Common Drug Review
Clinical Review Report

August 2016

Drug	Teduglutide (Revestive)
Indication	For the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support
Listing request	As per indication
Dosage form(s)	5 mg vials for subcutaneous injection
NOC date	September 04, 2015
Manufacturer	Shire Pharma Canada ULC/NPS Pharma Holdings Ltd.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
EQ-5D	EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire
IBDQ	Inflammatory Bowel Disease Questionnaire
ITT	intention-to-treat population
MCID	minimal clinically important difference
PN	parenteral nutrition
PNALD	parenteral nutrition–associated liver disease
QoL	quality of life
SAE	serious adverse event
SBS	short bowel syndrome
TEAE	treatment-emergent adverse event

EXECUTIVE SUMMARY

Introduction

Short bowel syndrome (SBS) is a rare, serious, disabling, socially incapacitating, and potentially life-threatening condition. SBS results from surgical resection (due to malignancies, injuries, Crohn disease, or vascular disease) or congenital defect and is characterized by the inability to maintain protein energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted normal diet. Patients with SBS are highly prone to malnutrition, diarrhea, dehydration, and an inability to maintain weight because of the reduced intestinal capacity to absorb macronutrients, water, and electrolytes. In Canada, it is estimated that the number of adult patients in Canada receiving long-term home parenteral nutrition (PN) was about 400 between 2004 and 2006.

Teduglutide 0.05 mg/kg/day subcutaneous injection is indicated for the treatment of adult patients with SBS, who are dependent on parenteral support. The objective of this review was to perform a systematic review of the beneficial and harmful effects of teduglutide 5 mg/vial for the treatment of adult patients with SBS who are dependent on parenteral support.

Indication under review
For the treatment of adult patients with short bowel syndrome who are dependent on parenteral support
Listing criteria requested by sponsor
For the treatment of adult patients who are dependent on parenteral support, and who have been stabilized on parenteral nutrition/intravenous fluids after a period of intestinal adaptation

Results and Interpretation

Included Studies

Two phase 3, double-blind randomized controlled trials met the inclusion criteria for the systematic review (CL04 and CL20).[1,2] The objective of the included studies was to evaluate the efficacy, safety, and tolerability of teduglutide compared with placebo in patients with PN-dependent SBS. In CL04, 84 patients were randomized in a 1:2:2 ratio to one of three treatment arms: placebo, teduglutide 0.05 mg/kg/day, or teduglutide 0.10 mg/kg/day. In CL20, 86 patients were randomized in a 1:1 ratio to one of two treatment groups: teduglutide 0.05 mg/kg/day or placebo. “Graded response score” was the primary outcome in CL04, and it was a secondary outcome in CL20. It is a scoring algorithm that takes both response intensity (20% to 100% reduction from baseline in weekly PN and/or intravenous [PN/IV] hydration) and duration between weeks 16 and 24 into account. The primary efficacy variable in CL20 was the percentage of patients who demonstrated a response (20% to 100% reduction from baseline in weekly PN/IV) at week 20, and who maintained that response at week 24 (responder). In CL04, quality of life (QoL) was evaluated using the Short Form (36) Health Survey (SF-36), EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D), and Inflammatory Bowel Disease Questionnaire (IBDQ); none of these measures had a specific minimal clinically important difference (MCID) for patients with SBS. In CL20, QoL was evaluated using a disease-specific scale—the Short Bowel Syndrome-Quality of Life (SBS-QoL). The manufacturer defined MCID for SBS-QoL as a positive change of the patients’ QoL from baseline above the two-fold measurement error of the SBS-QoL (i.e., 18.4).
The two studies had very selective inclusion criteria and excluded several diseases that may result in SBS, such as radiation enteritis, scleroderma, and celiac disease. Furthermore, they had relatively small

sample sizes, short double-blind treatment duration, and showed some imbalance of baseline characteristics. In study CL04, there was a major deviation from the statistical analysis plan that affects the interpretation of findings.

Efficacy

There were no death cases reported in the included studies. In terms of PN reduction, both trials showed that teduglutide 0.05 mg/kg/day was associated with better graded response scores than placebo, and two patients in CL04 were reported to be weaned from PN. However, results from CL04 should be interpreted as exploratory because the first step in the statistical hierarchical testing procedure failed to show a statistical difference between the 0.10 mg dose and placebo. In terms of reducing the mean weekly PN volume, the two trials showed inconsistent results. For example, CL04 showed that neither of the teduglutide doses were statistically different from placebo in reducing the weekly PN volume, whereas CL20 showed that teduglutide 0.05 mg/kg/day was associated with statistically significant higher reduction in PN volume than placebo. CL04 evaluated the impact of teduglutide in reducing the number of PN days per week, and showed that neither dose was statistically different from placebo.

Intestinal emptying was not evaluated in the included studies, and only CL04 compared fluid requirements and renal emptying between baseline and the end of trial. It was reported that patients receiving teduglutide took in less fluid orally and excreted more urine (net effect about 500 mL per 48 hours total). Placebo patients took in more fluid (400 mL) and excreted 200 mL more urine, with an overall increase in fluids of 200 mL in median 48-hour measurements at 24 weeks. However, no statistical comparison between groups was reported. Both studies failed to show any major effect of treatment on patient's QoL.

Harms

The number of patients with adverse events (AEs), serious adverse events (SAEs), or discontinuations due to treatment-emergent SAEs was comparable between treatment groups. The most frequently reported treatment-emergent AEs in the teduglutide group were of gastrointestinal origin, such as abdominal pain, nausea, gastrointestinal stoma complication, or abdominal distension. There were no major findings reported in the laboratory and/or chemistry or hematology tests of the teduglutide-treated versus placebo patients.

Conclusions

Two double-blind, placebo-controlled, randomized trials (CL04 and CL20)[1,2] were included in this review. The main limitations of the included studies were the relatively small size, highly selective inclusion criteria, and the deviation of CL04 analyses from the statistical plan. Teduglutide administered according to the Health Canada–approved dose (0.05 mg/kg/day) was associated with better response rates than placebo in terms of parental feeding graded response. However, the two trials were inconsistent in showing a statistically significant different reduction of mean weekly PN volume between teduglutide and placebo. Furthermore, the reviewed trials were unable to show a consistent difference between teduglutide and placebo in reducing the number of PN days per week. The trials failed to show a difference in affecting patients' QoL. The inconsistencies could be due to random variability of the sample or a different weaning algorithm in the two trials. The number of patients with AEs, serious AEs, or discontinuations due to treatment-emergent SAEs was comparable between treatment groups. Patients already on treatment for 24 weeks in the original trial continued to withdraw due to adverse effects in the extension trials.

TABLE 1: SUMMARY OF RESULTS

	CL04				
	Placebo	Teduglutide 0.05	Teduglutide 0.10	Placebo	Teduglutide 0.05
N	N = 16	N = 35	N = 32	N = 43	N = 43
Efficacy					
Survival	**No deaths were reported in the included studies**				
Parenteral feeding					
• **Graded response score**[a]					
○ **Difference versus placebo**		**0.007**	0.08		**0.004**
• **≥ 20% reduction of PN at both week 20 and week 24, n (%)**	1 (6.3)	16 (45.7)	8 (25.0)	13 (30.2)	27 (62.8)
○ **Difference versus placebo, % (*P* value)**		**39.5% (0.009)**	18.8% (0.238)		**32.6% (0.002)**
• **Reduction from baseline in mean weekly PN volume (L), mean (SD)**	–0.90 (1.41)	–2.48 (2.34)	–2.47 (3.33)	–2.29 (2.74)	–4.37 (3.81)
○ **Difference versus placebo, L/week (*P* value)**		–1.408 (0.768)	–1.426 (0.755)		**< 0.00**[a]
Quality of life, difference versus placebo in mean change from baseline (SD); *P* value					
○ **SF-36 — Physical Component Summary**		4.30 (2.76); 0.1233	4.42 (2.77); 0.1154	**Not evaluated**	
○ **SF-36 — Mental Health Component Summary**		–1.44 (2.75); 0.6029	–2.68 (2.76); 0.3333		
○ **IBDQ score**		–0.98 (8.58); 0.9093	2.73 (8.68); 0.7539		
○ **EQ-5D index**		0.06 (0.046); 0.1663	0.04 (0.046); 0.3588		
○ **EQ-5D health rating**		9.74 (4.71); **0.0418**	1.67 (4.75); 0.7258		
○ **Short Bowel Syndrome–Quality of Life (influence of treatment on quality of life score)**		Not evaluated			*P* = 0.8112
Harms					
Patients with > 0 TEAEs, N (%)	15 (93.8)	33 (94.3)	31 (96.9)	34 (79.1)	35 (83.3)
Patients with > 0 SAEs, N (%)	5 (31.3)	13 (37.1)	11 (34.4)	12 (27.9)	15 (35.7)

	CL04				
	Placebo	Teduglutide 0.05	Teduglutide 0.10	Placebo	Teduglutide 0.05
N	N = 16	N = 35	N = 32	N = 43	N = 43
WDAEs, N (%)	1 (6.3)	6 (17.1)	2 (6.3)	3 (7.0)	2 (4.8)
Number of deaths, N (%)	0	0	0	0	0

EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; PN = parenteral nutrition; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
[a] A scoring algorithm that takes both response intensity (PN volume reduction) and duration between weeks 16 and 24 into account.
Source: Clinical Study Reports.[1,2]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Short bowel syndrome (SBS) is a rare, serious, disabling, socially incapacitating, and potentially life-threatening condition.[3] SBS results from surgical resection (due to malignancies, injuries, Crohn disease, or vascular disease) or congenital defect and is characterized by the inability to maintain protein energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted normal diet.[4] Patients with SBS are highly prone to malnutrition, diarrhea, dehydration, and an inability to maintain weight because of the reduced intestinal capacity to absorb macronutrients, water, and electrolytes.[5-10] Additional potential consequences of SBS include dehydration, electrolyte disturbances, malabsorption of nutrients, gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhea, diarrhea, small bowel bacterial overgrowth, and weight loss.[3,4]

The severity of SBS is illustrated by the shortened lifespan in patients with moderate to severe disease.[11] In SBS, survival can be affected by the underlying condition, by severe clinical manifestations of malabsorption, and treatment-associated life-threatening complications.[4] Depending on each patient's requirements, current medical management may include dietary adjustments, enteral nutrition, total parenteral nutrition (PN), or even surgery. With current medical management practices, the overall 10-year survival in adult SBS patients is 52%, and is significantly lower in patients who remain chronically PN-dependent compared with patients who wean off PN (40.7% versus 67%).[12]

SBS received a rare disease or an orphan drug designation by the European Medicines Agency and the FDA. Between 2004 and 2006, Raman et al. (2007)[13] estimated the number of adult patients in Canada receiving long-term home PN to be about 400.

1.2 Standards of Therapy

The clinical care of SBS is mainly supportive and focuses on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, and antidiarrheal and antisecretory drugs. Despite intestinal adaptation following resection, many SBS patients require the chronic use of parenteral support (PN and/or intravenous [PN/IV} hydration) to supplement and stabilize their nutritional and hydration needs.

Although PN/IV can meet basic nutrition and fluid requirements, it does not improve the body's ability to absorb nutrients. In addition, PN/IV is associated with shortened lifespan,[11,14] life-threatening complications (e.g., sepsis, blood clots, or liver damage), and reduced quality of life (QoL).[15-17] The development of PN-associated liver disease (PNALD) predisposes patients to an increased incidence of sepsis, increased mortality rates, and the potential to develop irreversible liver damage.[18] There is no specific Canadian guideline for SBS; the American Gastroenterological Association medical position statement on short bowel syndrome recommends that a potential treatment option for PNALD should attempt to reduce the toxic exposure to PN constituents administered to patients.[19]

1.3 Drug

Teduglutide 0.05 mg/kg/day subcutaneous injection is indicated for the treatment of adult patients with SBS who are dependent on parenteral support. Teduglutide is a 33-amino acid recombinant analogue of human glucagon-like peptide-2 (GLP-2), a peptide secreted primarily from the lower gastrointestinal tract. Teduglutide binds to the GLP-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 (IGF)-1, vasoactive intestinal polypeptide (VIP), nitric oxide, and keratinocyte growth factor (KGF). 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 fluids, and consequent decreases in fecal or stomal output of fat, nitrogen, sodium, potassium, calories, and gastrointestinal fluid.[20]

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2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of teduglutide 5 mg/vial for the treatment of adult patients with SBS who are dependent on parenteral support.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with short bowel syndrome who are dependent on parenteral support
Intervention	Teduglutide 0.05 mg/kg
Comparators	Combination of glutamine with growth hormone Placebo
Outcomes	**Key efficacy outcomes:** Survival Parenteral feeding and fluid requirements Intestinal emptying (frequency, quantity and weight) Renal emptying Quality of life Body weight change Changes in liver enzymes concentration Health care resource utilization **Harms outcomes:** AEs, SAEs, WDAEs, mortality **Notable harms:** Bowel narrowing or obstruction, intestinal polyps and cancers, and abdominal discomfort
Study Design	Published and unpublished RCTs

AE = adverse events; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with In-Process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Patient Headings), and keywords. The main search concepts were Revestive (teduglutide) and SBS.

