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Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study

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Abstract

Background: This study evaluated the safety and efficacy of teduglutide in pediatric patients with short bowel syndrome–associated intestinal failure (SBS-IF). *Methods:* A 24-week, phase III trial with 2 randomized, double-blind teduglutide dose groups and a nonblinded standard of care (SOC) arm was used; patients received 0.025 mg/kg or 0.05 mg/kg teduglutide once daily. Safety end points included treatment-emergent adverse events (TEAEs) and growth parameters. The primary efficacy/pharmacodynamic end point was the number of patients who achieved a ≥20% reduction in parenteral support (PS) from baseline at week 24. *Results:* All 59 enrolled patients completed the study (0.025 mg/kg, n = 24; 0.05 mg/kg, n = 26; SOC, n = 9). Baseline demographics and disease characteristics were comparable among groups. TEAEs were reported by 98% and 100% of patients in the teduglutide and SOC groups, respectively. The most common TEAEs in the teduglutide-treated groups were pyrexia and vomiting. The primary end point was achieved by 13 (54.2%), 18 (69.2%), and 1 (11.1%) patients who received 0.025 mg/kg teduglutide, 0.05 mg/kg teduglutide, and SOC, respectively ($P < 0.05$ vs SOC). Both 0.025-mg/kg and 0.05-mg/kg teduglutide groups showed clinically significant reductions in PS volume ($P < 0.05$ vs SOC), PS calories, days per week and hours per day of PS infusions, and increases in enteral nutrition and plasma citrulline at week 24 compared with baseline. Two (8.3%, 0.025 mg/kg teduglutide) and 3 patients (11.5%, 0.05 mg/kg teduglutide) achieved enteral autonomy. *Conclusion:* The safety profile of teduglutide was similar to that reported previously in children and adults. Treatment with teduglutide was associated with significant reductions in PS for pediatric patients with SBS-IF over 24 weeks. (*JPEN J Parenter Enteral Nutr.* 2020;44:621–631)

Keywords
gastroenterology; parenteral nutrition; pediatrics; short bowel syndrome

Clinical Relevancy Statement

Parenteral support (PS)–dependent children with short bowel syndrome–associated intestinal failure (SBS-IF) have a high disease burden. In this 24-week, phase III study of 2 randomized, double-blind teduglutide dose groups and a nonblinded standard of care group, treatment with teduglutide reduced PS volume, calories, and infusion time in pediatric patients with SBS-IF. The safety profile was consistent with previous experience in adults and children with SBS-IF. In conjunction with expert management by intestinal rehabilitation specialists in this study, daily teduglutide injection was well tolerated and promoted intestinal adaptation, as evidenced by reductions of PS requirements in children with SBS-IF.

Introduction

Short bowel syndrome (SBS) is the most common cause of intestinal failure (IF), defined as gut function inadequate for satisfactory absorption of macronutrients, water, or electrolytes to maintain growth and development.[1] Long-term administration of parenteral support (PS; parenteral nutrition and/or intravenous fluids) is life-saving but associated with potentially life-threatening complications, including IF-associated liver disease, central line–associated blood stream infections, and central venous thrombosis.[1-3] Enhancing intestinal adaptation minimizes dependence on PS, thereby reducing the risk of complications[4-6] and potentially improving quality of life.[7,8]

Glucagon-like peptide-2 (GLP-2), a hormone secreted by enteroendocrine L cells in the distal ileum and proximal colon in response to the presence of unabsorbed luminal nutrients,[9,10] is a key component of the adaptive response to intestinal malabsorption.[9-12] Teduglutide, a recombinant human GLP-2 analogue, is approved in the United States and Europe for the treatment of patients ≥1 year of age with SBS-IF at a dose of 0.05 mg/kg administered subcutaneously once daily.[13,14] Teduglutide enables PS reductions in heterogeneous populations of adult and pediatric patients

with SBS-IF.[5,15-19] A previous 12-week, open-label trial in pediatric patients with SBS-IF (NCT01952080; EudraCT: 2013-004588-30) evaluated the safety of 3 different doses and showed reduced PS requirements among patients receiving 0.025 and 0.05 mg/kg teduglutide.[5] This manuscript reports results from a subsequent 24-week study that further evaluated the safety and efficacy of 0.025 and 0.05 mg/kg teduglutide in children with SBS who were dependent on PS.

Methods

A 24-week, phase III trial composed of 2 teduglutide dose groups and 1 standard of care (SOC) arm enrolled teduglutide-naïve patients at 24 centers in North America and Europe from June 2016 to August 2017 (ClinicalTrials.gov, NCT02682381, EudraCT 2015-002252-27). The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and the World Medical Association Declaration of Helsinki. Upon approval from institutional review boards or independent ethics committees, centers obtained written informed consent from parents for study participation of children and adolescents from 1 to 17 years of age requiring PS for SBS. Inclusion and exclusion criteria were similar to those of the previous 12-week study.[5] Patients considered incapable of advancing enteral nutrition (EN) were excluded. A minimum enrollment of 28 patients (10 into each teduglutide dose group and 8 into the SOC arm) was planned. During the minimum 2-week screening period, families chose to enroll the patient in either the teduglutide or SOC treatment arm. Patients in the teduglutide treatment arm were randomized 1:1 into 2 parallel-dose groups to receive a once-daily subcutaneous injection of 0.025 mg/kg or 0.05 mg/kg teduglutide according to a randomization scheme generated by the sponsor, with a block size of 4 within an age group stratum. The volume of teduglutide administered per kilogram was identical for both groups, and investigators were blinded to the teduglutide concentration received by patients.

