fecal output was measured during the prospective period only. [redacted] during the teduglutide treatment period; patients in the TED/TED arm had [redacted] and [redacted]. [redacted]. Stool diaper weight [redacted]; the average stool diaper weight in the TED/TED arm [redacted] and [redacted]. Of the [redacted], the [redacted] in the TED/TED arm had an average total ostomy output of [redacted].

In Study 304, the daily stool output was [redacted] during the teduglutide treatment period. Patients in the TED/TED arm had [redacted] and [redacted]. Stool diaper weight [redacted]; the average stool diaper weight in the TED/TED arm [redacted] and [redacted]. Of the [redacted], the average total ostomy output was [redacted].

Urine output

[redacted]. In Study 303, the average total urine output in the TED/TED arm was [redacted] and [redacted] during teduglutide treatment C1. In Study 304, the average total urine output in the TED/TED arm was [redacted] and [redacted]. In both studies, [redacted].

Harms

Results for the safety end points are summarized for all trials in Table 21. Overall, the majority of the patients in both trials reported at least one AE, although most were mild to moderate in severity.

Study 303

In Study 303, a total of [redacted] AEs were reported during the retrospective period. [redacted]. Patients in the retrospective TED/NTT arm reported [redacted] compared with the retrospective TED/TED arm [redacted]. Patients in the retrospective TED/NTT arm also experienced [redacted] compared with the retrospective TED/TED arm [redacted]. [redacted]. There were [redacted]. It was mentioned that [redacted].

During the prospective period in Study 303, a total of [redacted] AEs were reported. [redacted] were reported in the TED/TED arm [redacted] compared with the TED/NTT arm [redacted]. [redacted] with [redacted] SAEs in [redacted] patients in the TED/TED group, and [redacted] SAEs in [redacted] patients in the TED/NTT group. [redacted].

There were no events of polyps of the colon or neoplasia during either period of Study 303.

Study 304

In Study 304, patients in the TED/TED arm had the highest reported incidence of AEs, [redacted] AEs in 41 patients in the TED/TED group, [redacted]. The most frequent AEs included vomiting, pyrexia,

abdominal pain, increased alanine aminotransferase, URTI, and product issues. [redacted]

Table 21: Summary of Harm Outcomes

	Study 303				Study 304			
	Retrospective TED/NTT (N = 24)	Retrospective TED/TED (N = 5)	Prospective TED/NTT (N = 8)	Prospective TED/TED (N = 16)	NTT/NTT (N = 6)	NTT/TED (N = 2)	TED/NTT (N = 3)	TED/TED (N = 44)
Any AEs	23 (95.8)	4 (80.0)	[redacted]	15 (93.8)	[redacted]	[redacted]	[redacted]	41 (93.2)
Most common AEs (incidence ≥ 10%)								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13 (29.5)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8 (18.2)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (25.0)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Study 303				Study 304			
	Retrospective TED/NTT (N = 24)	Retrospective TED/TED (N = 5)	Prospective TED/NTT (N = 8)	Prospective TED/TED (N = 16)	NTT/NTT (N = 6)	NTT/TED (N = 2)	TED/NTT (N = 3)	TED/TED (N = 44)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
SAEs								
[redacted]								
[redacted]								
[redacted]								
Infections and infestations	19 (79.2)	3 (60.0)						
[redacted]								
[redacted]								
[redacted]								
[redacted]								

AE = adverse event; NTT = no teduglutide treatment; SAE = serious adverse event; TED = teduglutide; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

Note: Percentages were based on the number of patients enrolled in the defined treatment groups. Patients were counted no more than once for incidence but could be counted multiple times for the number of events. Empty cells indicate a lower frequency/percentage than the indicated cut-off and should not be represented as an absence of the specified event.

Sources: Clinical Study Reports of Studies 303[29] and 304.[30]

Antibody formation was considered an important treatment consideration by the participating clinical experts in the review. In Study 303, five out of the 16 patients in TED/TED had

antibodies to teduglutide at C1 EOT during the prospective period. None of the patients had neutralizing antibodies present or experienced an injection site reaction. Of the seven patients remaining in the subsequent 4-week follow-up, two reported anti-teduglutide antibodies without any neutralizing antibodies. At the time of the data cut-off, one of the five patients continuing teduglutide C2 reported anti-teduglutide antibodies without any neutralizing antibodies.