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year 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 December 22, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on April 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment (HTA) Agencies; Health Economics; Clinical Practice Guidelines; Drug Regulation; Advisories and Warnings; Drug Class Reviews; Canadian Drug Formularies and Internet Search sections. Google and other Internet search engines were used to search for additional Web-based materials, including conference abstracts. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (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. Included studies are presented in Table 3; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of 291 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

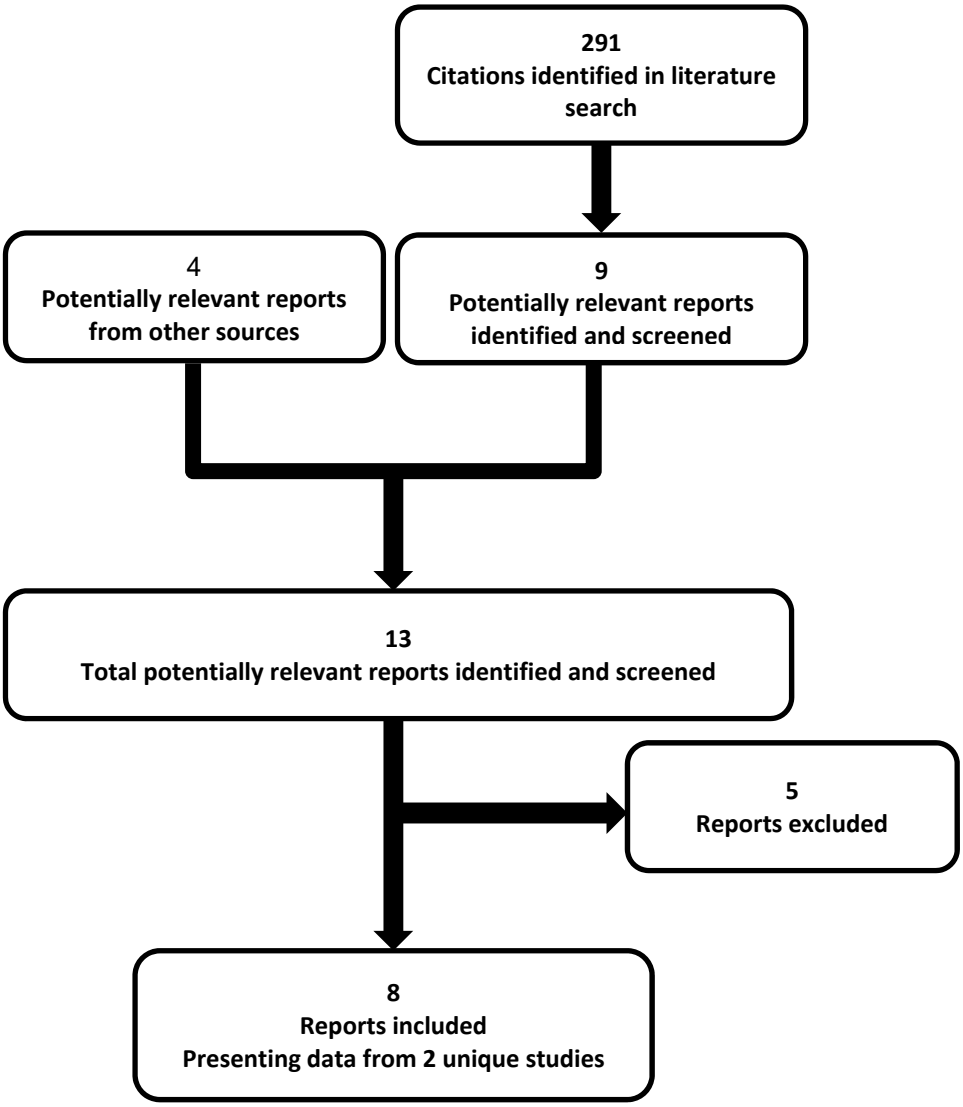


TABLE 3: DETAILS OF INCLUDED STUDIES

		CL04	CL20
DESIGNS & POPULATIONS	**Study Design**	DB RCT	
	Locations	Canada, US, and 13 European countries	Canada, US, and 8 European countries
	Randomized (N)	84	86
	Inclusion Criteria	1. Age ≥ 18 years 2. SBS as a result of major intestinal resection; e.g., due to injury, volvulus, vascular disease, cancer, Crohn disease 3. Patients who have undergone major intestinal resection resulting in PN dependency at least 12 months prior to randomization 4. PN required at least 3 times weekly to meet their caloric, fluid, or electrolyte needs due to ongoing malabsorption 5. Stable for at least 4 consecutive weeks immediately prior to randomization	
	Exclusion Criteria	Cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state. History of alcohol or drug abuse (within previous year)	
DRUGS	**Intervention**	Teduglutide: SC 0.05 mg/kg/day Teduglutide: SC 0.10 mg/kg/day	Teduglutide: SC 0.05 mg/kg/day
	Comparator(s)	Placebo	
DURATION	**Phase**	**3**	
	Run-in	3 days to 8 weeks: PN optimization (find patient's minimally tolerated stable volume of PN) 4 to 8 weeks: PN stabilization	
	Double-blind	24 weeks	
	Follow-up	4 weeks **or** enrolment in CL-005	Optional enrolment in CL21
OUTCOMES	**Primary End Point**	20% to 100% reduction from baseline in weekly PN volume at weeks 16, 20, and 24 (graded response)	20% to 100% reduction from baseline in weekly PN volume at weeks 20 and 24 (binary outcome)
	Other End Points	• Achievement of at least a 20% reduction from baseline in weekly PN volume at week 20 through week 24 (binary) • Direct changes of improved intestinal absorption of fluid and macronutrients • Quality of life and health care resource utilization	• Absolute and percentage reduction in PN volume • Duration of response • Achievement 20% to 100% reduction or at least a 2 L reduction • Number of patients who stopped PN/IV • Graded (or ordered categorical) response • Quality of life
NOTES	**Publications**	Jeppesen et al.[21]	Jeppesen et al.,[22] Jeppesen et al.,[23] and Vipperla and O'keefe[24]
		Seidner et al.[25]	

DB = double-blind; IV = intravenous; PN = parenteral nutrition; PN/IV = parenteral nutrition and/or intravenous hydration; RCT = randomized controlled trial; SBS = short bowel syndrome; SC = subcutaneous.
Note: Three additional reports were included (FDA reports,[26,27] and Health Canada reviewers' report[28]).
Source: Clinical Study Reports[1,2]

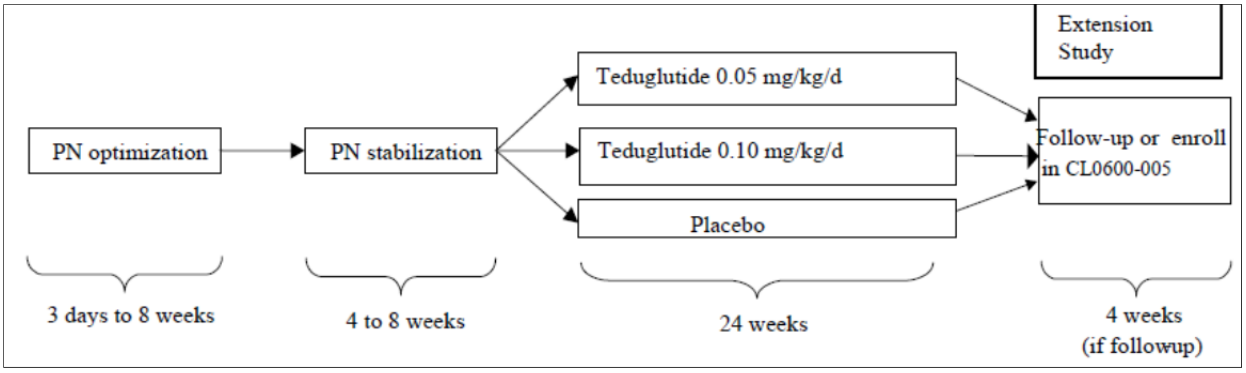
3.2 Included Studies

3.2.1 Description of Studies

Two phase 3, double-blind randomized controlled trials met the inclusion criteria for the systematic review (CL04 and CL20). The objective of the included studies was to evaluate the efficacy, safety, and tolerability of teduglutide compared with placebo in patients with PN-dependent SBS. In CL04, 84 patients were randomized in a 1:2:2 ratio to one of three treatment arms: placebo, teduglutide 0.05 mg/kg/day, or teduglutide 0.10 mg/kg/day. In CL20, 86 patients were randomized in a 1:1 ratio to one of two treatment groups: teduglutide 0.05 mg/kg/day or placebo.

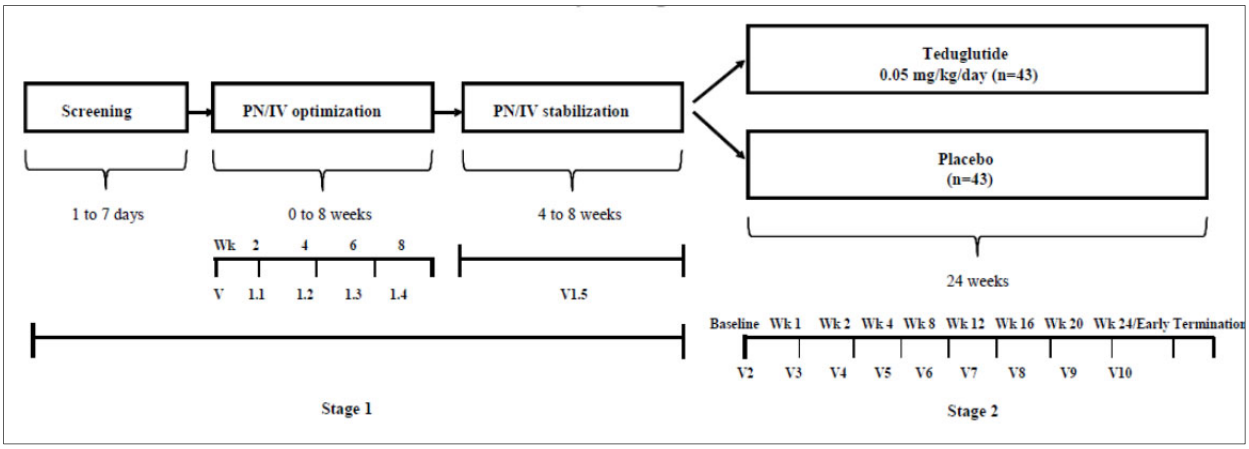
In both studies, screened patients were entered into a PN optimization phase, which was defined as the lowest amount of PN that could be prescribed to an individual without putting them at risk for biochemical, nutritional, or hydration abnormalities. After reaching the optimum PN regimen for each patient, patients were stabilized on their regimens for four to eight weeks before randomization (Figure 2 and Figure 3). If there was evidence of dehydration during the study, the PN was restored to the previous level. The investigator requested that patients be randomized at the baseline/dosing day 1 visit using an interactive response system called the Fisher Automated Clinical Trials Services (FACTS). At the time of randomization in CL04, those patients randomized to placebo were further randomized prospectively for possible inclusion in the Extension Study CL05 to either the teduglutide 0.05 mg/kg/day or the 0.10 mg/kg/day treatment for 28 weeks. All patients who completed study CL20 had the option to continue taking teduglutide 0.05 mg/kg/day for up to two years in a long-term safety study (CL21).

FIGURE 2: STUDY CL04 DIAGRAM



d = day; PN = parenteral nutrition.
Source: Clinical Study Report.[2]

FIGURE 3: STUDY CL20 DIAGRAM



PN/IV = parenteral nutrition and/or intravenous hydration; wk = week.
Source: Clinical Study Report.[1]

3.2.2 Populations

a) Inclusion and exclusion criteria

In addition to the inclusion criteria mentioned in Table 3, patients had to meet the following conditions:

- Men and women aged 18 years or older.
- For patients with a history of cancer, the patient was to be disease-free for at least five years.
- For patients with a history of Crohn disease, the patient was to be in clinical remission, as determined by clinical assessment.
- Body weight was to be less than 90 kg at the time of enrolment.
- Major intestinal resection resulting in at least 12 months of PN dependency prior to the date of enrolment.
- At baseline, patients must have required PN treatment to meet their caloric or electrolyte needs due to ongoing malabsorption at least three times weekly.
- They had to have been stable for at least four consecutive weeks immediately prior to randomization. Stability was based on the following:
  - Usage and volume of PN
  - 48-hour urinary output (1.0 to 2.0 L/day)
  - Urine sodium (greater than 20 mmol/day)
  - Adequate renal function (serum creatinine and blood urea nitrogen [BUN] are 1.5 x upper limit of normal [ULN] or less)
  - Hematocrit indicating satisfactory hydration (ULN or less)
  - Motility-altering medications (e.g., loperamide, diphenoxylate, codeine, or other opiates)
  - Body mass index (BMI) is 18 to 27 kg/m^2
  - Adequate hepatic function (alanine aminotransferase [ALT] [SGPT] and aspartate aminotransferase [AST] [SGOT] were less than 2.0 x ULN; total bilirubin was less than 1.25 x ULN; and alkaline phosphatase was less than 2.5 x ULN).

Patients with the following medical conditions were excluded:

- Related to SBS:
  - Radiation enteritis
  - Scleroderma
  - Celiac disease

  - Refractory or tropical sprue
  - Pseudo-obstruction
- Gastrointestinal
  - Active inflammatory bowel disease (which required chronic systemic immunosuppressant therapy that had been introduced or changed during the last three months)
  - Untreated premalignant or malignant tissue detected in colonoscopy biopsy or polypectomy
  - Surgery scheduled within the time frame of the study
- Immune system
  - HIV-positive test
  - Immunological disorders (e.g., severe combined immunodeficiency)
  - Possible allergies to teduglutide or its constituents
- Significant active, uncontrolled, untreated systemic diseases
- Patients with clinically significant laboratory abnormalities.

b) Baseline characteristics

Baseline demographics are summarized in Table 4**.**

CL04: The majority of patients enrolled in CL04 were Caucasian (92.8%), were between 19 and 79 years of age (mean age 48.8 years), and 38.6% of patients were 55 years of age or older (Table 4). More female (55.4%) than male (44.6%) patients participated in this study. The 0.10 mg dose group had a larger number of patients (34.4%) dependent on PN six to seven times a week and fewer patients receiving only IV fluids (9.4%) compared with the low-dose and placebo groups, but the differences were not significant among any of the treatment groups for any of the PN consumption levels. The 0.10 mg dose group had fewer current smokers (18%) compared with 31% in the other two groups.

CL20: In general, baseline demographic data were similar between treatment groups. The majority of patients enrolled in this study were Caucasian (96.5%), between 45 and 65 years of age (mean age 50.3 years), and (15.1%) of patients were aged 65 years or older. Patients ranged in age from 18 to 82 years. The distribution of participating males and females was 46.5% male and 53.5% female.

TABLE 4: SUMMARY OF BASELINE DEMOGRAPHICS

	CL 04			CL20	
	Placebo	Teduglutide 0.05 mg/kg/day	Teduglutide 0.10 mg/kg/day	Placebo	Teduglutide 0.05 mg/kg/day
N	16	35	32	43	43
Age (years), mean (SD)	49.4 (15.1)	47.1 (14.2)	50.3 (14.0)	49.7 (15.6)	50.9 (12.6)
Gender (Male), n (%)	7 (43.8)	17 (48.6)	13 (40.6)	19 (44.2)	21 (48.8)
Race (Caucasian), n (%)	15 (93.8)	32 (91.4)	30 (93.8)	41 (95.3)	42 (97.7)
PN consumption, n (%)					
• IV fluids 3 to 7 x week	4 (25.0)	8 (22.9)	3 (9.4)	NR	NR
• PN 3 to 5 x week	8 (50.0)	19 (54.3)	18 (56.3)	NR	NR
• PN 6 to7 x week	4 (25.0)	8 (22.9)	11 (34.4)	NR	NR
• ≤ 6 L/week	NR	NR	NR	7 (16.3)	8 (18.6)
• > 6 L/week	NR	NR	NR	36 (83.7)	35 (81.4)
Height, mean (SD)	167.5 (9.4)	167.5 (10.8)	165.2 (7.1)	165.9 (9.6)	166.9 (9.7)
Weight (kg), mean (SD)	61.5 (8.6)	59.2 (8.7)	59.6 (10.0)	61.7 (12.6)	62.7 (11.4)
Ever smoked, n (%)	8 (50.0)	19 (54.3)	17 (53.1)	NR	NR
Current smoker, n (%)	5 (31.3)	11 (31.4)	6 (18.8)	NR	NR
Alcohol use, n (%)	10 (62.5)	20 (57.1)	17 (53.1)	NR	NR

NR = not reported ; PN = parenteral nutrition; SD = standard deviation.
Source: Clinical Study Reports.[1,2]

Baseline disease characteristics are summarized in Table 5.