All patients followed the same study visit schedule (Figure 1). During the study period, PS and specialized EN were recorded in intake diaries by the child's parent or guardian. At all site visits and during telephone contacts, safety was monitored and PS requirements reviewed and adjusted to maintain satisfactory hydration, nutrition status, and growth. Guidelines for nutrition support management and details of the algorithms for weaning off PS were provided to the investigators for their consideration (Supplementary Figure S1). Because of the requirement to incorporate clinical judgment into decision making, lack of adherence was not considered a protocol deviation. Compliance with dosing was monitored by parental reports and study drug accountability by counting used and unused vials. Data collected at each visit included predefined safety parameters, vital signs, blood samples, urine and stool output, body weight, body mass index (BMI), and nutrition support. Height and head circumference (for patients ≤36 months of age) were recorded at selected visits. Samples for analysis of specific antiteduglutide antibodies

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Conflicts of interest: S. Hu and A. A. Grimm worked for Shire Human Genetic Therapies, Inc., Lexington, MA, USA, a member of the Takeda group of companies, which manufactures teduglutide, during the study period and manuscript preparation.

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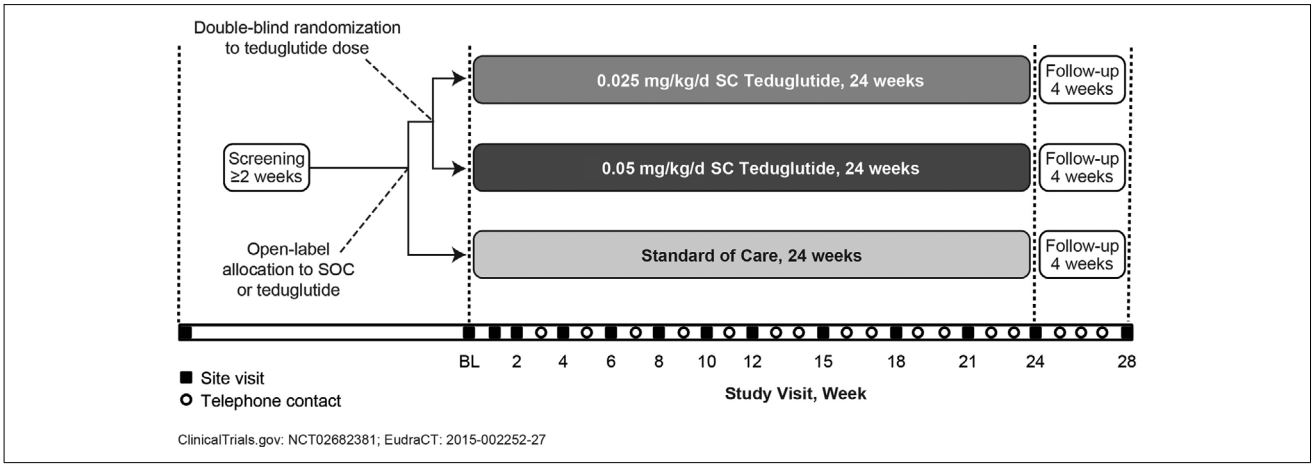


Figure 1. Study design. After screening, site visits occurred at baseline (day 0) and at the indicated study weeks. For all other study weeks, patients were contacted by telephone. BL, baseline; SC, subcutaneous; SOC, standard of care.

were collected at baseline, end of treatment (EOT), and end of study (EOS) visits. Plasma citrulline levels were measured at baseline, week 12, week 24, and EOS. All data collected were entered into patient electronic case report forms used for validation and statistical evaluation. Safety and tolerability were evaluated by a Data Monitoring Committee approximately every 3 months during the treatment period.

The intent-to-treat (ITT) population (all enrolled patients) and the safety population (all patients who received SOC or ≥1 dose of teduglutide and had 1 postbaseline safety assessment) were identical. Safety end points included adverse events (AEs), weight, height, head circumference, BMI *z*-score, vital signs, chemistry, hematology, and urinalysis. Treatment-emergent AEs (TEAEs; an AE that started or worsened after the SOC baseline/first dose visit) and treatment-emergent serious AEs (TESAEs; any medical occurrence that was judged by the investigator to be an important medical event) were coded using the Medical Dictionary for Regulatory Activities, version 19.1. PS data presented herein from patient diaries were similar to those from prescription data. The primary efficacy/pharmacodynamics (PD) end point, ≥20% reduction in PS volume at week 24 compared with baseline, was reported as the number and percentage of patients who achieved this end point. Other end points included the PS and EN volume and calories change from baseline at week 24, enteral autonomy at EOT (ie, no prescribed PS at EOT and no recorded PS administration for the week before EOT), and the change from baseline in days per week and hours per day of PS. Enteral intake data were limited to specialized enteral formula. PS and EN volume and calories were normalized to body weight. PD effects on gut mucosa were captured as the change from baseline in citrulline. All analyses were performed on the ITT/safety population. Given the rarity of SBS, the planned sample size was based on the estimated feasibility of enrollment in the pediatric population with SBS rather than on power calculations, and no statistical hypothesis testing of efficacy was therefore prespecified in the protocol. However, because of unexpectedly high enrollment, post hoc statistical analysis of the primary end point and the mean reduction in PS volume was performed. Limited post hoc statistical comparison on the primary end point and the most relevant secondary efficacy end point, PS volume, was performed. Post hoc analysis of the primary end point between each teduglutide dose group and the SOC arm, and between each other, employed Fisher exact test and 95% CI of the difference using the Newcombe-Wilson method with continuity correction. Additionally, the percentage change in PS volume from baseline to EOT was compared between each teduglutide dose group and the SOC arm, and between each other, using the Wilcoxon rank sum test. The resulting *P*-values and CI were not adjusted for multiplicity. All data values are reported as mean ± SD, unless otherwise stated.

Deidentified participant data from this study will be made available. Data requests should follow the process outlined in the Data Sharing section on Shire's website (www.shiretrials.com) and should be directed to clinicaltrialdata@shire.com.