In Study 304, 14 patients had antibodies to teduglutide at C1 EOT, one of whom had neutralizing antibodies. Of the six patients in the subsequent 4-week follow-up, one had antibodies to teduglutide without any neutralizing antibodies. [redacted]

Limitations

Major limitations in the extension studies that are relevant for the interpretation of the results are discussed here.

The studies included a small number of patients. Given the small and imbalanced sample size between the treatment arms and the lack of any formal statistical analyses, no conclusion with respect to the comparative benefits and harms between teduglutide and no teduglutide can be made. The duration of the prospective follow-up was relatively short in both trials. Furthermore, fewer patients were available beyond the first cycle in either teduglutide or no teduglutide periods. The duration of teduglutide exposure during the retrospective period in Study 303 was also short, and the dosage was not specified in the Clinical Study Report. Together, these factors present a challenge in assessing the continued efficacy of the treatment. Another result of the short prospective follow-up duration is that rare AEs, including the SAEs of greatest interest, e.g., intestinal metaplasia, polyp formation, and cancer, are unlikely to be captured during this period. Patients were allowed to switch between periods of teduglutide and no teduglutide cycles; however, there was no information on washouts between treatment cycles or exposure at each time interval. Therefore, it is unclear whether, and to what extent, the treatment effects were biased due to carryover effects. The outcomes assessed in the trial were clinically relevant, objective, and measured using standard equipment and procedures. The clinical experts reached a consensus that the primary outcome, a greater than and equal to 20% reduction in PS volume, was a clinically meaningful change. However, the experts agreed that the magnitude of change in PS volume was not translated to clinically observable end points like changes to hours per day or days per week of PS infusion time. HRQoL measures targeted at specific aspects of the treatment such as daily needle use as well overall quality of life were not assessed for this interim analysis. Of the clinical end points, parenteral nutrition was measured using intake diaries and investigator-prescribed data. The sponsor mentioned that the diary data were more representative of patients' parenteral nutrition intake, a statement not shared by the clinical experts consulted for this review. However, results using both methods were consistent, therefore, any bias introduced from subjective reporting of parenteral nutrition intake by the patients is likely minimal. Nutritional support was adjusted according to pre-specified guidelines (developed with SBS expert input) for decisions regarding PS reduction and enteral feeds based on clinical status (weight gain, urine and stool output, and clinical stability), and was attempted to be made consistent across centres; however, departure from the guidelines was not considered a protocol deviation in the extension studies.

Issues related to generalizability were consistent with that in the core studies since no new inclusion or exclusion criteria were imposed during the extension period. In general, patients with more severe conditions were excluded, including those with body weight less than 10 kg, hepatic, pancreatic, or biliary disease. The experts indicated that patients with severe liver disease are more likely to receive a treatment that minimizes PS need and therefore, would be an ideal candidate for teduglutide therapy. However, the experts acknowledged that excluding severe patients in clinical trials for pragmatic reasons is not uncommon. Notably among the baseline characteristics, patients receiving teduglutide during the retrospective period had an average age that was double that of patients receiving no teduglutide. The reason for this notable imbalance as well as its impact on the results is unclear.

Conclusion

Study 303 and 304 were phase III, open-label trials designed to assess the long-term safety and efficacy of teduglutide treatment; and consisted of patients (aged one year to 17 years) with SBS who completed the core studies 003 and 006, respectively. Study 303 had a retrospective period of 2.4 years to 3.3 years, and both studies had an ongoing prospective period with at least six months of follow-up data. Patients underwent multiple recurring cycles of no teduglutide or 28-week teduglutide treatment and were allowed to switch depending on disease course.