CL04: The primary cause for intestinal resection was Crohn disease (36.1%) or vascular disease (30.1%). Stoma was present in 34.9% of the patients. The mean length ± SD (standard deviation) of the remaining small intestine was 65.8 ± 45.4 cm (range: 6 to 200 cm; median 60 cm). The 0.05 mg group had a relatively shorter remaining small intestine (58 cm) than placebo (77 cm) or the 0.10 mg dose group (68 cm). The colon was included in resection in 27 (32.5%) patients. Of the 56 (67.5%) patients with some degree of colon in continuity, 20 patients (35.7%) had 75% to 100% of the remaining colon and 19 patients (33.9%) had only > 25% to 50% of the remaining colon. The remaining 17 (30.4%) patients had a degree of colon present between > 50% and 75%. Of the 17 (20.5%) patients with distal and/or terminal ileum, the ileocecal valve was present in nine (52.9%) patients and absent in eight (47.1%) patients. In the majority of the patients (63.9%), the remaining small bowel length was determined by surgery.

CL20: The most prevalent causes for major intestinal resection were vascular disease (34.1%), Crohn disease (21.2%), or "other" reason (21.2%). Stoma was present in 38/85 patients (44.7%), with the most common types being jejunostomy and/or ileostomy (31/38 patients, 81.6%). The mean length ± SD of the remaining small intestine was 77.3 ± 64.4 cm (range: 5 to 343 cm). Patients in the teduglutide group had a numerically greater length of small intestine (86.2 cm) than the placebo group (68.7 cm).

The colon was not in continuity in 37 (43.5%) patients. The mean per cent of colon remaining was 63.1%. Patients in the placebo group had a higher numerical percentage of colon remaining (70.3%) than the teduglutide group (55.6%). Of the 24 patients with remaining distal and/or terminal ileum, the ileocecal valve was present in 13 patients (54.2%).

TABLE 5: SUMMARY OF BASELINE DISEASE CHARACTERISTICS

	CL04			CL20	
	Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/kg/day
N	16	35	32	43	42
Cause of intestinal resection, n (%)					
• Crohn disease	7 (43.8)	10 (28.6)	13 (40.6)	8 (18.6)	10 (23.8)
• Vascular disease	3 (18.8)	14 (40.0)	8 (25.0)	16 (37.2)	13 (31.0)
• Injury	1 (6.3)	3 (8.6)	2 (6.3)	4 (9.3)	4 (9.5)
• Volvulus	2 (12.5)	5 (14.3)	4 (12.5)	6 (14.0)	3 (7.1)
• Cancer	NR	NR	NR	2 (4.7)	1 (2.4)
• Other	3 (18.8)	3 (8.6)	5 (15.6)	7 (16.3)	11 (26.2)
Stoma, n (%)					
• Yes	5 (31.3)	10 (28.6)	14 (43.8)	17 (39.5)	21 (50.0)
Type:					
○ Jejunostomy	4 (80.0)	6 (60.0)	4 (28.6)	5 (29.4)	11 (52.4)
○ Ileostomy	1 (20.0)	2 (20.0)	7 (50.0)	9 (52.9)	6 (28.6)
○ Colostomy	0	2 (20.0)	3 (21.4)	1 (5.9)	4 (19.0)
○ Other	Not reported			2 (11.8)	0
Colon in continuity, n (%)					
• Yes	11 (68.8)	26 (74.3)	19 (59.4)	23 (53.5)	25 (59.5)
Remaining amount:					
○ > 25% to 50%	4 (36.4)	7 (26.9)	8 (42.1)	Not reported	
○ > 50% to 75%	4 (36.4)	9 (34.6)	4 (21.1)		
○ > 75% to 100%	3 (27.3)	10 (38.5)	7 (36.8)		
○ Mean (SD)	Not reported			70.3 (27.1)	55.6 (20.8)
Remaining small intestine length (cm)					
• N	15	31	27	40	39
• Mean (SD)	77.3 (52.9)	58.3 (43.6)	68.1 (43.1)	68.7	86.2
• Median (range)	60 (15, 200)	50 (6, 200)	60 (10, 200)	48 (5, 343)	70 (20, 250)
• < 60 cm	Not reported			24 (55.8)	15 (35.7)
• ≥ 60 cm				16 (37.2)	24 (57.1)
Distal and/or terminal ileum, n (%)					
• Yes	3 (18.8)	6 (17.1)	8 (25.0)	14 (32.6)	10 (23.8)
• Ileocecal valve present	1 (33.3)	5 (83.3)	3 (37.5)	10 (71.4)	3 (30.0)

NR = not reported; SD = standard deviation.
Source: Clinical Study Reports.[1,2]

PN history is summarized in Table 6.

TABLE 6: SUMMARY OF PARENTERAL NUTRITION HISTORY

	CL04 (ITT Population)			CL20 (Safety Population)	
	Placebo	Teduglutide 0.05 mg/kg/day	Teduglutide 0.10 mg/kg/day	Placebo	Teduglutide 0.05 mg/kg/day
N	**16**	**35**	**32**	**43**	**42**
Years since start of PN dependency					
• Mean (SD)	Not reported			5.9 (5.7)	6.6 (6.3)
Current prescribed PN/IV per week (L)					
• Mean (SD)	11.4 (5.7)	10.5 (5.3)	13.1 (6.6)	13.3 (7.5)	12.4 (7.7)
Estimated PN/IV volume used per week					
• Mean (SD)	11.4 (5.7)	10.5 (5.3)	12.9 (6.7)	13.4 (7.0)	12.5 (7.4)
• Median (range)	9.3 (5, 25)	10.8 (4, 28)	11.2 (3, 3.3)	12.4 (3.6, 35)	12.2 (0.9, 33)
Type of IV access, n (%)					
• Central venous	14 (87.5)	29 (82.9)	28 (87.5)	37 (86.0)	38 (90.5)
• PICC line	1 (6.3)	6 (17.1)	3 (9.4)	6 (14.0)	3 (7.1)
• Other	1 (6.3)	0	1 (3.1)	0	1 (2.4)
Treated for IV line infections, thromboses, occlusions in the past 6 months, n (%)					
• Yes	3 (18.8)	**12 (34.3)**	**8 (25.0)**	7 (16.3)	6 (14.3)
• If yes, number of IV line infections, mean (SD)	1.0 (1.0)	1.3 (1.2)	1.1 (0.99)	5 (11.6)	5 (11.9)
Frequency of IV line infections, n (%)					
• 0	1 (6.3)	3 (8.6)	2 (6.3)	Not reported	
• 1	1 (6.3)	5 (14.3)	4 (12.5)		
• 2	1 (6.3)	2 (5.7)	1 (3.1)		
• 3	0	1 (2.9)	1 (3.1)		
• 4	0	1 (2.9)	0		
If yes, number of hospitalizations for IV line infections, mean (SD)	0.3 (0.58)	1.1 (1.2)	1.1 (0.99)		
Frequency of hospitalization for IV line infections, n (%)					
• 0	2 (12.5)	4 (11.4)	2 (6.3)	Not reported	
• 1	1 (6.3)	5 (14.3)	4 (12.5)		
• 2	0	2 (5.7)	1 (3.1)		
• 3	0	0	1 (3.1)		
• 4	0	1 (2.9)	0		
If yes, number of thromboses, occlusions, mean (SD)	0.3 (0.6)	0.5 (0.7)	0.5 (0.8)	Throm: 2 (4.7) Occlu: 1 (2.3)	Throm: 1 (2.4) Occlu: 0
Frequency of thromboses, occlusion, n (%)					
• 0	2 (12.5)	7 (20.0)	5 (15.6)	Not reported	
• 1	1 (6.3)	4 (11.4)	2 (6.3)		
• 2	0	1 (2.9)	1 (3.1)		

	CL04 (ITT Population)			CL20 (Safety Population)	
	Placebo	Teduglutide 0.05 mg/kg/day	Teduglutide 0.10 mg/kg/day	Placebo	Teduglutide 0.05 mg/kg/day
N	**16**	**35**	**32**	**43**	**42**
Frequency of hospitalization for thromboses, occlusions, n (%)					
• 0	3 (18.8)	10 (28.6)	7 (21.9)	Not reported	
• 1	0	2 (5.7)	1 (3.1)		

ITT = intention-to-treat; IV = intravenous; Occlu = occlusion; PICC = peripherally inserted central catheter; PN = parenteral nutrition; PN/IV = parenteral nutrition and/or intravenous hydration; SD = standard deviation; Throm = thrombosis.
Source: Clinical Study Reports.[1,2]

CL04: The mean (± SD) prescribed weekly PN/IV volume was 11.7 L (± 5.96) at baseline and most patients (71; 85.5%) had a central venous line IV access (Table 6). About one-fourth of the patients (27.7%) were treated for IV line infections, thromboses, or occlusions during the past six months; the frequency of these events was consistently higher in the teduglutide 0.05 and 0.10 mg/kg/day arms than in the placebo arms.

CL20: The mean (± SD) years since the start of PN/IV dependency was 6.25 (± 5.98) years. Mean (± SD) prescribed weekly PN/IV volume at study entry was 13.17 L (± 7.15) at screening. Mean prescribed days per week requiring PN/IV infusion was 5.76 (+ 1.63) days. Most of the patients (88.2%) had a subclavian central venous IV access. Ten patients (11.8%) were treated for IV line infections during the six months prior to screening.

3.2.3 Interventions

The study drug (0.05 mg/kg/day or 0.10 mg/kg/day teduglutide, or placebo) was administered immediately after reconstitution by subcutaneous injection into one of the four quadrants of the abdomen or into either thigh. The first subcutaneous injection was to be administered under the supervision of the investigator or designee. Patients with a stoma were permitted to avoid the use of the abdominal quadrant in which the stoma was sited.

Treatment compliance for study drug dosing was evaluated by an independent third party (i.e., Fisher Clinical Services), whose responsibility was to count and examine the returned used and unused vials. In addition, compliance was checked at every visit by asking each patient if he or she had taken his or her study drug according to instructions, and by reviewing the patient's diary.

The following medications were allowed provided they were used at a stable dose for at least four weeks prior to the baseline visit:

- Antimotility drugs; e.g., loperamide, diphenoxylate, codeine, or other opiates
- H_2 antagonists
- Antidiarrheal agents
- Bile acid sequestering agents
- Oral glutamine
- Proton pump inhibitors
- Diuretics
- Rehydration fluid.

No new medications were to be started during the stabilization period or throughout the 24-week treatment period unless medically necessary and prescribed by the investigator or by another qualified physician involved in the patient's clinical care and who was aware of the patient's study participation.

a) Concomitant Therapies and Nutrient Supplements:

All included patients in CL04 and the majority of CL20 patients reported having taken at least one concomitant medication (teduglutide, 41/42 patients, 97.6%; and placebo, 41/43 patients, 95.3%) (Table 7). The most frequently reported concomitant medications were proton pump inhibitors (esomeprazole, omeprazole, and pantoprazole) and antipropulsives (loperamide).

TABLE 7: CONCOMITANT MEDICATIONS AND NUTRITIONAL SUPPLEMENTS USED

	CL04			CL20 (Safety Population)	
	Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/ kg/day
N	**16**	**35**	**32**	**43**	**42**
At least 1 concomitant medication	16 (100)	35 (100)	32 (100)	41 (95.3)	41 (97.6)
Proton pump inhibitors	Not reported			22 (51.2)	24 (57.1)
Antipropulsives				12 (27.9)	21 (50.0)
Vitamin D and analogues				18 (41.9)	16 (38.1)
Heparin group				13 (30.2)	14 (33.3)
Calcium				13 (30.2)	12 (28.6)
Anilides				13 (30.2)	9 (21.4)
Fluoroquinolones				10 (23.3)	7 (16.7)
Multivitamins, plain				7 (16.3)	7 (16.7)
Thyroid hormones				2 (4.7)	7 (16.7)

Source: Clinical Study Reports[1,2]

3.2.4 Outcomes

Graded response score was the primary outcome in CL04, and it was a secondary outcome in CL20. It is a scoring algorithm that takes into account both response intensity (PN volume reduction) and duration between weeks 16 and 24 (

Table 8). The actual PN volumes were collected in diary booklets that patients were expected to complete daily between the clinical visits scheduled at four-week intervals; i.e., baseline, weeks 4, 8, 12, 16, 20, 24, and follow-up at week 28. The weekly PN volume was calculated in two-week intervals, as the PN-prescribed volume prescription from the physician could stipulate dosing over two weeks (because of some days on and some days off PN). The "weekly" PN volume calculation was:

- "Weekly" PN volume for 14 days = [Sum (PN volume for 14 days)/14 days)] x 7 days.
- If < 14 days of data recorded = [(sum of 'PN volume for x days prior to following visit)/(number of days summed)] x 7.