Results

Of 59 patients enrolled, 50 patients chose to receive teduglutide and 9 chose to receive SOC; 24 were randomized to receive 0.025 mg/kg and 26 to receive 0.05 mg/kg teduglutide (Figure 2). All patients completed the 24-week treatment period and 4-week follow-up period. Baseline demographics and characteristics are summarized in Table 1. The number of patients receiving EN at baseline was 18 (75%), 25 (96%), and 9 (100%) for the 0.025-mg/kg teduglutide group, 0.05-mg/kg teduglutide group, and SOC group, respectively. The duration of teduglutide exposure was similar

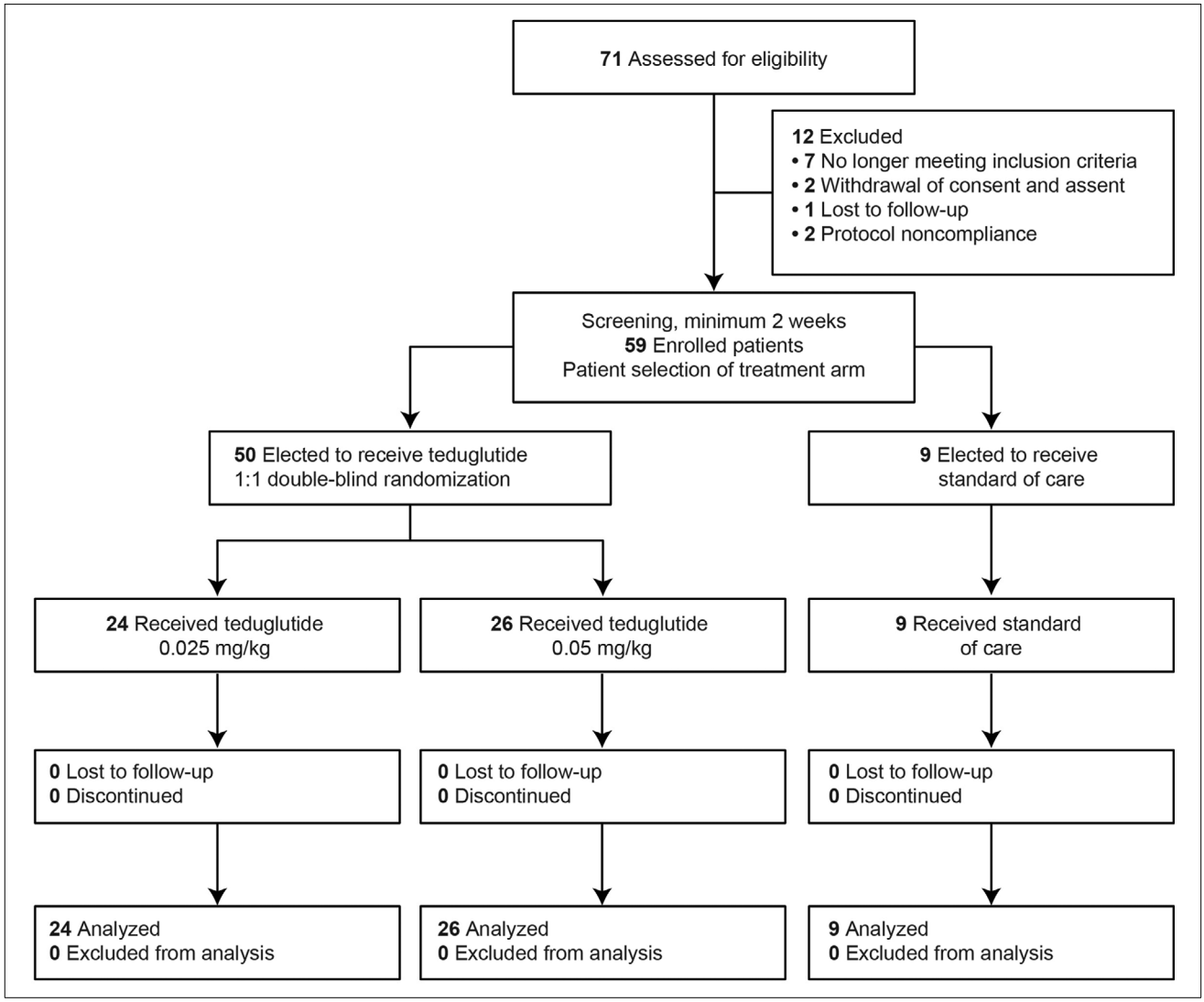


Figure 2. CONSORT diagram. Patients in the teduglutide treatment arm received a once-daily subcutaneous injection of 0.025 mg/kg or 0.05 mg/kg teduglutide.

in the 2 dose groups: 169.0 ± 2.69 days in the 0.025-mg/kg teduglutide group and 167.8 ± 1.33 days in the 0.05-mg/kg teduglutide group.

Throughout the study, nutrition status remained stable in all groups. Hydration-related tests showed no clinically meaningful changes in urine or stool output, urine specific gravity, blood urea nitrogen, or creatinine (Supplementary Table S1). The change from baseline at week 24 in height *z*-score was –0.09 ± 0.30, 0.04 ± 0.24, and –0.23 ± 0.26 and in BMI *z*-score was 0.11 ± 0.49, –0.05 ± 0.70, and 0.37 ± 0.59 for the 0.025-mg/kg teduglutide group, 0.05-mg/kg teduglutide group, and SOC group, respectively (Supplementary Figure S2).

All patients in the SOC arm and 98% of patients in the teduglutide dose groups experienced ≥1 TEAE; none led to treatment discontinuation. Most patients reported only mild TEAEs (17%, 0.025 mg/kg teduglutide; 27%, 0.05 mg/kg teduglutide; 44%, SOC) or moderate TEAEs (63%, 35%, and 56%, respectively). Severe TEAEs (ie, an intensity level that interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention) were reported by 21%, 35%, and 0%, respectively. The most common TEAEs among teduglutide-treated patients were pyrexia and vomiting and in the SOC arm were vomiting, pyrexia, and upper respiratory tract infection (Table 2). Other frequently reported gastrointestinal-related TEAEs were diarrhea and abdominal pain; overall, gastrointestinal-related TEAEs were reported by 79%, 77%, and 56% of patients in the 0.025-mg/kg teduglutide group, 0.05-mg/kg teduglutide group, and SOC group, respectively. Three patients (all in the 0.025-mg/kg teduglutide dose group) had 3 unrelated

Table 1. Baseline Patient Demographics and Characteristics.