Overall, treatment with teduglutide appeared to be associated with a clinically meaningful reduction in PS requirement in some patients. It is unclear if the improvement in PS need translates to enteral autonomy or body growth, as the magnitude of change in these end points was small or minimal. Notably, the clinical improvements were largely limited to the patients who continued through the treatment cycles, as fewer patients were available with more follow-up data. Prospective follow-up was limited to two teduglutide treatment cycles and three no teduglutide treatment cycles at the time of the data cut-off, limiting the assessment of the efficacy of teduglutide beyond these short cycles. Furthermore, a comparison between teduglutide and no teduglutide could not be drawn due to the imbalanced sample size between the treatment groups, and the provision to switch treatments at any point during the study. In combination with the already small sample set, these factors present a challenge in assessing the long-term efficacy of teduglutide treatment, or the comparative efficacy between teduglutide and no teduglutide treatment.

The safety profile of teduglutide was generally consistent with the results from the core studies of teduglutide in pediatric SBS patients. However, the relatively short duration and small sample size in both trials limits the ability to extrapolate the long-term safety of teduglutide until the final report with longer follow-up data is available.

Discussion

Summary of Available Evidence

Two phase III studies (Study 006, double-blind RCT, N = 59; and Study 003, open-label non-RCT, N = 42) submitted by the manufacturer are included in this systematic review. The trials included pediatric patients (greater than one year of age) with SBS as a result of major intestinal resection. The patients required PS that provided at least 30% of caloric and/or fluid/electrolyte needs for at least three months prior to screening and was stable for more than three months prior to and during screening. The two studies evaluated the efficacy and safety of 24-week (Study 006) or 12-week (Study 003) teduglutide therapy (0.0125 mg/kg/day, 0.025 mg/kg/day, and 0.05 mg/kg/day) in children with SBS compared with SOC. Teduglutide 0.05 mg/kg/day is the only Health Canada–approved dosage for the study population. The main efficacy outcome in the two studies was change in parenteral feeding from baseline, with response defined as a greater than and equal to 20% reduction in PS volume from baseline to study end point (week 24 for Study 006 and week 12 for Study 003). Other efficacy outcomes include change in EN and change in nutritional status (measured with height and weight for age). Harm outcomes associated with the use of teduglutide were also examined.

The major limitations of the included studies are the study design and a lack of statistical comparison between treatment groups. Patients were not randomized to receive the study drug versus placebo or SOC. Patients and their caregivers decided which treatment they wanted to receive. Therefore, systematic differences in age, race, nutritional status, underlying causes for SBS, and remaining small intestinal length were observed between treatment groups and have an impact on data interpretation. Statistical testing was not performed, and data were descriptively summarized only. No adjustments on covariates were planned and no adjustment on multiple comparisons. Subgroup analysis and sensitivity analysis were performed; however, the results should be interpreted with caution given the small sample size. Predictors of response were not determined.

Interpretation of Results

Efficacy

In the two studies, parenteral feeding was evaluated by measuring the proportion of patients with a greater than and equal to 20% reduction in PS volume at EOT (week 24) in Study 006 or week 12 in Study 003, change from baseline in PS volume, and the change from baseline in PS infusion time (days per week or hours per day).

In Study 006, 54.2% of patients in the teduglutide 0.025 mg group, 69.2% in the teduglutide 0.05 mg group, and 11.1% in the SOC group were responders (defined as patients who achieved a greater than and equal to 20% reduction in PS at EOT) based on patient diary data. Analysis of investigator-prescribed PS volumes gave consistent results. The percentage of patients achieving a greater than and equal to 20% reduction in PS volume at EOT was higher in the two teduglutide dosage groups compared with SOC (54.2% versus 69.2% versus 22.2%, respectively). The experts consulted on this review considered these differences between treatment and SOC to be clinically meaningful, even though a statistical comparison was not performed. Treatment with both teduglutide dosages (0.025 mg and 0.05 mg) was related to greater reduction in PS volume from baseline to EOT compared with the SOC group. In addition, patients in the teduglutide dosage groups experienced

shorter infusion time (fewer PS days per week and fewer PS hours per day) as compared with the SOC group at EOT.