The response variable was calculated for each patient, as follows:

Response score (y) = y1 + y2 + y3 + y4 + y5
= 0, 1, 2, 3, 4 or 5

Where,

Y1 = 1 if 20% reduction from baseline in PN volume at week 20 is sustained to week 24
= 0 if not

Y2 = 1 if 20% reduction from baseline in PN volume at week 16 is sustained to week 24
= 0 if not

Y3 = 1 if [0% reduction from baseline in PN volume at either week 16 or 20 is sustained to week 24] and [40 % reduction from baseline in PN volume from week 16 to week 20 or from week 20 to week 24]
= 0 if not

Y4 = 1 if 40% reduction from baseline in PN volume at week 16 is sustained to week 24
= 0 if not

Y5 =1 if 100% reduction in PN volume (i.e., off PN) at week 20 is sustained to week 24
= 0 if not

TABLE 8: CRITERION VALUES FOR RESPONSE IN CL04 AND CL20

Weeks 16 to 20	Week 20 to 24			
	< 20 % Reduction	20% to 39% Reduction	40% to 99% Reduction	100% Reduction
< 20% reduction	0	1	2	3
20% to 39% reduction	0	2	3	4
≥ 40% reduction	0	3	4	5

Source: Clinical Study Reports.[1,2]

In CL20, the primary efficacy variable was the percentage of patients who demonstrated a response at week 20, and who maintained that response at week 24 (responder). In both trials, a response at a given visit was defined as the achievement of a 20% to 100% reduction from baseline in weekly PN/IV volume. The weekly actual PN/IV volume was used to determine the per cent reduction. A patient was considered a responder if both the week 20 volume and week 24 volume reflected a 20% to 100% reduction. The weekly PN/IV volume was defined using data from the last 14 days prior to the visit.

QoL was reported in both trials. In CL04, QoL was evaluated using the SF-36, EQ-5D, and IBDQ; none of these measures had a specific minimal clinically important difference (MCID) for patients with SBS.

The IBDQ has a total of 32 items, which form four domains: bowel symptoms (10 items); systemic symptoms (5 items); emotional functions (12 items); and social functions (5 items). An IBDQ total score can be generated by summing the scores of all the items. The total score ranges from 32 to 224. Higher scores represent better function.

The EQ-5D has two parts: the descriptive system and visual analogue scale (EQ VAS). The descriptive system includes five questions, which represent five dimensions in mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. The second part is the EQ VAS, which has end points labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Both were used in the current study. The EQ-5D utility index values range from 0.0 = death to 1.0 = perfect health, and the EQ VAS ranges from 0 to 100.

In CL20, QoL was evaluated using a disease-specific measure called the Short Bowel Syndrome–Quality of Life (SBS-QoL) questionnaire. The manufacturer defined MCID for SBS-QoL as a positive change of the patients' QoL from baseline above the two-fold measurement error of the SBS-QoL (i.e., 18.4).

3.2.5 Statistical Analysis

CL04[2]: Randomization was stratified for participation in the 72-hour nutrient absorption test, and PN at three levels of PN consumption (IV fluids and electrolytes only three to seven times weekly, PN three to five times weekly, and PN six to seven times weekly).

A sample size of 80 patients was required to have 90% power to detect a difference of an event rate of 5% in the placebo group to 50% in the teduglutide group for the outcome of a minimum response (20% decrease for weeks 20 to 24, only) (two-sided alpha = 0.05).

Overall treatment comparisons were made using rank analysis of covariance (ANCOVA), with strata for the baseline PN consumption level used for the stratification of the randomization, and treatment group with the baseline weekly PN volume as a covariate. A step-down procedure was used to adjust for multiple comparisons when testing multiple hypotheses of treatment effect, as stated in the protocol. In this procedure, the high dose versus placebo comparison needed to be significant at a *P* = 0.05 level before testing the low dose versus placebo.

For change from baseline variables, pairwise differences between treatment groups and the corresponding 95% confidence intervals (CIs) utilized estimates from a two-way repeated measures ANCOVA. The model included effects for baseline PN stratification of the randomization, treatment group, and baseline weekly PN volume as covariates.

CL20[1]: The number and percentage of responders was defined as those who demonstrated a 20% to 100% reduction in both week 20 and week 24 (20% to 100% reduction in PN/IV volume). The number and percentage of responders was presented by treatment group. The analysis compared the event rates for the two treatment groups using the Cochran–Mantel–Haenszel test statistics adjusted for the randomization stratification variable (≤ 6 or > 6 L/week of PN at baseline).

A sample size of 86 was calculated to have 90% power based on an event rate of 35% in the teduglutide arm and 6% in the placebo arm (two-sided alpha = 0.05).

Graded response analyses were done by comparing the graded response categories for the two treatment groups using extended Cochran–Mantel–Haenszel test statistics (with standardized mid-ranks) adjusted for the randomization stratification variable.

In both studies, the analysis data sets included the data available. No imputation or last observation carried forward methods were used for missing diary and safety data. The weekly PN/IV volume recorded in the patient e-diaries were calculated in 14-day intervals. Missing

daily PN/IV volumes from patient e-diaries were not imputed, and a maximum of five missing days (or at least nine days of non-missing data) from the 14-day intervals were allowed; otherwise, the interval was classified as missing, with two exceptions. One exception to this rule was the baseline interval, which was filtered back within the stabilization period beyond 14 days until nine data points were obtained. The other exception was that PN/IV adjustments due to an AE were excluded, in which case the last 14 days during the interval that were not considered to be impacted by the AE were used. These exceptions were identified prior to database hard lock.

A step-down testing procedure was used to adjust for multiple comparisons based upon the primary and secondary efficacy parameters. Each step was conducted in the intention-to-treat (ITT) population at the 0.05 level to evaluate the efficacy of teduglutide compared with placebo.

a) Analysis populations

CL04 and CL20[1,2]: ITT population: Included all patients who were randomized into the study. This was the primary study population from which efficacy claims were made. All efficacy analyses were conducted on this study population. Patients were included in the treatment group to which they were randomized, regardless of the actual drug they received.

Per-protocol (PP): The determination of which protocol violations would be considered major was made prior to database lock during a blind data review meeting, based on a review of data that included inclusion and exclusion criteria, study drug compliance, and intake of prohibited medication. Patients who terminated the study early were not included in this population. Only the primary and secondary efficacy outcomes were evaluated using the PP population.

Safety population: Included all patients in the ITT population who received at least one dose of double-blind study drug. For reporting purposes, these patients were included in the treatment group, reflective of the treatment they actually received.

3.3 Patient Disposition

In CL04, a total of 139 patients were screened at 32 study centres. Of these 139 patients, 84 were randomized and 55 were screen failures. The major reasons for screen failure were not meeting inclusion or exclusion criteria (23 patients), withdrawal of consent (14 patients), other reasons (12 patients), and investigator decision (four patients); no reason was given for two patients. Of the 84 randomized patients, 71 completed 24 weeks of the study. One patient who was randomized did not receive the study drug. Thus, a total of 83 patients were randomized into the study and received the study drug.

In CL20, a total of 132 patients were screened, of whom 86 were randomized. The reasons for screen failure were not reported. One patient who was randomized to the teduglutide group did not receive the study drug.

TABLE 9: PATIENT DISPOSITION

	CL04			CL20	
	Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/ kg/day
Screened, N	139			132	
Randomized, N	16	35	33	43	43
Discontinued, N (%)	1 (6.3)	8 (22.9)	3 (9.4)	4 (9.3)	4 (9.3)
• **Due to adverse events**	1 (6.3)	5 (14.3)	2 (6.3)	3 (7)	2 (4.7)
ITT, N	16	35	32	43	43
PP, N	15 (93.8)	26 (74.3)	29 (87.9)	38	37
Safety, N	15	35	32	43	42
Continued to extension study, N	13 (81.3)	25 (71.4)	27 (81.8)		

ITT = intention-to-treat; PP = per-protocol.
Source: Clinical Study Reports.[1,2]

3.4 Exposure to Study Treatments

In CL04, patient compliance (defined as ≥ 80% of actual doses taken) was observed in both treatment groups for all dosing weeks, with no noticeable difference between treatment groups. The overall treatment compliance was 92% for all dosing weeks, with 100% compliance reported at dosing weeks 12, 16, and 20 in the high-dose group. In CL20, 100% of patients were classified as compliant.

TABLE 10: SUMMARY OF STUDY DRUG EXPOSURE AND PATIENTS' COMPLIANCE

	CL04			CL20	
	Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/ kg/day
N	**16**	**35**	**32**	**43**	**42**
Number of weeks on study drug, mean (SD)	24.3 (1.3)	20.7 (8.0)	23.2 (5.6)	22.6 (5.1)	22.7 (6.0)
Overall compliance					
• Yes	15 (93.8)	31 (88.6)	30 (93.8)	43 (100)	42 (100)
• No	1 (6.3)	4 (11.4)	2 (6.3)		

SD = standard deviation.
Source: Clinical Study Reports.[1,2]

3.5 Critical Appraisal

3.5.1 Internal Validity

Teduglutide and placebo were identical in appearance. The study centre personnel, the sponsor, and all personnel associated with the monitoring or data management for the clinical study were blinded to the treatment assignment. The person responsible for adjusting PN was different from the person conducting physical examinations and assessing safety because the observation of stomal swelling may unblind the observer. In the event that unblinding of an individual patient was deemed necessary for the treatment of a patient, the investigator was permitted to request unblinding by the sponsor or sponsor designee.

In study CL20, patients in the teduglutide group had a numerically greater mean length of small intestine (86.2 cm) than the placebo group (68.7 cm). However, depending on what proportion of patients this difference came from, this may have resulted in an overestimation of difference in PN volume given that the patients' malnutrition is highly correlated with their remaining small intestines. Likewise, in study CL04, there are notable differences on the mean length of small intestine ranging from 9 cm to 19 cm, with the shortest in the 0.05 mg/kg/day arm, which could have biased the estimate of treatment effect as well. Moreover, eight patients in the 0.05 mg/kg/day arm discontinued from the study compared with three from the 0.10 mg/kg/day arm and one from placebo. The remaining patients were perhaps more likely tolerant of the drug and received a beneficial treatment effect. Given that the study sample size was so small, this may have explained why there were statistically significant findings in the 0.05 mg/kg/day arm, whereas there were no statistical significant findings in the high-dose 0.10 mg/kg/day arm, even though a similar trend was noted. These differences could also be at least partly attributed to imbalances of baseline characteristics at baseline.

Studies CL04 and CL20 were nearly identical in study design, such as inclusion and exclusion criteria. The one major exception is the weaning algorithm in both trials. In CL04, weaning rates were restricted to a maximum of 10% every four weeks, versus 10% to 30% every two weeks in CL20. Any difference in treatment effects should be readily attributable to random variation across the two studies. However, the response scores varied markedly for the same low dose at teduglutide 0.05 mg/kg/day in the main response category 1 and 2 between the two studies (17 versus 7% and 17 versus 30% in study CL04 and CL20, respectively) (Table 11). This would indicate a high unreliability of treatment effect estimates. In the placebo arm, there was also marked variation: 6.3% versus 14%. Given the relatively small sample size, the precise estimate of treatment effect is highly uncertain.

As stated above, while there are inherent limitations in comparing event rates between trials, the overall populations appear similar in both CL04 and CL20; but in CL20, the proportion of patients achieving a response (20% to 100% reduction in PN volume) in the placebo group was 30.2%, versus 6.3% in CL04. While this may be attributable to random variation, it may also indicate that the patients in this trial were not as well optimized on PN prior to the trial.

In study CL04, the sample size was calculated using the secondary outcome, not the primary outcome. In addition, for both CL04 and CL20, the event rates observed in the trials were not what was anticipated in the sample size calculations, possibly leading to the trials being underpowered to detect a difference.

According to CL04 protocol, a step-down procedure was to be done, and if the 0.10 mg/kg/day dose was not significant, no further statistical testing was to be carried out. However, the authors continued with the 0.05 mg/kg/day testing despite the fact that the 0.10 mg/kg/day dose did not differ with statistical significance from placebo. Therefore, comparative results between the low dose (0.05 mg/kg/day) and placebo should be interpreted as exploratory only. Furthermore, no literature was identified to validate the graded response algorithm or the 20% PN reduction as a response threshold.

3.5.2 External Validity

The included population was heterogeneous with regard to SBS and PN history. According to the clinical expert consulted on this review, the population reflects the heterogeneity of Canadian SBS patients. However, the study inclusion and exclusion criteria resulted in a highly selective study population, which would have made the benefit-risk more favourable to the study drug. Not all reasons for adult patients to develop SBS would have been eligible for inclusion, even if otherwise clinically stable. In addition, patients with clinically significant laboratory abnormalities would have been excluded from the trial, further limiting generalizability. Patients with various comorbidities who are more likely suffering from the unfavourable side effects were excluded from the study, but, in reality, those patients may still receive the study drug in clinical practice.

While there is an extension to the trial, comparative data are still of relatively short duration, which may limit the information collected on long-term safety. As noted by the clinical expert consulted on this review—if a patient is responsive to treatment, this therapy would likely be indefinite.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 2).

3.6.1 Survival

This outcome was not evaluated in the included studies. However, neither study reported any deaths.

3.6.2 Parenteral Feeding

Parenteral feeding was evaluated using the following measures:

a) Patients who achieved both intensity (20% to 100% PN reduction) and sustainability at weeks 16, 20, and 24 (graded response):

Results for the graded response outcome are summarized in Table 11.

In CL04, there was no statistically significant difference between the placebo and teduglutide 0.10 mg/kg/day groups when using the step-down procedure. Despite the PP decision rule to only test the teduglutide 0.05 mg/kg/day dose if the teduglutide 0.10 mg/kg/day dose was significant, the authors decided to test the statistical significance of the teduglutide 0.05 mg/kg/day dose, and they reported that the graded score for the teduglutide 0.05 mg/kg/day treatment group was statistically significantly higher than placebo (P = 0.007). However, this analysis falls outside the testing procedure, and should be interpreted as exploratory only. These findings were confirmed in CL20, and the rank test was statistically significant between placebo and the teduglutide 0.05 mg/kg/day groups (P = 0.004). Of note, the response scores varied markedly at teduglutide 0.05 mg/kg/day in categories 1 and 2 between the two studies (17 versus 7% and 17 versus 30%). In the placebo arm, there was also marked variation in category 2, 6.3 versus 14%.

TABLE 11: SUMMARY OF RESULTS FOR THE GRADED RESPONSE SCORE

	CL04 (Primary Outcome)			CL20 (Secondary Outcome)	
	Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/ kg/day
Response category, n (%)	**N = 16**	**N = 35**	**N = 32**	**N = 43**	**N = 43**
0 (No response)	15 (93.8)	19 (54.3)	24 (75.0)	30 (69.8)	16 (37.2)
1	0	6 (17.1)	2 (6.3)	1 (2.3)	3 (7.0)
2	1 (6.3)	6 (17.1)	4 (12.5)	6 (14.0)	13 (30.2)
3				2 (4.7)	4 (9.3)
4	0	2 (5.7)	2 (6.3)	4 (9.3)	7 (16.3)
5 (Off PN)	0	2 (5.7)	0	0	0
Difference versus placebo, ***P value***		**0.007**[a]	0.08[a] (vs. placebo) 0.161 (vs. 0.05 mg/kg/day)		**0.004**[b]

PN = parenteral nutrition; vs. = versus.
[a] Test statistic is based on pairwise analysis of covariance (ANCOVA) test after adjustment for the baseline PN consumption level and baseline PN volume as a covariate.
[b] The treatment comparison is based on an extended Cochran–Mantel–Haenszel test, with standardized mid-ranks adjusted for the randomization stratification variable.
Source: Clinical Study Reports.[1,2]

b) Patients who achieved a response of ≥ 20% reduction of PN at both week 20 and week 24:
Table 12 provides a summary of patients achieving ≥ 20% PN reduction from baseline.