Variable/Characteristic	Teduglutide 0.025 mg/kg (n = 24)	Teduglutide 0.05 mg/kg (n = 26)	SOC (n = 9)
Age, years, mean (SD)	7 (4)	6 (4)	6 (5)
Age group, years, n (%)			
1–<12	22 (92)	24 (92)	8 (89)
12–<17	2 (8)	2 (8)	0
17–<18	0	0	1 (11)
Sex, n (%)			
Male	16 (67)	19 (73)	6 (67)
Race, n (%)			
White	16 (67)	21 (81)	2 (22)
Black or African American	3 (13)	3 (11)	1 (11)
Asian	1 (4)	1 (4)	1 (11)
Other	1 (4)	0	2 (22)
Not allowed based on local regulations	3 (13)	1 (4)	3 (33)
Primary reason for SBS diagnosis, n (%)			
Necrotizing enterocolitis	5 (21)	3 (12)	2 (22)
Midgut volvulus	10 (42)	6 (23)	3 (33)
Intestinal atresia	2 (8)	1 (4)	0
Gastroschisis	6 (25)	14 (54)	2 (22)
Hirschsprung disease	1 (4)	1 (4)	2 (22)
Other	0	1 (4)	0
Patients with a stoma, n (%)	5 (21)	5 (20)	3 (33)
Type of stoma[a]			
Jejunostomy	3 (60)[b]	4 (80)	2 (67)
Ileostomy	0	1 (20)	1 (33)
Colostomy	2 (40)	0	0
Total estimated remaining small intestine length, cm, mean (SD)	38 (39)	47 (28)	45 (31)
Patients with remaining colon, n (%)	22 (92)	25 (96)	6 (67)
Estimated percentage of colon remaining, mean (SD)	61 (36)	69 (31)	60 (34)
Colon-in-continuity,[c] n (%)	22 (100)	22 (88)	6 (100)
Distal/terminal ileum present, n (%)	9 (38)	9 (35)	3 (33)
Ileocecal valve present,[d] n (%)	6 (67)	7 (78)	3 (100)
Growth parameter at baseline, mean (SD)			
Weight *z*-score	–0.9 (1.1)	–0.9 (1.1)	–0.2 (0.8)
Height *z*-score	–1.3 (1.2)	–1.3 (1.2)	–0.4 (1.6)
BMI *z*-score	–0.1 (1.1)	–0.0 (1.2)	0.1 (0.6)
Head circumference *z*-score[e]	–1.8 (0.5)	–0.1 (0.5)	–1 (N/A)

Patient demographics and baseline disease characteristics were similar in both study arms.
BMI, body mass index; N/A, not available; SBS, short bowel syndrome; SOC, standard of care.
[a]Percentages are based on the number of patients with a stoma in each treatment group.
[b]One patient had a small percentage of colon remaining in continuity, with ileocecal valve.
[c]Percentages are based on the number of patients who have remaining colon in each treatment group.
[d]Percentages are based on the number of patients with distal/terminal ileum present in each treatment group.
[e]For patients aged ≤36 months at time of measurement; n = 3 (0.025 mg/kg), n = 4 (0.05 mg/kg), n = 1 (SOC).

TEAEs for hepatobiliary disorders (1 event each of cholelithiasis, cholestasis, and liver disorder), and 1 patient in the 0.025-mg/kg teduglutide dose group reported an unrelated TEAE of increased lipase (>3× upper limit of normal). In the SOC arm, 1 patient had a TEAE of drug-induced liver injury due to voriconazole. TEAEs deemed related to teduglutide treatment by investigators are listed in Supplementary Table S2. There were 17 types of related TEAEs in 15 patients; the majority were experienced by a single patient (injection site bruising, abdominal pain, and vomiting each occurred in 2 patients). Peripheral edema occurred in a patient who received 0.025 mg/kg teduglutide. Fifteen patients (63%) in the 0.025-mg/kg teduglutide dose group, 20 patients (77%) in the 0.05-mg/kg teduglutide dose group, and 4 patients (44%) in the SOC arm reported TESAEs (Supplementary Table S3). Two patients (4%) treated with teduglutide (both in the 0.025-mg/kg dose group) experienced TESAEs deemed treatment related by the investigator: 1 patient was reported to have a fecaloma that was later clarified by the investigator to be a "hard

Table 2. TEAEs Occurring in ≥5% of Patients in Either Teduglutide Treatment Arm.