In Study 003, 12.5% of the patients in the teduglutide 0.0125 mg group, 71.4% in the teduglutide 0.025 mg group, 46.7% in the teduglutide 0.05 mg group, and no patient in the SOC group achieved a greater than and equal to 20% reduction in PS volume at week 12, based on patient diary data. When analyzed using the investigator-prescribed data, the percentage of patients achieving a greater than and equal to 20% reduction in PS volume at week 12 was [redacted]. The experts considered these differences between teduglutide and SOC to be clinically meaningful, even though a statistical comparison was not performed. All teduglutide dosage groups were related to greater reduction in PS volume from baseline to week 12 compared with the SOC group. In addition, patients in the teduglutide dosage groups (0.025 mg and 0.05 mg groups) experienced shorter infusion time (fewer PS days per week and fewer PS hours per day) as compared with the SOC group at week 12. Change in the infusion time from baseline to week 12 reported in the teduglutide 0.0125 mg group was similar to that reported in the SOC group.

The effect of teduglutide on reducing PS was notable. However, it is unclear how this can be translated to important clinical benefits, such as prolonged survival, symptom relief, decreased SBS-related complication or PS-related complication, improved health-related quality of life and normal growth in children. The clinical panellists for this review acknowledge the lack of evidence to link the reduction in PS with these clinical benefits, especially in the long run, but indicate that reduced parenteral nutrition can result in reduced infusion time, and thus can be expected to reduce some severe PS-related complications, resulting in more enteral feeding, and eventual enteral autonomy for some patients.

Additional efficacy outcomes were examined. For change in EN, results of Study 006 showed that both teduglutide groups (0.025 mg and 0.05 mg) experienced greater increase in EN volume from baseline to EOT compared with the SOC group (percentage change of 76.89%, 79.52%, and 2.50% for teduglutide 0.025 mg, teduglutide 0.05 mg group, and the SOC group, respectively). In Study 003, [redacted]teduglutide groups [redacted]in EN volume from baseline to EOT compared with the SOC group (percentage change of [redacted]and [redacted]for teduglutide 0.0125 mg group, teduglutide 0.025 mg, teduglutide 0.05 mg group, and the SOC group, respectively).

In Study 006, two patients (8.3%) in the teduglutide 0.025 mg group and three (11.5%) patients in the teduglutide 0.05 mg group achieved enteral autonomy, which was defined as complete weaning off PS at EOT. No patients from the SOC group achieved enteral autonomy. In Study 003, one patient (7.1%) in teduglutide 0.025 mg group and [redacted]in the teduglutide 0.05 mg group achieved enteral autonomy at week 12. Achieving enteral autonomy is one of the main treatment goals for pediatric patients with SBS. The clinical experts consulted for this review indicate that even though the chance of achieving enteral autonomy is low in the study population, the results still show the benefit of the study drug.

Improvement in nutritional status was evaluated by measuring change in height and weight in Study 003. Overall, improvements in weight and height were observed after 12 weeks of treatment with teduglutide or SOC, compared with baseline. The clinical experts consulted for this review indicate that the change from baseline was small and not considered clinically meaningful.

Open-label extension studies (Studies 303 and 304) were designed to assess the long-term safety and efficacy of teduglutide treatment. They enrolled patients (one year to 17 years) with SBS who had completed the original core studies (Studies 006 and 003, respectively). Study 303 had a retrospective period of 2.4 years to 3.3 years, and both studies had an ongoing prospective period with at least six months of follow-up data. Patients underwent multiple recurring cycles of no teduglutide treatment or 28-week teduglutide treatment and were allowed to switch depending on disease course.

Overall, treatment with teduglutide was associated with clinical benefit in reducing PS requirement in some patients. It is unclear if the improvement in PS need translates to enteral autonomy or body growth, as the magnitude of change in these end points was small or minimal. Notably, the clinical improvements were largely limited to the patients who continued through the treatment cycles, as fewer patients were available with more follow-up data. Prospective follow-up was limited to two teduglutide treatment cycles and three no teduglutide treatment cycles at the time of the data cut-off, limiting the assessment of the efficacy of teduglutide beyond these short cycles. Furthermore, a comparison between teduglutide and no teduglutide could not be drawn due to the imbalanced sample size between the treatment groups, and the provision to switch treatments at any point during the study. In combination with the already small sample set, these factors present a challenge in assessing the long-term efficacy of teduglutide treatment, or comparative efficacy between teduglutide and no teduglutide treatment.