CL04: There was no significant difference between teduglutide 0.10 mg/kg/day and placebo (25% versus 6.3%, *P* = 0.172). There was a statistically significantly higher rate of responders in the teduglutide 0.05 mg/kg/day dose compared with placebo (45.7% versus 6.3%; *P* = 0.005). However, this analysis falls outside the testing procedure, and should be interpreted as exploratory only.

CL20: The proportion of patients who were responders was 62.8% in the teduglutide group and 30.2% in the placebo group. The responder rate was statistically significantly higher in the teduglutide group than in the placebo group (*P* = 0.002).

TABLE 12: PERCENTAGE OF PATIENTS ACHIEVING ≥ 20% PARENTERAL NUTRITION REDUCTION FROM BASELINE TO WEEK 20 AND MAINTAINED TO WEEK 24

	CL04 (Secondary Outcome)			CL20 (Primary Outcome)	
	Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/ kg/day
N	**16**	**35**	**32**	**43**	**43**
Responders, n (%)	1 (6.3)	16 (45.7)	8 (25.0)	13 (30.2)	27 (62.8)
Difference from placebo for % responders	39.5		18.8	Not reported	
***P* value for treatment comparison versus placebo**	0.009[a]		0.238[a]	0.002[b]	

[a] Treatment comparisons for difference from placebo are based on Fisher's exact test.
[b] The treatment comparison is based on a Cochran–Mantel–Haenszel test adjusted for the randomization stratification variable.
Source: Clinical Study Reports.[1,2]

c) Reduction of mean weekly PN volume:

Results of reduction in weekly PN volume are provided in Table 13.

CL04: At week 24, both active treatment groups demonstrated a numerically larger reduction of mean weekly PN volume; 2.5 L reduction for both active treatments versus 0.9 L in the placebo group (*P* = 0.08 for each comparison). Of note, this analysis falls outside testing procedure and should be interpreted as exploratory only.

CL20: At week 24, the teduglutide group was associated with a statistically significant larger reduction in weekly PN volume from baseline compared with placebo (4.4 L/week versus 2.3 L/week; *P* < 0.0001). The percentage change in actual PN/IV reduction volume at week 24 was 32% compared with 21% (*P* = 0.03).

TABLE 13: REDUCTION FROM BASELINE IN WEEKLY PARENTERAL NUTRITION VOLUME

	CL04			CL20	
	Placebo	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.10 mg/ kg/day**	**Placebo**	**Teduglutide 0.05 mg/kg/day**
Baseline, N	**16**	**34**	**32**	**43**	**43**
• Mean (SD)	10.72 (6.12)	9.62 (4.47)	12.71 (7.06)		
Change to dosing week 24, N	**15**	**27**	**29**	**39**	**39**
• Mean (SD)	–0.90 (1.41)	–2.48 (2.34)	–2.47 (3.33)	–2.29 (2.74) (absolute) –21.3% (25.4%) (percentage)	–4.37 (3.81) –32.4% (18.9)
• Difference vs. placebo (*P* value)		–1.408 (0.768)	–1.426 (0.755)		Absolute: < 0.00 [a] Percentage: 0.03 [a]
Last dosing, N	**16**	**34**	**32**	**43**	**43**
• Mean (SD)	–0.84 (1.38)	–1.83 (2.97)	–2.29 (3.22)	–2.38 (2.79) –21.0% (24.4%)	–4.28 (3.81)[a] –32.1% (18.7%)[a]
• Difference vs. placebo, *P* value					Absolute: < 0.001[a] Percentage: 0.023[a]

IV = intravenous; PN = parenteral nutrition; SD = standard deviation; vs. = versus.
[a] The treatment comparison for the absolute and per cent change was based on an analysis of covariance (ANCOVA) model, with treatment and interaction of treatment by baseline PN/IV volume as effects and baseline PN/IV volume as a covariate.
Source: Clinical Study Reports.[1,2]

d) Patients who achieved ≥ 20% to 100% OR 2 L reduction of PN from baseline (CL20 only)

The proportion of patients with a 20% to 100% reduction or a 2 L reduction in PN/IV volume at weeks 20 and 24 was higher in the teduglutide group (30/43 patients, 69.8%) than in the placebo group (16/43 patients, 37.2%). This was statistically significant (*P* = 0.002) between the treatment groups.

e) Patients who stopped PN (CL20 only)

No patients had been weaned off PN/IV as of week 20. There was only one patient in the placebo group who had stopped PN/IV during the 14 days prior to week 24, according to the e-diary. This patient was not considered successful in weaning off PN/IV infusion because PN/IV was only temporarily interrupted because of hospitalization and catheter replacement (the implanted catheter was not working) immediately prior to week 24.

f) Patients who achieved at least a one-day reduction in weekly PN:

In CL04, 11/35 (31.4 %) patients in the teduglutide 0.05 mg/kg/day treatment group and 3/32 (9.4%) patients in the teduglutide 0.10 mg/kg/day group achieved at least a one-day reduction in weekly PN. These results were not statistically different from placebo (4/16; 25% reduction) and should be interpreted as exploratory only.

In CL20, more patients achieved a one-day reduction in PN in the teduglutide group (21/39 [54%]) than in the placebo group (9/39 [23%]; *P* < 0.005). However, this analysis should be considered exploratory only.

g) Reduction in weekly PN kilojoules (CL04 only):

The mean reductions from baseline in weekly PN kilojoules at dosing week 24 and last dose visit were not statistically significantly different from placebo.

TABLE 14: CHANGE FROM BASELINE IN WEEKLY PARENTERAL NUTRITION KILOJOULES

	CL04		
	Placebo	**Teduglutide 0.05 mg/kg/day**	**Teduglutide 0.10 mg/kg/day**
Baseline, N	**16**	**35**	**32**
• **Mean (SD)**	23693.1 (18137.5)	27945.2 (18822.8)	37071.1 (19911.9)
Dosing week 24, N	**15**	**28**	**29**
• **Mean (SD)**	–1701.0 (3151.3)	–6385.6 (9328.8)	–3128.2 (7357.8)
• **Least-squares mean**	–3544.6	–6993.9	–1587.3
• **Difference vs. placebo, *P* value**		0.1355	0.4233
Last dosing, N	**16**	**35**	**32**
• **Mean (SD)**	–1594.7 (3074.0)	–5445.2 (8732.3)	–3394.7 (7320.9)
• **Least-squares mean**	–2609.1	–5842.0	–2453.6
• **Difference vs. placebo, *P* value**		0.1337	0.9446

PN = parenteral nutrition; SD = standard deviation; vs. = versus.
Source: Clinical Study Reports.[1,2]

3.6.3 Intestinal Emptying

This outcome was not evaluated in the included studies.

3.6.4 Fluid Requirements and Renal Emptying (CL04 Only)

Patients receiving teduglutide took in less fluid orally and excreted more urine (net effect about 500 mL per 48 hours total). Placebo patients took in more fluid (400 mL) and excreted 200 mL more urine, with an overall increase in fluids of 200 mL in median 48-hour measurements at 24 weeks. No statistical analysis was completed for these data. These data were not reported for CL20.

TABLE 15: REDUCTION FROM BASELINE IN WEEKLY PARENTERAL NUTRITION VOLUME

	CL04		
	Placebo	**Teduglutide 0.05 mg/kg/day**	**Teduglutide 0.10 mg/kg/day**
Baseline, N	**13**	**31**	**30**
• 48 h oral (mL), mean (SD)	4898.1 (3605.6)	3881.5 (1787.6)	4549.8 (1946.2)
Change to week 24, N	**13**	**24**	**26**
• 48 h oral (mL), mean (SD)	–99.3 (1735.04)	121.5 (1869.81)	–784.6 (1293.74)
• Difference vs. placebo (*P* value)		Not reported	
Baseline, N	**13**	**29**	**30**
• 48 h urine (mL), mean (SD)	3165.8 (454.74)	2793.8 (734.69)	3000.6 (1116.05)
Change to week 24, N	**13**	**23**	**26**

	CL04		
• 48 h urine (mL), mean (SD)	232.2 (830.60)	733.7 (970.95)	–74.1 (1121.98)
• Difference vs. placebo (*P* value)		Not reported	

h = hour; PN = parenteral nutrition; SD = standard deviation; vs. = versus.
Source: Clinical Study Reports[1,2]

3.6.5 Quality of Life

CL04: The overall results from three QoL assessments (SF-36, EQ-5D, and IBDQ) indicated no major effect on QoL parameters.

SF-36v2 results are summarized in Table 16. Score changes were not reported for all visits or treatment groups; instead, differences between groups were reported for each component of the SF-36v2. Of note, significant differences by visits were observed between the placebo group and both treatment arms on the Physical Functioning scale. However, this difference was observed at baseline and lasted throughout the trial period. Similar results were observed for physical component summary scores, although in this case differences between placebo and each of the two treatment arms were attenuated and did not reach statistical significance at week 24. No other significant differences were observed between the two treatment arms.

TABLE 16: ANALYSES OF THE SF-36V2

SF-36v2 Domain		CL04	
		Teduglutide 0.05 mg/kg/day	Teduglutide 0.10 mg/kg/day
Physical Functioning	**Baseline**		
	• Difference versus placebo (SE), *P* value	7.34 (2.32); **0.0021**	6.05 (2.34); **0.0114**
	Change to week 24		
	• Difference versus placebo (SE), *P* value	6.96 (2.79); **0.0147**	8.18 (2.81); **0.0046**
Physical Role	**Baseline**		
	• Difference versus placebo (SE), *P* value	3.24 (3.22); 0.3160	4.07 (3.24); 0.2118
	Change to week 24		
	• Difference versus placebo (SE), *P* value	–0.94 (3.18); 0.7687	–0.39 (3.18); 0.9019
Bodily Pain	**Baseline**		
	• Difference versus placebo (SE), *P* value	4.58 (3.00); 0.1303	3.37 (3.02); 0.2682
	Change to week 24		
	• Difference versus placebo (SE), *P* value	2.67 (3.32); 0.4224	1.54 (3.32); 0.6443
General Health	**Baseline**		
	• Difference versus placebo (SE), *P* value	0.34 (2.92); 0.9075	0.09 (2.95); 0.9766
	Change to week 24		
	• Difference versus placebo (SE), *P* value	2.68 (3.02); 0.3772	0.22 (3.04); 0.9431
Vitality	**Baseline**		
	• Difference versus placebo (SE), *P* value	1.06 (2.70); 0.6957	0.21 (2.72); 0.9386
	Change to week 24		
	• Difference versus placebo (SE), *P* value	–0.44 (3.03); 0.8838	–0.77 (3.03); 0.7994

SF-36v2 Domain		CL04	
		Teduglutide 0.05 mg/kg/day	Teduglutide 0.10 mg/kg/day
Social Functioning	**Baseline**		
	• Difference versus placebo (SE), *P* value	0.87 (2.68); 0.7455	0.60 (2.70); 0.8237
	Change to week 24		
	• Difference versus placebo (SE), *P* value	0.48 (2.84); 0.8647	0.88 (2.84); 0.7573
Role Emotional	**Baseline**		
	• Difference versus placebo (SE), *P* value	1.05 (2.94); 0.7220	–0.73 (2.96); 0.8044
	Change to week 24		
	• Difference versus placebo (SE), *P* value	0.60 (3.10); 0.8462	–1.19 (3.09); 0.7002
Mental Health	**Baseline**		
	• Difference versus placebo (SE), *P* value	–1.07 (2.64); 0.6863	–1.67 (2.66); 0.5316
	Change to week 24		
	• Difference versus placebo (SE), *P* value	–1.56 (2.72); 0.5691	–1.12 (2.73); 0.6820
Physical Component Summary	**Baseline, N**		
	• Difference versus placebo (SE), *P* value	5.33 (2.67); **0.0488**	4.96 (2.69); 0.0690
	Change to week 24		
	• Difference versus placebo (SE), *P* value	4.30 (2.76); 0.1233	4.42 (2.77); 0.1154
Mental Health Component Summary	**Baseline**		
	• Difference versus placebo (SE), *P* value	–1.65 (2.68); 0.5395	–3.28 (2.70); 0.2272
	Change to week 24		
	• Difference versus placebo (SE), *P* value	–1.44 (2.75); 0.6029	–2.68 (2.76); 0.3333

SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.
Note: Bolding of the *P*-value indicates statistical significance
Source: Clinical Study Reports.[2]

IBDQ results are summarized in Table 17. There was no significant difference between treatment groups and placebo groups on all IBDQ domains and total scores at any of the examined time points.

TABLE 17: SUMMARY OF INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE SCORE

		CL04	
		Teduglutide 0.05 mg/kg/day	Teduglutide 0.10 mg/kg/day
Total score	**Baseline**		
	• Difference versus placebo (SE), *P* value	5.34 (7.63); 0.4859	4.77 (7.73); 0.5392
	Change to week 24		
	• Difference versus placebo (SE), *P* value	–0.98 (8.58); 0.9093	2.73 (8.68); 0.7539

SE = standard error.
Source: Clinical Study Reports[2]

EQ-5D results are summarized in Table 18. There was no significant difference between treatment groups and placebo groups on the mean EQ-5D index; teduglutide 0.05 mg/kg/day was associated with a statistically different change from baseline than placebo in the EQ5D Health Rating score, with 9.7 points difference (*P* = 0.0418).

TABLE 18: SUMMARY OF EQ-5D SCORE

		CL04	
		Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day
EQ-5D Index	**Baseline**		
	• Difference versus placebo (SE), *P* value	0.06 (0.044); 0.1626	0.02 (0.045); 0.6182
	Change to week 24		
	• Difference versus placebo (SE), *P* value	0.06 (0.046); 0.1663	0.04 (0.046); 0.3588
EQ-5D Health Rating	**Baseline**		
	• Difference versus placebo (SE), *P* value	7.03 (4.21); 0.0984	–0.19 (4.25); 0.9640
	Change to week 24		
	• Difference versus placebo (SE), *P* value	9.74 (4.71); 0.0418	1.67 (4.75); 0.7258

EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life questionnaire; SE = standard error.
Source: Clinical Study Report.[2]

CL20: The study did not show statistically significant QoL differences between the teduglutide and the placebo groups after 24 weeks of treatment, as measured with SBS-QoL (Table 19).