AE Preferred Term, n (%)	Teduglutide 0.025 mg/kg (n = 24)	Teduglutide 0.05 mg/kg (n = 26)	SOC (n = 9)
Pyrexia	8 (33)	11 (42)	4 (44)
Vomiting	10 (42)	8 (31)	5 (56)
Cough	2 (8)	10 (39)	3 (33)
Diarrhea	8 (33)	3 (12)	1 (11)
Dehydration	8 (33)	1 (4)	0
Upper respiratory tract infection	7 (29)	8 (31)	4 (44)
Alanine aminotransferase increased	7 (29)	2 (8)	0
Nasopharyngitis	4 (17)	6 (23)	2 (22)
Abdominal pain	4 (17)	6 (23)	0
Aspartate aminotransferase increased	5 (21)	0	0
Headache	3 (13)	5 (19)	1 (11)
Device-related infection	1 (4)	5 (19)	0
Rhinitis	1 (4)	5 (19)	0
Blood bicarbonate decreased	4 (17)	0	0
Abdominal pain upper	3 (13)	3 (12)	1 (11)
Nausea	3 (13)	3 (12)	1 (11)
Viral infection	3 (13)	3 (12)	1 (11)
Device breakage	3 (13)	3 (12)	0
Conjunctivitis	3 (13)	1 (4)	0
Device occlusion	3 (13)	1 (4)	0
Injection site bruising	3 (13)	1 (4)	0
Rhinorrhea	3 (13)	0	1 (11)
Gastroenteritis viral	3 (13)	0	0
Influenza	2 (8)	3 (12)	0
Ear infection	1 (4)	3 (12)	1 (11)
Catheter site infection	1 (4)	3 (12)	0
Urinary tract infection	2 (8)	1 (4)	1 (11)
Acidosis	2 (8)	1 (4)	0
Blood triglycerides increased	2 (8)	1 (4)	0
Device dislocation	2 (8)	1 (4)	0
Metabolic acidosis	2 (8)	1 (4)	0
Pain	2 (8)	1 (4)	0
Lymph node palpable	2 (8)	0	1 (11)
Cellulitis	2 (8)	0	0
Gastrointestinal bacterial overgrowth	2 (8)	0	0
Abdominal pain lower	2 (8)	0	0
Dermatitis diaper	2 (8)	0	0
γ-Glutamyltransferase increased	2 (8)	0	0
Pain in extremity	2 (8)	0	0
Seasonal allergy	1 (4)	2 (8)	0
Pharyngitis	0	2 (8)	0
Respiratory tract infection	0	2 (8)	0
Stoma site erythema	0	2 (8)	0
Abdominal distension	0	2 (8)	0

AE, adverse event; SOC, standard of care; TEAE, treatment-emergent adverse event.

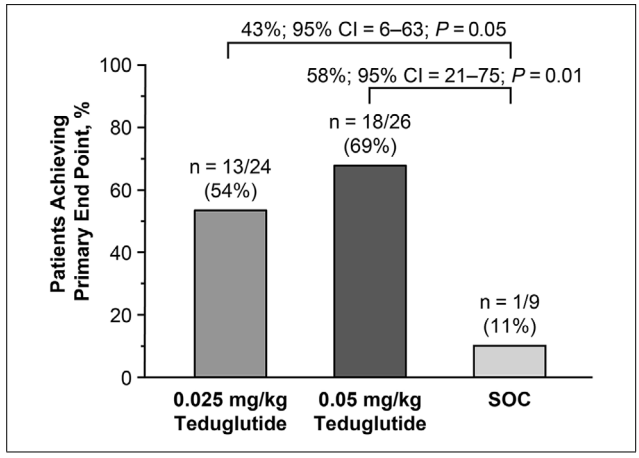
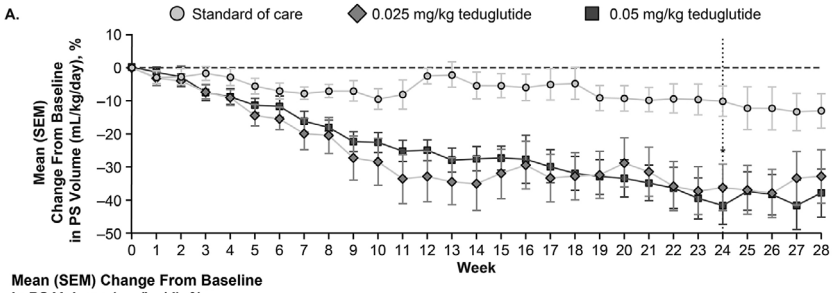


Figure 3. Patients achieving the primary study efficacy/PD end point. Horizontal bars represent the difference in the percentage of patients achieving a ≥20% reduction in PS volume at week 24 for each teduglutide group and SOC group. PD, pharmacodynamics; PS, parenteral support; SOC, standard of care.

stool." Another patient developed an adynamic ileus (no small bowel obstruction was confirmed). Both events were serious because of unexpected hospitalization, were moderate in severity, resolved after transient interruption of teduglutide, and did not recur upon rechallenge. Neither polyps nor neoplasia were detected during any colonoscopy or fecal occult blood testing. There were no AEs of intestinal stenosis, congestive heart failure, or AEs attributable to increased absorption of concomitant oral medications. None of the participants died during the study.

At week 24, 3 patients (13%) treated with 0.025 mg/kg teduglutide and 5 patients (20%) treated with 0.05 mg/kg teduglutide had antibodies to teduglutide. Of these 8 patients, 1 (4%) receiving 0.025 mg/kg teduglutide and 2 (8%) receiving 0.05 mg/kg teduglutide had neutralizing antibodies present at week 24. At the week-28 follow-up visit, 4 patients (17%) treated with 0.025 mg/kg and 5 patients (19%) treated with 0.05 mg/kg teduglutide had antibodies to teduglutide. Of these 9 patients, only 1 (4%) receiving 0.025 mg/kg teduglutide had neutralizing antibodies. The presence of antiteduglutide antibodies was not associated with TEAEs of hypersensitivity. All injection site reactions were mild and nonserious and did not necessitate drug discontinuation.