Harms

Almost all patients reported TEAEs in Studies 006 and 003. The majority of the AEs were mild or moderate in severity. The most common AEs were vomiting, diarrhea, abdominal pain, pyrexia, URTI, nasopharyngitis, dehydration, and headache. Although the proportion of patients with AEs was higher in the teduglutide groups for most of the reported AEs, the risk of certain AEs was higher in the SOC group, such as vomiting, pyrexia, and URTI.

In Study 006, the incidence of SAEs was higher in teduglutide-treated groups (63% to 77%) than in the SOC group (44%), while in Study 003, treatment with higher dosage teduglutide (0.05 mg/kg/day) or SOC was associated with more SAEs, as compared with teduglutide 0.0125 mg/kg/day or teduglutide 0.025 mg/kg/day. The common SAEs in the included studies were pyrexia, dehydration, and central line-related breakage or infection.

No patients withdrew due to AEs in either study. No deaths were reported in either study. In terms of AEs of special interest, during the study, there were no reports of gastrointestinal tract polyp formation, biliary complications, neoplasia, or intestinal obstruction in either study. At the end of the study, antibody development was found in eight patients in Study 006 (three in teduglutide 0.025 mg group, five in teduglutide 0.05 mg group) and one patient (teduglutide 0.025 mg group) in Study 003.

Results of the long-term extension studies suggest that the safety profile of teduglutide was generally consistent with the results from the pivotal trials of teduglutide in pediatric SBS patients. However, the relatively short duration and small sample size in both trials limit the extrapolation of the long-term safety of teduglutide, until longer follow-up data are available.

Conclusions

Two phase III studies (one double-blind, 24-week, randomized controlled trial and one open-label, 12-week, non-randomized controlled trial) were included in this review. The main limitations of the included studies were the small size, non-randomized comparison of teduglutide with SOC, extensive exclusion criteria, and no statistical testing between treatment groups. Teduglutide administered according to the Health Canada–approved dosage (0.05 mg/kg/day) was associated with better response rates than SOC in reducing parenteral nutrition volume and time. Treatment with teduglutide was also related to increased enteral feeding and complete weaning off parenteral nutrition for some patients. The studies did not demonstrate clinically meaningful improvement in nutritional status as measured by weight and height. Almost all study participants reported TEAEs, and the use of teduglutide was related to higher risk of some AEs. The majority of the reported AEs were mild to moderate in intensity. There were no deaths during the core studies, and no patients withdrew due to AEs. Results of the extension studies suggest that the treatment with teduglutide may be associated with clinical benefit in reduction in parenteral nutrition requirement in some patients and suggest that there are no new safety signals in the study population, but follow-up is continuing.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 29, 2019
Alerts:	Weekly search updates until project completion
Limits:	Publication date limit: No date limits used Language limit: No language limits used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase);
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY
1. (revestive* or teduglutide* or gattex* or revestine* or 7M19191IKG or ALX0600 or "ALX 0600").ti,ab,ot,rn,nm,hw,kf.
2. 1 use medall
3. *teduglutide/
4. (revestive* or teduglutide* or gattex* or revestine* or ALX0600 or "ALX 0600").ti,ab,kw,dq.
5. 3 or 4
6. 5 use oemezd
7. 6 or 2
8. conference abstract.pt.
9. 7 NOT 8
10. remove duplicates from 9

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search – teduglutide]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search teduglutide]

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.

Grey Literature

Dates for Search:	December 23, 2018 to January 4, 2019
Keywords:	Revestive, teduglutide, short bowel syndrome.
Limits:	Publication years: 1996 to present

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool For Searching Health-Related *Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals.

Appendix 2: Excluded Studies

Table 22: Excluded Studies

Reference	Reason for Exclusion
No studies were excluded.	

References

1. Clinical Study Report: 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 [**CONFIDENTIAL** internal manufacturer's report]. Shire; 2018 Feb 06.
2. Clinical Study Report: TED-C13-003. A 12-week pharmacokinetic, safety, and pharmacodynamic study of teduglutide in pediatric subjects aged 1 through 17 years, with short bowel syndrome who are dependent on parenteral support [**CONFIDENTIAL** internal manufacturer's report]. Shire; 2015 Jun 15.
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