TABLE 19: ANCOVA MODEL, *P* VALUES FOR FACTORS INFLUENCING CHANGE IN QUALITY OF LIFE AT WEEK 24

	CL20
Influencing Factors	**ITT Population (N = 86)**
Baseline SBS-QoL value	**< 0.0001**
Treatment (teduglutide vs. placebo)	0.8112
PN volume reduction (yes/no)	**0.0051**
Interaction between treatment and PN volume reduction	**0.0117**

ANCOVA = analysis of covariance; ITT = intention-to-treat; PN = parenteral nutrition; QoL = quality of life; SBS-QoL = Short Bowel Syndrome–Quality of Life scale; vs. = versus.
Source: Clinical Study Report.[1]

3.6.6 Change in Body Weight

This outcome was not evaluated in the included studies.

3.6.7 Changes in Liver Enzymes Concentration

A summary of liver function tests is provided in Table 20.

In CL04, the mean change from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was numerically greater in the teduglutide groups than in placebo, but the differences from placebo were not statistically significant. However, this analysis falls outside testing procedure and should be interpreted as exploratory only.

In CL20, there were more patients in the teduglutide group than in placebo who had > 10% decrease in ALT (24 [63.2%] versus 12 [30.8%]; *P* = 0.007), AST (24 [63.2%] versus 12 [30.8%]; *P* = 0.019), and bilirubin (26 [68.4%] versus 11 [28.2%]; *P* < 0.001).

TABLE 20: SUMMARY OF LIVER FUNCTION TESTS

		CL04			CL20	
		Placebo	Teduglutide 0.05 mg/kg/day	Teduglutide 0.10 mg/kg/day	Placebo	Teduglutide 0.05 mg/kg/day
Albumin (g/L)	**Baseline, N**	**16**	**34**	**32**	**43**	**42**
	Mean (SD)	40.8 (5.04)	39.3 (4.69)	38.3 (3.86)	41.8 (42.0)	42.4 (42.5)
	Week 24, N	**16**	**26**	**29**	**39**	**38**
	> 10% increase				1 (2.6%)	0
	Within 10%				33 (84.6%)	36 (94.7%)
	> 10% decrease				5 (12.8%)	2 (5.3%)
	P value (X^2)[a]				0.344	
	Mean change (SD)	–2.0 (2.96)	–2.5 (4.59)	–0.9 (3.97)	–1.7 (2.4)	–0.4 (2.3)
	P value[b]		Not reported			
Alkaline phosphatase (U/L)	**Baseline, N**	**16**	**34**	**32**	**43**	**42**
	Mean (SD)	162 (118)	184 (95)	159 (79)	152 (85)	135 (66)
	Week 24, N	**16**	**25**	**29**	**39**	**38**
	> 10% increase				13 (33.3%)	6 (15.8%)
	Within 10%				10 (25.6%)	9 (23.7%)
	> 10% decrease				16 (41.0%)	23 (60.5%)
	P value (X^2)[a]				0.159	
	Mean change (SD)	–23.3 (86)	–11.6 (166.86)	–18.9 (67.08)	–4.9 (46.4)	–29.2 (34.8)
	P value[b]		Not reported			
ALT (U/L)	**Baseline, N**	**15**	**34**	**32**	**43**	**42**
	Mean (SD)	35.8 (19.1)	45.9 (33.4)	50.2 (35.7)	44.2 (35.0)	43.0 (29.1)
	Week 24, N	**15**	**26**	**29**	**39**	**38**
	> 10% increase				14 (35.9%)	4 (10.5%)
	Within 10%				13 (33.3%)	10 (25.3%)
	> 10% decrease				12 (30.8%)	24 (63.2%)

		CL04			CL20	
		Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/kg/day
	P value (X^2)[a]				**0.007**	
	Mean change (SD)	–1.3 (12.1)	–13.5 (24.4)	–7.3 (32.6)	0.6 (17.5)	–13.5 (17.8)
	P value[b]		> 0.05	> 0.05	Not reported	
AST (U/L)	**Baseline, N**	**16**	**34**	**32**	**43**	**42**
	Mean (SD)	33.6 (13.3)	37.9 (21.78)	41.1 (21.79)	34.6 (21.1)	32.4 (16.0)
	Week 24, N	**15**	**26**	**29**	**39**	**38**
	> 10% increase	Not reported			13 (33.3%)	6 (15.8%)
	Within 10%				14 (35.9%)	8 (21.1%)
	> 10% decrease				12 (30.8%)	24 (63.2%)
	P value (X^2)[a]				**0.019**	
	Mean change (SD)	–3.8 (12.5)	–6.8 (14.29)	–4.8 (23.34)	2.8 (23.4)	–5.8 (10.4)
	P value[b]		> 0.05	> 0.05	Not reported	
Bilirubin (umol/L)	**Baseline, N**	**16**	**34**	**32**	**43**	**42**
	Mean (SD)	Not reported			9.95 (7.80)	12.20 (9.80)
	Week 24, N				**39**	**38**
	> 10% increase				22 (56.4%)	6 (15.8%)
	Within 10%				6 (15.4%)	6 (15.8%)
	> 10% decrease				11 (28.2%)	26 (68.4%)
	P value (X^2)[a]				**< 0.001**	
	Mean change (SD)				3.42 (8.68)	–3.68 (5.53)
	P value[b]				Not reported	
GGT (U/L)	**Baseline, N**	**16**	**34**	**32**	**43**	**42**
	Mean (SD)	Not reported			85.7 (77.9)	75.1 (68.5)
	Week 24, N				**39**	**38**
	> 10% increase				11 (28.2%)	10 (26.3%)
	Within 10%				11 (28.2%)	5 (13.2%)
	> 10% decrease				17	23 (60.5%)

		CL04			CL20	
		Placebo	Teduglutide 0.05 mg/ kg/day	Teduglutide 0.10 mg/ kg/day	Placebo	Teduglutide 0.05 mg/kg/day
					(43.6%)	
	P value (X^2)[a]				0.222	
	Mean change (SD)				–3.2 (34.5)	–13.6 (36.9)
	P value[b]				Not reported	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; SD = standard deviation; U/L = units per litre.
[a] Class comparison of teduglutide versus placebo.
[b] For the difference in mean change between teduglutide and placebo.
Source: Clinical Study Reports.[1,2]

3.6.8 Health Care Resources Utilization

A summary of health care resources utilization in CL04 is provided in Table 21.

By the end of 24 weeks of treatment, the teduglutide 0.05 mg/kg/day group had a higher rate of hospitalization than placebo (17% versus 6%), but it had a lower rate of outpatient medical care (31% versus 50%). There was no statistical testing of the differences.

TABLE 21: HEALTH CARE RESOURCE UTILIZATION AT BASELINE, DOSING WEEK 24, AND LAST DOSING WEEK

	CL 040					
	Placebo		Teduglutide 0.05 mg/kg/day		Teduglutide 0.10 mg/kg/day	
N	**16**		**35**		**32**	
	Baseline	**Week 24**	**Baseline**	**Week 24**	**Baseline**	**Week 24**
Hospitalization, n (%)	**0**	**1 (6)**	**1 (3)**	**6 (17)**	**4 (13)**	**2 (6)**
• < 5 days	0	0	0	0	1 (25)	1 (50)
• ≥ 5 and < 10 days	0	0	0	3 (50)	2 (50)	0
• ≥ 10 days	0	1 (100)	1 (100)	3 (50)	1 (25)	1 (50)
Received outpatient medical care, n (%)	**6 (38)**	**8 (50)**	**14 (40)**	**11 (31)**	**12 (38)**	**10(31)**
• 1 Visit	4 (67)	4 (50)	8 (57)	4 (37)	6 (50)	3 (30)
• 2 Visits	0	1 (13)	3 (21)	1 (9)	1 (8)	2 (20)
• ≥ 3 Visits	2 (33)	2 (25)	3 (21)	6 (55)	5 (42)	5 (50)
• Missing data	0	1 (13)	0	0	0	0

Source: Clinical Study Reports.[1,2]

3.7 Harms

Only those harms identified in the review protocol are subsequently reported (see 2.2.1, Protocol). Harms data are summarized in Table 22.

In CL04, 15 (93.8%) placebo patients and 64 (95.5%) teduglutide patients reported at least one AE; this was similar across treatment groups. There were no deaths of patients who received the study drug in the study; however, one patient died during the screening period prior to randomization into the study. The incidence of serious adverse events (SAEs) was distributed similarly across treatment groups. A total of 29 patients were reported to have SAEs during the study (five [31.3%] patients in the placebo group, 13 [37.1%] patients in the teduglutide 0.05 mg/kg/day group, and 11 [34.4%] patients in the teduglutide 0.10 mg/kg/day group). The incidence of AE(s) that led to study discontinuation was greater in the teduglutide 0.05 mg/kg/day group (6 [17.1%] patients) compared with the placebo (one [6.3%] patients) and the teduglutide 0.10 mg/kg/day groups (2 [6.3%] patients).

In CL20, 69 patients were reported to have at least one treatment-emergent AE (TEAE) during the study (35/42 patients [83.3%] in the teduglutide group versus 34/43 patients [79.1%] in the placebo group). A total of 27 patients were reported to have at least one treatment-emergent SAE during the study (15/42 patients [35.7%] in the teduglutide group versus 12/43 patients [27.9%] in the placebo group). A total of 2/42 patients (4.8%) on teduglutide had treatment-emergent SAEs that the investigator considered to be related to the study drug. There were no related treatment-emergent SAEs reported in the placebo group. A total of five patients were reported to have experienced TEAEs leading to discontinuation during the study (2/42 patients [4.8%] in the teduglutide group versus 3/43 patients [7.0%] in the placebo group).

Higher rates of abdominal pain were reported in both CL04 and CL20, with the teduglutide 0.05 mg/kg/day dose over placebo, with 7/35 patients (20%) versus 2/16 patients (12.5%) reporting abdominal pain in CL04 and 13/42 patients (31%) versus 10/43 patients (23.3%) in the placebo group. Infections were reported at a higher rate as well, with 7/35 (20%) versus 2/16 (12.5%) reporting adverse effects with teduglutide 0.05 mg/kg/day versus placebo, respectively, in CL04; and 13/42 patients (31%) versus 8/43 patients (18.6%) for teduglutide versus placebo, respectively, in CL20. Other adverse effects that were reported had varying rates, with less consistent trends between the two trials.

TABLE 22: HARMS

	CL04			CL20	
AEs	**Placebo**	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.10 mg/ kg/day**	**Placebo**	**Teduglutide 0.05 mg/ kg/day**
N	**16**	**35**	**32**	**43**	**42**
Patients with > 0 TEAEs, N (%)	**15 (93.8)**	**33 (94.3)**	**31 (96.9)**	**34 (79.1)**	**35 (83.3)**
Most common TEAEs[a]					
• Abdominal pain	2 (12.5)	7 (20.0)	9 (28.1)	10 (23.3)	13 (31.0)
• Nausea	4 (25.0)	5 (14.3)	10 (31.3)	8 (18.6)	12 (28.6)
• Gastrointestinal stoma complication	0	1 (2.9)	5 (15.6)	3 (7.0)	10 (23.8)
• Abdominal distension	0	6 (17.1)	3 (9.4)	1 (2.3)	9 (21.4)
• Central line systemic infections				7 (16.3)	7 (16.7)
• Edema peripheral	0	1 (2.9)	1 (3.1)	2 (4.7)	7 (16.7)
• Urinary tract infection	3 (18.8)	3 (8.6)	5 (15.6)	4 (9.3)	6 (14.3)

	CL04			CL20	
AEs	**Placebo**	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.10 mg/ kg/day**	**Placebo**	**Teduglutide 0.05 mg/ kg/day**
N	**16**	**35**	**32**	**43**	**42**
• Flatulence	0	0	1 (3.1)	3 (7.0)	5 (11.9)
• Vomiting	2 (12.5)	2 (12.5)	2 (12.5)	4 (9.3)	5 (11.9)
• Fatigue	0	0	1 (3.1)	3 (7.0)	4 (9.5)
• Pyrexia	0	1 (2.9)	0	4 (9.3)	4 (9.5)
• Diarrhea	0	0	3 (9.4)	5 (11.6)	3 (7.1)
• Dyspnea				0	3 (7.1)
• Nasopharyngitis	2 (12.5)	6 (17.1)	5 (15.6)	0	3 (7.1)
• Weight increased	0	1 (2.9)	0	3 (7.0)	3 (7.1)
SAEs					
Patients with > 0 SAEs, N (%)	5 (31.3)	13 (37.1)	11 (34.4)	12 (27.9)	15 (35.7)
Most common SAEs[a]					
Infections and infestations	**2 (12.5)**	**7 (20.0)**	**5 (15.6)**	**8 (18.6)**	**13 (31.0)**
• Central line systemic infections				7 (16.3)	7 (16.7)
• Catheter-related infection	0	0	1 (3.1)	1 (2.3)	5 (11.9)
• Central line infection				3 (7.0)	2 (4.8)
• Urinary tract infection	0	1 (2.9)	0	1 (2.3)	2 (4.8)
• Bacteremia				3 (7.0)	0
GI disorders	**0**	**4 (11.4)**	**2 (6.3)**	**0**	**1 (2.4)**
General disorder and administration	**3 (18.8)**	**2 (5.7)**	**3 (9.4)**	**1 (2.3)**	**2 (4.8)**
• Catheter-related complication	3 (18.8)	0	3 (9.4)	0	1 (2.4)
• Implant site extravasation				1 (2.3)	1 (2.4)
• Pyrexia	0	2 (5.7)	0		
Metabolism and nutrition disorders				**0**	**1 (2.4)**
• Dehydration				0	1 (2.4)
Vascular disorders				**0**	**1 (2.4)**
• Subclavian vein thrombosis				0	1 (2.4)
Hepatobiliary disorders				**1 (2.3)**	**1 (2.4)**
• Cholecystitis, acute				0	1 (2.4)
• Hepatitis, cholestatic				1 (2.3)	0
WDAEs					
WDAEs, N (%)	**1 (6.3)**	**6 (17.1)**	**2 (6.3)**	**3 (7.0)**	**2 (4.8)**
Most common reasons					
• Abdominal distension	0	4 (11.4)	1 (3.1)	0	1
• Abdominal pain				0	1
• Intestinal polyp				1	0
• Fecal volume increased				1	0
• Frequent bowel movements				1	0
• Constipation	0	2 (5.7)	0		
Deaths					
Number of deaths, N (%)	**0**	**0**	**0**	**0**	**0**

AE = adverse event; GI = gastrointestinal; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse events.