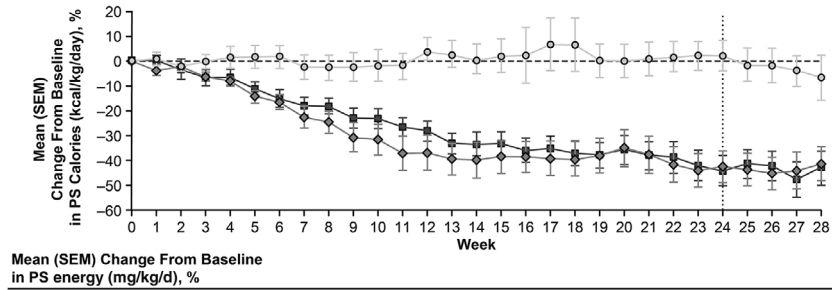
The primary efficacy/PD end point, a ≥20% reduction in PS volume at week 24, was achieved by 13 patients (54%) who received 0.025 mg/kg teduglutide, 18 patients (69%) who received 0.05 mg/kg teduglutide, and 1 patient (11%) who received SOC (Figure 3). Post hoc analysis evaluated the statistical differences in response rates between the 0.025-mg/kg group and SOC group of 43.1% (95% CI, 5.5%-63.2%; $P = 0.03$), between the 0.05-mg/kg and SOC groups of 58.1% (95% CI, 20.5%-75.1%; $P = 0.004$), and



Mean (SEM) Change From Baseline in PS Volume (mg/kg/d), %

Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
SOC[a]	0	–3	–3	–7	–7	–10	–3	–5	–6	–5	–9	–9	–10	–12	–13
	(0)	(2)	(3)	(2)	(2)	(3)	(2)	(4)	(4)	(5)	(4)	(4)	(5)	(7)	(5)
0.025 mg/kg teduglutide[b]	0	–4	–9	–16	–21	–29	–33	–35	–30	–33	–29	–36	–36	–38	–33
	(0)	(2)	(2)	(3)	(5)	(7)	(8)	(8)	(7)	(7)	(7)	(7)	(7)	(7)	(8)
0.05 mg/kg teduglutide[c]	0	–3	–9	–12	–18	–23	–25	–28	–28	–32	–34	–36	–42	–38	–38
	(0)	(3)	(2)	(3)	(2)	(3)	(3)	(4)	(7)	(5)	(6)	(6)	(6)	(6)	(7)

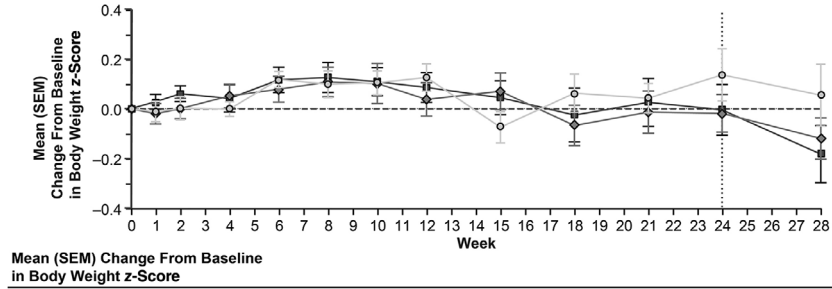
*P = .05 vs SOC.
[a]n=9 (except n=8 week 4–9, 11, 27; n=7 week 10, 25–26, 28).
[b]n=20 (except n=19 week 1, 11, 14, 16–17, 20, 22–23, 25–26; n=18 week 28, n=17 week 27).
[c]n=25 (except n=24 week 1, 11–12, 26; n=23 week 20, 22–23, 25; n=22 week 27–28).



Mean (SEM) Change From Baseline in PS energy (mg/kg/d), %

Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
SOC[a]	0	–2	1	1	–3	–2	4	0	2	6	0	1	2	–2	–7
	(0)	(1)	(4)	(5)	(5)	(6)	(6)	(7)	(11)	(11)	(7)	(6)	(6)	(7)	(9)
0.025 mg/kg teduglutide[b]	0	–3	–8	–17	–25	–32	–37	–40	–39	–40	–35	–42	–42	–45	–41
	(0)	(2)	(2)	(3)	(5)	(6)	(7)	(7)	(6)	(7)	(8)	(7)	(7)	(7)	(7)
0.05 mg/kg teduglutide[c]	0	–4	–7	–15	–18	–23	–28	–34	–36	–37	–36	–39	–44	–42	–43
	(0)	(3)	(3)	(4)	(3)	(4)	(4)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(7)

[a]n=9 (except n=8 week 4–9, 11, 27; n=7 week 10, 25–26, 28).
[b]n=20 (except n=19 week 1, 11, 14, 16–17, 20, 22–23, 25–26; n=18 week 28, n=17 week 27).
[c]n=25 (except n=24 week 1, 11–12, 26; n=23 week 20, 22–23, 25; n=22 week 27–28).



Mean (SEM) Change From Baseline in Body Weight *z*-Score

Week	0	2	4	6	8	10	12	15	18	21	24	28
SOC[a]	0	0.001	–0.002	0.117	0.098	0.104	0.125	–0.075	0.062	0.042	0.136	0.054
	(0)	(0.047)	(0.029)	(0.032)	(0.054)	(0.048)	(0.055)	(0.063)	(0.077)	(0.059)	(0.105)	(0.124)
0.025 mg/kg teduglutide[b]	0	0	0.051	0.078	0.107	0.101	0.037	0.070	–0.068	–0.014	–0.019	–0.120
	(0)	(0.041)	(0.048)	(0.052)	(0.060)	(0.081)	(0.067)	(0.073)	(0.081)	(0.085)	(0.076)	(0.083)
0.05 mg/kg teduglutide[c]	(0)	0.060	0.041	0.116	0.125	0.108	0.085	0.044	–0.026	0.025	–0.005	–0.183
		(0.032)	(0.055)	(0.051)	(0.060)	(0.056)	(0.060)	(0.068)	(0.108)	(0.096)	(0.102)	(0.115)

[a]n=9 (except n=8 week 4, 6, 8, 10).
[b]n=24 (except n=23 week 15).
[c]n=26 (except n=25 week 1, 4, 8).

Figure 4. Percentage change from baseline in (A) PS volume and (B) PS calories per patient diary data and *z*-score change from baseline in (C) body weight. Error bars represent the standard error. The week 24 vertical dotted line marks the end of the treatment period and the start of the follow-up period. PS, parenteral support; SEM, standard error of the mean; SOC, standard of care.