[a] Frequency > 7%.

[b] Frequency > 2%.

Source: Clinical Study Reports[1,2]

4. DISCUSSION

4.1 Summary of Available Evidence

Two double-blind, randomized trials (CL04 and CL20)[1,2] met the inclusion criteria for this systematic review. The trials included adults with SBS due to major intestinal resection; e.g., due to injury, volvulus, vascular disease, cancer, or Crohn disease. Patients had to have had PN dependency at least 12 months prior to randomization for at least three times weekly to meet their caloric, fluid, or electrolyte needs because of ongoing malabsorption. The trials evaluated 24 weeks of teduglutide compared with placebo; CL04 evaluated teduglutide 0.05 mg/kg/day and 0.10 mg/kg/day, while CL20 tested the teduglutide 0.05 mg/kg/day dose only.

The main outcome in CL04 was a graded categorical score that takes both response intensity and duration between weeks 16 and 24 into account. The main efficacy outcome in CL20 was the responder rate, defined as the number and percentage of patients with at least a 20% reduction in weekly PN volume from baseline to week 20 and maintained at week 24.

4.2 Interpretation of Results

4.2.1 Efficacy

The manufacturer is seeking listing for teduglutide 0.05 mg/kg/day for the treatment of adult patients who are dependent on parenteral support, and who have been stabilized on PN/IV fluids after a period of intestinal adaptation. The listing criteria reflect the Health Canada–approved indication and the evaluated evidence from the included studies. In patient group input received by CDR for this submission, patients' expectations for the drug were to control symptoms of SBS, reduce dependence on PN, and improve their QoL.

Frequent PN is associated with PNALD. PN predisposes patients to an increased incidence of sepsis, increased mortality rates, and the potential to develop irreversible liver damage (Tazuke and Teitelbaum, 2009).[18] Therefore, reducing PN dependency is expected to prevent these complications. The included studies evaluated changes in PN dependency using various measures, but they did not evaluate the impact of these changes on patients' survival. A graded response score was used in both studies to evaluate response intensity and duration between weeks 16 and 24 of treatment. There is no published evidence of the validity, reliability, or MCID of this measure. In CL04, a step-down procedure was to be done and if the teduglutide 0.10 mg/kg/day dose was not significant, no further statistical testing was to be done. However, the authors continued with the teduglutide 0.05 mg/kg/day testing despite the fact that the trial did not achieve statistical significance for the dose of teduglutide 0.10 mg/kg/day. Therefore, comparative results between the low dose (teduglutide 0.05 mg/kg/day) and placebo in CL04 should be interpreted as exploratory only. Both trials showed that teduglutide 0.05 mg/kg/day was associated with better response rates than placebo, and two patients in CL04 were reported to be weaned from PN. Regarding reducing the mean weekly PN volume, the two trials showed inconsistent results. For instance, CL04 showed that neither teduglutide dose was statistically different from placebo in reducing the weekly PN volume, whereas CL20 showed that teduglutide 0.05 mg/kg/day was associated with a statistically significantly higher reduction in PN volume than placebo. CL04 evaluated the impact of teduglutide in reducing the number of PN days per week, and showed that neither dose was statistically different from placebo, whereas in CL 20, more patients achieved a one-day reduction in PN.

SBS has a direct impact on bowel movement and fluid balance in the body, and these factors potentially affect body dehydration and patients' QoL. The included studies did not evaluate intestinal emptying, and only CL04 reported changes in oral fluid intake and urine discharge. The trial showed that patients in the placebo and teduglutide 0.10 mg/kg/day groups had a decrease in oral fluid intake, whereas teduglutide 0.05 mg/kg/day was associated with increased fluid intake. However, the differences between active treatment and placebo were not evaluated statistically or clinically.

QoL is a main concern for SBS patients, and it was expected that changes in PN and fluid requirements would have a positive impact on patient's QoL. Three generic QoL measures were used in CL04; these were SF36, EQ5D, and IBDQ. None of these measures had a specific MCID for patients with SBS. For CL20, however, a disease-specific QoL measure was developed by the manufacturer and used in the trial SBS-QoL. The manufacturer reported that this measure has an MCID equivalent to two-fold the measurement error of the SBS-QoL (i.e., 18.4). The overall results from both trials failed to show any major effect of treatment on patients' QoL.

4.2.2 Harms

The number of patients with AEs, SAEs, or discontinuations due to treatment-emergent SAEs was comparable between treatment groups. The most frequently reported TEAEs in the teduglutide group were of gastrointestinal origin, such as abdominal pain, nausea, gastrointestinal stoma complication, or abdominal distension. There were no major findings reported in the laboratory and/or chemistry or hematology tests of the teduglutide-treated versus placebo patients. The rate of infections appears higher in the teduglutide-treated groups versus placebo in both studies.

Teduglutide has a similar mechanism of action to growth factors, and it may potentially induce overgrowths or tumours at its sites of action. However, the reviewed evidence did not show an increased risk of developing tumours in the treated patients. This should be interpreted with caution because of the relatively short duration of the reviewed evidence and the slow development of these tumours.

CL05[29] and CL21[30] are 28-week and two-year extension studies, respectively (APPENDIX 5). Safety results were similar across the extension and the original studies despite some higher AEs in CL21, which were due to the long-term observation.[30] It is notable that patients already on treatment for 24 weeks in the original trial continued to withdraw due to adverse effects in the extension trials.

4.3 Potential Place in Therapy[1]

According to the American Gastroenterological Association guidelines on SBS, [19] there are a number of drugs that can be used to improve absorption through various physiological effects. These drugs were not studied using randomized clinical trials, and the evidence is based mainly on expert opinion or, at best, case series or cohort studies, underlying the difficulty using randomized controlled trials in this small heterogeneous population. However, it is ultimately the anatomical characteristics of the individual patient that will determine who will have permanent intestinal failure and require PN for life.

Based on the available evidence, teduglutide is an intestinal trophic factor that also slows down gastric emptying. [31] It improves intestinal absorption of fluid and electrolytes and, if used long-term, as in the extension studies (CL05, CL21), it may allow for better absorption of nutrients and possibly

[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.

carbohydrates, potentially leading to the discontinuation of PN in some patients. The ability to discontinue PN is significant, considering that PN is generally a lifelong therapy in patients who were unable to be weaned within one year.

Clinically, PN patients who would probably benefit the most from teduglutide are those who require PN three to four days a week and have continuity with all or part of their colon, as they are the most likely to discontinue PN. However, any improvement in fluid and electrolyte absorption that allows for a PN reduction of at least 20% was considered clinically meaningful according to the clinical expert consulted by CDR, as it reduces infusion time, allows for better hydration, and may prevent kidney dysfunction.

PN patients are followed in specialized academic centres, allowing proper evaluation and PN monitoring. Patients on teduglutide would be treated in the same centres, and this regimen would be incorporated into the routine care of PN patients. However, for those with a colon, surveillance colonoscopies every two years may be required, as teduglutide is a trophic factor and there is concern that this may increase the risk of polyps and colon cancer.

5. CONCLUSIONS

Two double-blind, placebo-controlled, randomized trials (CL04 and CL20)[1,2] were included in this review. The main limitations of the included studies were the relatively small size, highly selective inclusion criteria, and the deviation of CL04 analyses from the statistical plan. Teduglutide administered according to the Health Canada–approved dose (0.05 mg/kg/day) was associated with better response rates than placebo in terms of parental feeding graded response. However, the two trials were inconsistent in showing a statistically significant different reduction of mean weekly PN volume between teduglutide and placebo. Furthermore, the reviewed trials were unable to show a consistent difference between teduglutide and placebo in reducing the number of PN days per week. The trials failed to show a difference in affecting patients' QoL. The inconsistencies could be due to random variability of the sample or a different weaning algorithm in the two trials. The number of patients with AEs, serious AEs, or discontinuations due to treatment-emergent SAEs was comparable between treatment groups. Patients already on treatment for 24 weeks in the original trial continued to withdraw due to adverse effects in the extension trials.

APPENDIX 1: PATIENT 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 GI (Gastrointestinal) Society, provided patients' input. The GI Society mission is to improve the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting GI and liver health.

Pharmaceutical companies from which the GI Society received support of any kind — such as charitable donations or grants, sponsorships, or subscriptions to the *Inside Tract* newsletter — in the last two years include AbbVie Corporation; Allergan, Inc.; AstraZeneca Canada; Canada's Research-Based Pharmaceutical Companies (Rx&D); Ferring Pharmaceuticals Inc.; Gilead Sciences Canada Inc.; GSK (GlaxoSmithKline Inc.); Hoffmann-La Roche Ltd.; Janssen Inc.; NPS Pharma Holdings; Merck Canada Inc.; Pfizer Canada Inc.; and Takeda Canada Inc. The group reported that the submission was solely prepared by them, with no outside help or influence.

2. Condition-Related Information

Information was obtained through contact (interviews, etc.) with patients with SBS and included several who participated in the clinical trials for teduglutide (Revestive). Additional information came from the Short Bowel Syndrome Oley Conference Roundtable in the US, which provided a forum to discuss issues amongst several patients with SBS and caregivers. A discussion of care issues with three health care providers, a physician, a nurse, and a hospital pharmacist was also part of the patient-group submission.

SBS is a potentially fatal gastrointestinal disorder in which patients are unable to absorb sufficient nutrients and fluids through the intestines. It occurs when the small intestine doesn't function properly due to trauma, disease, or when too much is removed. Conditions that could lead to a short bowel include Crohn disease, gastrointestinal cancer, perforated bowel, blocked or restricted blood flow to the bowel, or congenital abnormalities.

The symptoms and severity vary according to the part of the intestine that has been removed, as the small intestine is not identical in composition throughout its entire distance. Different sections of the small intestine are responsible for different nutrient absorption. As such, patient experiences can vary. Common symptoms include vitamin and mineral deficiencies, frequent diarrhea, extreme fatigue, cramping, dehydration, and weight loss. Complications of these can include peptic ulcer disease, kidney stones, gallstones, small bowel bacterial overgrowth, and metabolic bone disease.

Caregivers need to devote physical, emotional, and financial resources to a family member with SBS. They might need to take time off work and other necessary obligations to assist with preparing and administering feeding. Their time will also be limited by assisting the patient with other tasks. These can include cooking, cleaning, errands, physical hygiene care, and transporting the patient to medical appointments. These demands can result in financial hardship, stress, and anxiety. Relationships may become strained, which could lead to struggles within the family dynamic.

3. Current Therapy-Related Information
Treatment is determined according to the individual needs of the patient. Many will need to use a combination of therapies. These are listed below.

Dietary Adjustments
A dietitian will devise and monitor customized menus and eating plans for each patient's individual medical needs. In some cases, individuals need to ingest exceptionally large meals five to seven times a day because they cannot digest the amount of nutrients from regular meals. Other dietary adjustments may need to be made for the consumption of protein sources, carbohydrates, and fluids. However, cooking specialized meals can also be difficult and time-consuming. Nutritional supplements and formulas can also be expensive. Even with dietary adjustments, the individual will still suffer from insufficient nutrient and mineral absorption.

The patient group reported stories of two women; one was surviving on chicken broth, Ensure nutritional drinks, and only the tiniest bites of food all day long and, in spite of that, is still dealing with malnutrition, dehydration, weight loss, abdominal pain, nausea, and vomiting. Another woman explained how it was hard to participate in meals because she would often have to leave the table multiple times to empty her ostomy bag, as stool emptying into the bag was always liquefied and foul-smelling.

Enteral Nutrition
This process involves the delivery of a special liquid food mixture to the stomach or small intestine through a feeding tube. This could help maintain the absorptive properties of the remaining intestine, but patients must have a partially functioning gastrointestinal tract in order for this to be effective. This therapy can be difficult to manage, as blockages in the feeding tubes occur often. Bacterial contamination in the tube can cause serious infections.

Gastroesophageal reflux disease occurs frequently with enteral feeding. Symptoms such as abdominal bloating, cramps, nausea, diarrhea, and constipation are also common. Refeeding syndrome can also occur. This causes a large increase in insulin levels, which leads to a dramatic increase in oxygen consumption, and increased respiratory and cardiac demand.

Total Parenteral Nutrition
This process involves the delivery of fluids, electrolytes, and liquid nutrients into the bloodstream through a tube placed in the vein (intravenous [IV]). This is a complex and sometimes dangerous therapy. Complications include bacterial infections, IV catheter complications, blood clots, low bone calcium uptake, gallbladder disease, kidney disease, and liver problems. Liver and kidney problems can ultimately result in liver or kidney failure.

Infusions are usually done during sleep. Because of nausea caused by this feeding process, patients often become sleep-deprived. Mobility is compromised, as the equipment can be heavy or cumbersome. This can lead to limitations in employment, education, parenting, and social interactions. Total parenteral nutrition therapy is very expensive; it can cost more than $100,000 a year and still the patient has ongoing debilitating symptoms.

Surgery

There are a few surgical procedures that have been devised to increase the absorptive properties of the intestine. These involve artificially lengthening the intestine. Small bowel transplantation is sometimes attempted. However, complications from these surgeries can be severe and life-threatening. Patients may require frequent hospitalizations due to infections, and transplantation may cause serious damage to the liver or gallbladder.

4. Expectations About the Drug Being Reviewed

When other forms of management do not work well or specific patients cannot tolerate them, the patient group described teduglutide (Revestive) as an extremely valuable therapy to control symptoms of SBS, reduce dependence on total parenteral nutrition therapy and improve quality of life for patients. Patients group reported that patients who undertook treatment with teduglutide (Revestive) had more energy, less fatigue, and a general increase in quality of life. Patients also reported that they were able to eat, had less diarrhea, and had an increase in regular bowel movements.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 22, 2015
Alerts:	Bi-weekly search updates until April 20, 2016
Study Types:	No search filters were applied.
Limits:	No date or language limits were used. Conference abstracts were excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	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 words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(teduglutide* or gattex* or Revestive* or revestine* or UNII-7M19191IKG or UNII7M19191IKG or 7M19191IKG or "ALX 0600" or ALX0600 or 197922-42-2 or "197922422" or 197 922 422 or 197922 422).ti,ab,ot,kf,hw,rn,nm. use pmez
2	"(Gly2)GLP-2".ti,ab. use pmez
3	"Gly(2)-GLP-2".ti,ab. use pmez
4	"glucagon-like peptide 2 ".ti,ab. use pmez
5	"glucagon-like peptide II ".ti,ab. use pmez
6	(analog or analogs or analogue or analogues or recombinant*).ti,ab. use pmez
7	2 or 3 or 4 or 5
8	6 and 7
9	1 or 8
10	*teduglutide/ use oemezd
11	(teduglutide* or gattex* or Revestive* or revestine* or UNII-7M19191IKG or UNII7M19191IKG or 7M19191IKG or "ALX 0600" or ALX0600 or 197922-42-2 or "197922422" or 197 922 422 or 197922 422).ti,ab. use oemezd
12	"(Gly2)GLP-2".ti,ab. use oemezd
13	"Gly(2)-GLP-2".ti,ab. use oemezd
14	"glucagon-like peptide 2".ti,ab. use oemezd
15	"glucagon-like peptide II".ti,ab. use oemezd
16	(analog or analogs or analogue or analogues or recombinant*).ti,ab. use oemezd
17	12 or 13 or 14 or 15
18	16 and 17
19	*glucagon like peptide 2/ and Recombinant.hw. use oemezd
20	glucagon like peptide 2/ and Recombinant.hw. use pmez
21	9 or 20
22	10 or 11 or 18 or 19
23	conference abstract.pt.
24	22 not 23
25	21 or 24
26	remove duplicates from 25
27	*short bowel syndrome/ use oemezd
28	short bowel.ti,ab. use oemezd
29	27 or 28
30	*glucagon like peptide 2/ use oemezd
31	GLP-2.ti,ab. use oemezd
32	14 or 15 or 30 or 31
33	29 and 32
34	33 not 23
35	short bowel syndrome/ use pmez

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
36	short bowel.ti,ab. use pmez
37	35 or 36
38	glucagon like peptide 2/ use pmez
39	GLP-2.ti,ab. use pmez
40	4 or 5 or 38 or 39
41	37 and 40
42	34 or 41
43	remove duplicates from 42
44	26 or 43
OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	Search to December 2015
Keywords:	Teduglutide, short bowel
Limits:	No date or language limits used

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
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
O'keefe et al. 2013[29,32]	Not a comparator of interest
Jeppesen et al. 2005[33,34]	Study design: not randomized
Buchman et al. 2010[35]	Not a population of interest (not parenteral nutrition–dependent)

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the measurement properties (e.g., reliability, validity, minimal clinically important difference [MCID]) of the following outcome measures used in the manufacturer's pivotal studies to support the submission for Revestive for the treatment of adult patients with SBS who are dependent on parenteral support:

- 20% reduction from baseline in weekly parenteral nutrition (PN) volume
- Graded response score.

Findings

Table 23 provides a summary of the findings.

TABLE 23: VALIDITY OF OUTCOMES

Instrument	Description	Validated	MCID	References
20% reduction from baseline in weekly PN volume	• Achieving at least a 20% reduction from baseline in weekly PN volume	Unknown	Unknown	None found
Graded response score	• Algorithm where the magnitude of the reduction and time in which the response took place are taken into account	Unknown	Unknown	None found

MCID = minimally clinically important difference; PN = parenteral nutrition.

A. 20% reduction from baseline in weekly PN volume

Successful response was defined as achieving at least a 20% reduction from baseline in weekly PN volume.

No information was found on the validity and reliability of the 20% threshold used in trials. Similarly, what constitutes MCIDs in the reduction of PN volume is unknown. However, the clinical expert consulted for this review suggested that this reduction can be translated into meaningful improvements for patients.

B. Graded response score

The response was a graded response score (a scoring algorithm that takes both response intensity and duration between weeks 16 and 24 into account). The intensity of response relied on a reduction from baseline in weekly PN volume, where the protocol-defined reduction was set at a minimum of 20% and a maximum of 100%. Duration of response incorporated the responses at weeks 16 to 20 and weeks 20 to 24. Accordingly, the response variable was:

y = y1 + y2 + y3 + y4 + y5
= 0, 1, 2, 3, 4 or 5

Where

Y1 = 1 if 20% reduction from baseline in PN volume at week 20 is sustained to week 24
= 0 if not

Y2 = 1 if 20% reduction from baseline in PN volume at week 16 is sustained to week 24
= 0 if not

Y3 = [1 if 20% reduction from baseline in PN volume at either week 16 or 20 is sustained to week 24] and [40 % reduction from baseline in PN volume from week 16 to week 20 or from week 20 to week 24]
= 0 if not

Y4 = if 40% reduction from baseline in PN volume at week 16 is sustained to week 24
= 0 if not

Y5 = if 100% reduction in PN volume (i.e., off PN) at week 20 is sustained to week 24
= 0 if not

No information was found on the validity and reliability of the graded response score.

Conclusion

No published results of the validity, reliability, and MCID measures were identified. The clinical expert consulted for this review, however, confirmed that a reduction of 20% PN volume is an important clinical consideration.

APPENDIX 5: SUMMARY OF OTHER STUDIES

1. Objective

To summarize the results from the following extension studies:

1) CL05 (full name CL0600-005)[29] was a 28-week, double-blind, parallel-group extension study that included patients who completed 24 weeks of the CL04 study. The study aimed to evaluate the long-term safety and efficacy of once-daily subcutaneous (SC) teduglutide, administered at either 0.05 mg/kg/day or 0.10 mg/kg/day.
2) CL21 (full name CL0600-021)[30] is a two-year, open-label extension study that included patients who completed 24 weeks of CL20, or who were withdrawn because of non–drug-related adverse events (AEs), as determined by the investigator, or who were eligible to receive treatment but were not randomized because the trial had reached the required size. The study aimed to evaluate the long-term safety and efficacy of once-daily SC teduglutide 0.05 mg/kg/day.

2. Findings

Study Design

Both studies enrolled patients who completed the original trial. However, in addition to patients who completed the trial, CL21 also enrolled those who were withdrawn because of non–drug-related AEs, as determined by the investigator, and patients who were eligible to participate but did not do so due to completing the required trial number of patients.

In CL05 — a double-blind, parallel-group, extension study — 65 patients were enrolled. Patients who received teduglutide at either 0.05 mg/kg/day or 0.10 mg/kg/day doses in the original study (CL04) continued to receive the designated dose; this group of patients were referred to as the One-Year Active Group, and included 25 patients who continued to receive 0.05 mg/kg/day and 27 patients who received 0.10 mg/kg/day. Patients who were on placebo in CL04 were randomized to either 0.05 mg/kg/day or 0.10 mg/kg/day doses and were referred to as the Six-Month Active Group; this randomization yielded six patients who received a 0.05 mg/kg/day dose, and seven patients who received 0.10 mg/kg/day. CL21, a two-year, open-label extension study, assigned all patients to a 0.05 mg/kg/day dose, for a total of 88 participants. However, CL21 had two distinctive groups, depending on the previous study enrolment status, which would affect the overall exposure to the drug:

- The TED/TED group represented patients already exposed to active treatment for 24 weeks in CL20, and included 37 participants
- The NT, PBO/TED group represented patients who either participated in CL20 and received placebo (PBO) or who were eligible for randomization in study CL20 but qualified after enrolment number in SL20 was satisfied and thus were not treated (NT); this group included 51 participants.

Assessment

Both CL05 and CL21 aimed to study the long-term efficacy and safety of teduglutide. They shared many outcome variables but also differed slightly on others. However, CL05 assessed patients for the primary analysis at 28 weeks, whereas CL21 assessed patients after two years. Patients were assessed monthly in both studies, and results were descriptive, with no statistical measure of significance testing. For efficacy evaluation, CL05 used the data at baseline of study 004, which served as baseline for the One-Year Active Group, and the data at the end of study 004 (week 24), which served as baseline for the Six-Month Active Group. Similarly in CL21, the baseline was calculated from the first dose of the active study drug received in study CL0600-020 for patients who received teduglutide in that study. Patients who received placebo (or were not treated) in study CL0600-020 and started active treatment in study

CL0600-021 had the last visit prior to treatment in study CL0600-021 as the baseline for calculation purposes. Table 24 summarizes the different efficacy and safety end points in each study.

TABLE 24: SUMMARY OF OUTCOME MEASURES

	CL05	CL21
N	65	88
Efficacy Variables		
	Percentage of patients who were responders in study 004 (defined as at least a 20% reduction in weekly PN volume compared with baseline of study 004 at week 20 and week 24) and maintained or improved on that PN reduction at the end of dosing week 28 of study 005	Per cent and absolute change from baseline in weekly PN/IV volume by visit
	Percentage of patients who had a reduction of at least 20% compared with baseline in Weekly PN volume at week 28 (responders in study 005)	Binary response status by visit, where response at a given visit was defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume, with additional binary response status variables based on a 50% reduction, 75% reduction, and 100% reduction from baseline in weekly PN/IV volume, based on patient diary data
	Volume of PN reduction at week 28 compared with baseline	Duration of response (number of consecutive visits at the last visit with at least 20% reduction, 50% reduction, 75% reduction, and 100% reduction)
	Number and percentage of patients who discontinued PN	Patients who were weaned off PN/IV and the time of weaning off PN/IV
	Number and percentage of patients who experienced reduced IV catheter access compared with baseline at week 28	Change in days of weekly PN/IV
	Absolute reduction from baseline in PN kilojoules at week 28	Categorical reduction in days of weekly PN/IV (≥ 1-day reduction, ≥ 2-day reduction, ≥ 3-day reduction)
	Absolute reduction from baseline in weekly volume of PN at week 28	Binary response status by visit based on prescribed weekly PN/IV volume
	Changes from baseline in plasma citrulline at week 28	Patient-reported outcome SBS-specific QoL scale
	QoL measured by SF36.	
Safety Variables		
	AEs	AEs
	48-hour oral fluid intake	Laboratory safety data: hematology, clinical chemistry and urinalysis, including renal function based on BUN, creatinine, and urine sodium
	48-hour urine output	12-lead ECG
	Number and percentage of patients who experience IV catheter complications	Vital signs: blood pressure, pulse, body temperature
	Number of IV catheter complications	Body weight and BMI

	CL05	CL21
N	65	88
	12-lead ECG	48-hour urine output and 48-hour oral fluid intake
	Body weight	Antibodies to teduglutide
	Vital signs (BP, pulse, body temperature)	Antibodies to ECP
	Laboratory safety data: hematology, clinical chemistry, and urinalysis	

AE = adverse event; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; ECG = electrocardiogram; ECP = *Escherichia coli* protein; IV = Intravascular; PN = parenteral nutrition; PN/IV = parenteral nutrition and/or intravenous hydration; QoL = quality of life; SBS = short bowel syndrome.
Source: Clinical Study Reports.[29,30]

Results

Sixty-five patients were included in the final 24 weeks of analysis of CL05, whereas 88 patients were included in the final two years of analysis of CL21; patient disposition is presented in Table 25.

TABLE 25: PATIENTS' DISPOSITION

	CL05				CL21	
	6-Month Active		1-Year Active		NT, PBO/ TED	TED/ TED
	Teduglutide 0.05 mg/ kg/day	**Teduglutide 0.10 mg/ kg/day**	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.05 mg/ kg/day**
Patients completing original study, N	71				78	
Patients enrolling in extension study, N	65				88	
Randomized, N	6	7	25	27	51	37
Discontinued, N (%)	0 (0.0)	2 (28.6)	5 (20.0)	4 (14.8)	16 (31.4)	7 (18.9)

NT = not treated; PBO = placebo; TED = teduglutide.
Source: Clinical Study Reports.[29,30]

The results of the outcomes are represented in Table 26. For relevance reasons, only outcomes reported in the main body of this report will be included.

TABLE 26: EFFICACY AND SAFETY OUTCOMES FOR CL05 AND CL21

	CL05				CL21	
	6-Month Active		1-Year Active		NT, PBO/ TED	TED/ TED
	Teduglutide 0.05 mg/ kg/day	**Teduglutide 0.10 mg/ kg/day**	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.10 mg/ kg/day**	**Teduglutide 0.05 mg/ kg/day**	**Teduglutide 0.05 mg/ kg/day**
N	6	7	25	27	51	36
Patients achieving ≥ 20% PN reduction from baseline to week 28 (CL05) or 2 years (CL21)						
Responders, n (%)	5 (83.3)	3 (42.9)	17 (68.0)	14 (51.9)	20 (39.2)	33 (91.7)
Patients achieving least a 1-day reduction in weekly PN from baseline to week 28 (CL05) or 2 years (CL21)						
Responders, n (%)	4 (66.7)	2 (28.6)	17 (68.0)	10 (37.0)	17 (33.3)	21 (70.0)
Change weekly PN kilojoules from baseline to week 28 (CL05) or 2 years (CL21)						
Mean at baseline (SD)	18805 (10498)	20186 (14469)	26152 (13805)	39420 (20125)	NA	NA
Mean change (SD)	–5796 (6809)	–3209 (5389)	–14690 (12476)	–6512 (10405)	NA	NA
Reduction in weekly PN volume from baseline to week 28 (CL05) or 2 years (CL21)						
Mean at baseline (SD)	–2.8 (3.3)	–2.0 (1.9)	–4.9 (2.9)	–3.3 (4.6)	7.54 (5.471)	4.87 (4.795)
Mean (SD)	–2.8 (3.3)	–2.0 (1.9)	–4.9 (2.9)	–3.3 (4.6)	–3.27 (3.71)	–7.55 (4.93)
Patients with > 0 TEAEs						
n (%)	7 (100.0)	7 (100.0)	22 (88.0)	26 (96.3)	49 (96.1)	35 (94.6)
Patients with > 0 SAEs						
n (%)	2 (33.3)	3 (42.9)	13 (52.0)	9 (33.3)	32 (62.7)	24 (64.9)
Withdrawal due to adverse events						
n (%)	0 (0.0)	1 (14.3)	3 (12.0)	4 (14.8)	12 (23.5)	3 (8.1)
Deaths						
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	1 (2.7)

NA = not available; NT = not treated; PBO = placebo; PN = parenteral nutrition; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; TED = teduglutide.
Source: Clinical Study Reports.[29,30]

In CL05, at 52 weeks, four of 52 patients achieved independence from PN. In CL21, at 127 weeks, 13 of 88 patients achieved PN independence.

It appeared that the efficacy and safety results were similar across the extension and the original studies, despite some higher AEs in CL21, which could be due to the long-term observation.

3. Summary

The efficacy and safety results were similar across the extension trials and the original studies, despite some higher AEs in CL21, which were due to the long-term observation. It is notable that patients already on treatment for 24 weeks in the original trial continued to withdraw due to adverse effects in the extension trials.

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