Table 3. Characteristics of Patients Who Achieved Enteral Autonomy.

Patient	Teduglutide Dose Group	Sex, Age, Race	Underlying Diagnosis	Small Bowel Length, cm	Terminal Ileum Present, Ileocecal Valve Present (Yes/No)	% Colon Remaining in Continuity	Baseline PS Volume, mL/kg/d[a]/ Calorie, kcal/kg/d	Weeks to Attain Enteral Autonomy[b]
1	0.025 mg/kg	Female 14 y White	Midgut volvulus	122	No No	50	29/24	10
2	0.025 mg/kg	Female 14 y White	Intestinal atresia	55	No No	70	10/9	8
3	0.05 mg/kg	Female 4 y White	Gastroschisis, intestinal atresia	120	No No	Unknown	57/33	21
4	0.05 mg/kg	Female 6 y Black	Midgut volvulus	40	No No	70	57/40	21
5	0.05 mg/kg	Male 9 y White	Midgut volvulus	64	Yes Yes	90	29/14	14

PS, parenteral support.
[a]Based on prescription data; rounded to nearest whole number.
[b]Based on the first week when there was no PS prescribed.

between the 0.025-mg/kg group and 0.05-mg/kg group of 15.1% (95% CI, –11.2% to 38.9%; $P = 0.21$). The absolute PS volume change at week 24 was –16.2 ± 10.52 mL/kg/d from a baseline of 56.8 ± 25.24 mL/kg/d in the 0.025-mg/kg teduglutide dose group, –23.3 ± 17.50 mL/kg/d from a baseline of 60.1 ± 29.19 mL/kg/d in the 0.05-mg/kg teduglutide dose group, and –6.0 ± 4.55 mL/kg/d from a baseline of 79.6 ± 31.12 mL/kg/d in the SOC arm; corresponding percentage changes are illustrated in Figure 4A. Reductions in PS volume were paralleled by reductions in PS calories. The absolute PS calories change at week 24 was –14.9 ± 8.29 kcal/kg/d from a baseline of 43.3 ± 21.10 kcal/kg/d in the 0.025-mg/kg teduglutide group, –19.0 ± 14.28 kcal/kg/d from a baseline of 43.3 ± 16.52 kcal/kg/d in the 0.05-mg/kg teduglutide dose group, and −0.5 ± 4.95 kcal/kg/d from a baseline of 44.6 ± 22.53 kcal/kg/d in the SOC arm; corresponding percentage changes are illustrated in Figure 4B. At week 28, 4 weeks after the treatment period, PS volume and calories remained substantially reduced compared with those observed in the SOC arm (Figure 4A and 4B). The change from baseline in body weight *z*-score during the 24 weeks of treatment with teduglutide, and the follow-up period, is illustrated in Figure 4C. The number of days per week of PS required by patients who received teduglutide also declined; the change from baseline at week 24 was –0.9 ± 1.78 days per week from a baseline of 6.5 ± 1.10 days per week in the 0.025-mg/kg teduglutide group, –1.3 ± 2.24 days per week from a baseline of 6.6 ± 0.79 days per week in the 0.05-mg/kg teduglutide dose group, and 0 days per week from a baseline of 6.6 ± 1.33 days per week in the SOC arm. The duration of the infusion declined by –2.5 ± 2.73 hours per day from a baseline of 11.7 ± 3.03 hours per day in the 0.025-mg/kg teduglutide dose group, –3.0 ± 3.84 hours per day from a baseline of 11.2 ± 2.99 hours per day in the 0.05-mg/kg teduglutide dose group, and –0.2 ± 0.69 hours per day from a baseline of 12.6 ± 5.50 hours per day in the SOC arm. Two patients (8%) who received 0.025 mg/kg teduglutide and 3 patients (12%) who received 0.05 mg/kg teduglutide achieved enteral autonomy. No patient who received SOC achieved enteral autonomy. Characteristics of patients who achieved enteral autonomy are summarized in Table 3. At week 24, the number of patients receiving EN increased from baseline for the 0.025-mg/kg teduglutide group and 0.05-mg/kg teduglutide group (23, 96%; 26, 100%, respectively) and remained the same for the SOC arm (9, 100%). The percentage change in EN volume from baseline at week 24 was 76.9% ± 117.19% for the 0.025-mg/kg teduglutide group, 79.5% ± 134.49% for the 0.05-mg/kg teduglutide group, and –2.5% ± 33.87% for the SOC arm. The percentage change from baseline at week 24 in EN calories was 82.7% ± 136.27% for the 0.025-mg/kg teduglutide group, 86.47% ± 128.11% for the 0.05-mg/kg teduglutide group, and 37.1% ± 107.53% for the SOC arm. Plasma citrulline levels increased from baseline to week 24 during treatment with teduglutide, demonstrating PD effects on intestinal mass (Supplementary Table S4).

Discussion

The findings from this 24-week study support the safety, tolerability, and efficacy/PD of teduglutide in the treatment of SBS-IF in the pediatric population. This study included patients with a variety of underlying causes of SBS, remnant small bowel length, and anatomic configuration, similar to the epidemiology of the disease in children.[20,21] All patients completed the study, with ≥80% treatment compliance, and no patient discontinued the study drug, indicating that daily treatment was well tolerated. Safety data support findings of the prior 12-week dosing study of teduglutide in pediatric patients.[5] Most TEAEs considered by a study investigator to be teduglutide related were single patient events. AEs of abdominal pain, a known reaction to teduglutide, occurred more frequently in the teduglutide dose groups than the SOC arm. The spectrum of TEAEs was similar between the teduglutide dose groups, and none led to treatment discontinuation or death. More patients in the teduglutide dose groups than in the SOC arm reported TESAEs, but only 2 teduglutide-treated patients experienced a TESAE considered treatment related by an investigator. In the previous 12-week pediatric study, no patient developed neutralizing antibodies to teduglutide.[5] During this longer study, 3 of the 8 patients with antiteduglutide antibodies at week 24 developed neutralizing antibodies, but antibodies were not associated with lack of efficacy or with TEAEs of hypersensitivity. None of the mild, nonserious injection site reactions resulted in drug discontinuation.

Significantly more patients with SBS-IF treated with teduglutide than those on SOC achieved the primary end point of a ≥20% reduction in PS volume at week 24: 54% and 69% (0.025 mg/kg and 0.05 mg/kg teduglutide, respectively) vs 11% (SOC; differences with teduglutide dose groups, $P < 0.05$ for both). Teduglutide treatment resulted in clinically meaningful reductions in PS in pediatric patients over 24 weeks of treatment using diary and prescription data (not shown). From baseline to week 24, the mean percentage changes in PS volume were −36% and –42% in the 0.025-mg/kg teduglutide group and 0.05-mg/kg teduglutide dose groups, respectively, and –10% in the SOC arm. Reductions in PS volume and calories in the 2 teduglutide dose groups were associated with substantial increases in EN volume and calories. Limiting EN data to specialized formula missed potential improvements in other oral intake. No clinically meaningful changes in weight, height, BMI *z*-scores, and urine or stool output occurred, indicating that the reductions in PS in the teduglutide-treated patients did not compromise the patients' nutrition status. For the patients treated with 0.05 mg/kg teduglutide, PS infusions were reduced by an average of 1.3 days per week. Treatment with teduglutide was associated with increased plasma citrulline level consistent with a teduglutide-induced increase in intestinal epithelial mass. Four weeks after discontinuation of treatment, citrulline levels declined to near baseline levels, suggesting that continued treatment with teduglutide is necessary to maintain the trophic effect on the gut epithelium. The slight reduction in PS and increase in EN observed in the SOC arm during the study may reflect spontaneous adaptation or improved medical management without pharmacologic intervention. Unlike patients who received SOC, 2 patients from the 0.025-mg/kg teduglutide group and 3 from the 0.05-mg/kg teduglutide dose group achieved enteral autonomy by week 24. Of these 5 patients, 1 had an intact terminal ileum and ileocecal valve, 4 had colon-in-continuity, and 2 had remnant bowel length of ≥120 cm. Both teduglutide dose groups showed PS reductions similar to those observed in the previous 12-week study, suggesting that the majority of the PD effects occurred within 12 weeks. However, 3 of the 5 patients who achieved enteral autonomy did so only after 12 weeks of treatment. A long-term study is needed to determine whether further reductions in PS occur with additional teduglutide treatment and whether reductions in PS can be sustained if teduglutide treatment is discontinued. In this double-blind study comparing 0.025-mg/kg and 0.05-mg/kg doses, the 0.05-mg/kg teduglutide dose group showed a numerically greater effect in all efficacy and PD parameters, including responder rate; mean reductions in PS volume, calories, and infusion days per week; and higher plasma citrulline. These small differences, as illustrated in Figure 4, suggest that the dose-response relationship in children is relatively flat within this dose range and that doses above 0.05 mg/kg/d are unlikely to provide greater benefit.

Limitations of this study include open-label treatment allocation and ability to choose teduglutide vs SOC treatment, allowing selection and reporting bias. It is possible that patients with less frequent or severe complications of SBS at baseline may have chosen SOC rather than teduglutide. Selection bias may also account for the higher baseline weight and height *z*-scores in the SOC arm. The nonblinded SOC arm also makes the safety data for teduglutide vulnerable to reporting bias for AEs. Although investigators were to apply the same nutrition support adjustment algorithm to all patients, the nonblinded SOC arm coupled with expected clinical benefit from teduglutide may have biased PS adjustments. Future analyses from the ongoing extension studies (NCT02949362/EudraCT2016-000862-17, NCT02954458/EudraCT2016-000849-30) may identify characteristics predicting responsiveness to teduglutide in children with SBS-IF. Identifications of such factors may inform patient selection, which may be relevant for assessment of the cost-effectiveness of tedulglutide.

In this study, the safety profile was similar in both dosing groups and consistent with previous experience in adults and children with SBS-IF.[5,13,14] In conjunction with expert management by intestinal rehabilitation specialists in this study, daily injection of teduglutide was well tolerated and

promoted intestinal adaptation, as evidenced by reductions of PS requirements in children with SBS-IF. The post hoc statistical analysis of the primary efficacy end point and change in mean PS volume supports the clinically meaningful improvements observed in the teduglutide groups ($P < 0.05$ vs SOC). PS reductions in response to treatment with teduglutide are expected to reduce the long-term risks associated with PS and may also improve quality of life of children with SBS-IF.[7,8,22]

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Statement of Authorship

The sponsor of the study participated in the study design, data collection, data analysis, data interpretation, and review and approval of the final clinical study report and provided the study drug. S. A. Kocoshis, S. Hill, B. A. Carter, R. S. Venick, and A. A. Grimm contributed to the conception and design of the research; S. A. Kocoshis, R. J. Merritt, S. Hill, S. Protheroe, B. A. Carter, S. Horslen, S. S. Kaufman, D. F. Mercer, M. P. Pakarinen, R. S. Venick, and P. W. Wales contributed to the acquisition of the data; S. A. Kocoshis, R. J. Merritt, S. Hill, S. Protheroe, B. A. Carter, S. Horslen, S. Hu, S. S. Kaufman, D. F. Mercer, M. P. Pakarinen, R. S. Venick, P. W. Wales, and A. A. Grimm contributed to the analysis of the data; S. A. Kocoshis, R. J. Merritt, S. Hill, S. Protheroe, B. A. Carter, S. Horslen, S. Hu, S. S. Kaufman, D. F. Mercer, M. P. Pakarinen, R. S. Venick, P. W. Wales, and A. A. Grimm contributed to the interpretation of the data; and S. A. Kocoshis and A. A. Grimm drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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