

Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome

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OBJECTIVES: In the pivotal 24-week, phase III, placebo-controlled trial, teduglutide significantly reduced parenteral support (PS) requirements in patients with short bowel syndrome (SBS). STEPS-2 was a 2-year, open-label extension of that study designed to evaluate long-term safety and efficacy of teduglutide.

METHODS: Enrolled patients had completed 24 weeks of either teduglutide (TED/TED) or placebo (PBO/TED) in the initial placebo-controlled study or qualified for that study, but were not treated (NT/TED) because of full enrollment. Patients received subcutaneous teduglutide 0.05 mg/kg/day for up to 24 months (NT/TED and PBO/TED) or up to 30 months (TED/TED). Clinical response was defined as 20–100% reduction from baseline in weekly PS volume; baseline was considered the beginning of teduglutide treatment in the initial placebo-controlled study (TED/TED) or STEPS-2 (NT/TED and PBO/TED). Descriptive statistics summarized changes in efficacy and safety variables.

RESULTS: Of 88 enrolled patients, 65 (74%) completed STEPS-2. The most common treatment-emergent adverse events were abdominal pain (34%), catheter sepsis (28%), and decreased weight (25%). Mean weight, body mass index, and serum albumin remained stable. In patients who completed the study, clinical response was achieved in 28/30 (93%) TED/TED, 16/29 (55%) PBO/TED, and 4/6 (67%) NT/TED patients. Mean PS volume reductions from baseline were 7.6 (66%), 3.1 (28%), and 4.0 (39%) l/week in the TED/TED, PBO/TED, and NT/TED groups, respectively. Thirteen patients achieved full enteral autonomy.

CONCLUSIONS: In patients with SBS, long-term teduglutide treatment resulted in sustained, continued reductions in PS requirements. Overall health and nutritional status was maintained despite PS reductions.

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INTRODUCTION

Short bowel syndrome (SBS) is a malabsorptive condition characterized by an extreme reduction in functional intestinal length.¹ In the past, SBS has been defined by the presence of less than 150–200 cm of postduodenal small intestine.^{2,3} However, within this population, there is a spectrum of bowel dysfunction ranging from compensated intestinal insufficiency to intestinal failure (SBS-IF) requiring parenteral support (PS; consisting of parenteral nutrition and/or intravenous fluids) because the extent of bowel function depends on the health and anatomy of the residual bowel and the degree of compensatory intestinal and physiologic adaptation following resection.^{1,4,5} Thus, more recently, SBS-IF has been operationally defined as loss of absorptive capacity characterized by the inability to maintain proper hydration or protein-energy, electrolyte, or micronutrient balances while conforming to a conventional diet.⁶

SBS-IF is frequently associated with severe diarrhea, abdominal pain, dehydration, and malnutrition.⁷ Despite changes in PS constituents and improvements in catheter care in recent years, PS-dependent patients remain at risk for potentially life-threatening complications, including catheter-related central line sepsis, loss of vascular access, and progressive liver dysfunction.^{8–11} Among PS-dependent patients, catheter-related bloodstream infections occur at a rate of between 0.38 and 4.58 episodes/1000 catheter days.¹² In addition, PS dependence in patients with SBS is associated with a reduced quality of life.^{10,13} Patients who require chronic PS report disruptions in lifestyle, social engagement, and sleep patterns.¹⁰ Primary disease-related concerns for patients with SBS-IF include worries about burdening others, low energy levels, isolation, and fear of surgery.¹³

Intestinal rehabilitation for patients with SBS is aimed at controlling symptoms of malabsorption, optimizing nutritional status, maximizing the absorptive capacity of the remnant

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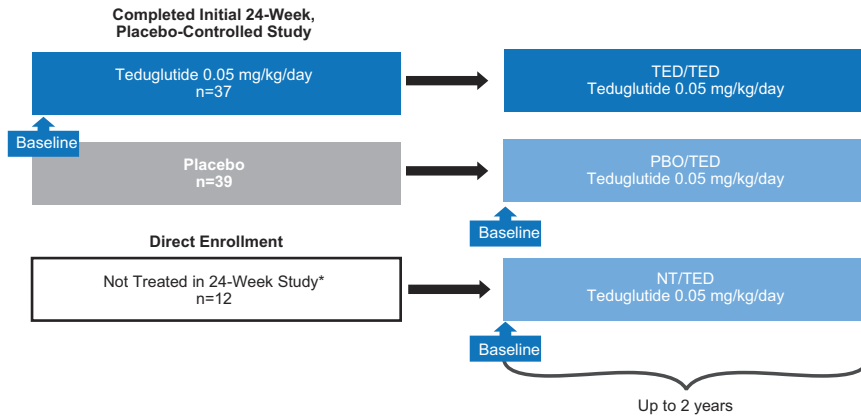


Figure 1 STEPS-2 study design. All patients who completed 24 weeks of treatment in the initial placebo-controlled study with either teduglutide or placebo or who completed the fluid optimization and stabilization phases in the initial placebo-controlled study but were not randomized were eligible for enrollment. Baseline was considered to be the start of teduglutide treatment. *Patients who completed fluid optimization and stabilization but were not randomized in the initial 24-week placebo-controlled study because of full study enrollment were eligible for direct enrollment into STEPS-2. NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2.

bowel, and reducing or eliminating the need for PS.^{5,14} Whereas traditional treatment modalities for SBS have focused on reducing malabsorptive losses through dietary modification and antidiarrheal/antisecretory agents,^{5,15} there has been interest in novel therapeutic approaches that enhance the absorptive capacity of the remnant bowel and decrease the need for PS.^{16,17} Teduglutide is a stable recombinant analog of glucagon-like peptide 2, a trophic hormone secreted by intestinal L cells.^{18–20} Teduglutide is approved in the United States and Europe for use in adult patients with SBS who are dependent on PS. In phase III studies, teduglutide enhanced intestinal absorption and reduced PS requirements in patients with SBS-IF.^{17,21} In the pivotal 24-week, multicenter, multinational, double-blind, placebo-controlled trial, 63% (27/43) of patients receiving teduglutide 0.05 mg/kg/day achieved the primary end point (20–100% reduction from baseline in weekly PS volume at weeks 20 and 24) compared with 30% (13/43) of patients receiving placebo ($P=0.002$). Mean PS volume reductions were 4.4 and 2.3 l/week among the treatment and placebo groups, respectively ($P\leq 0.001$). The most common adverse events (AEs) reported in teduglutide-treated patients were gastrointestinal related, including abdominal pain, nausea, stoma complications, and abdominal distension.¹⁷

The current study (STEPS-2) was a 24-month, open-label extension of the initial placebo-controlled study undertaken to assess the long-term safety, tolerability, and clinical efficacy of teduglutide in patients with SBS-IF.

METHODS

Study design and patients. STEPS-2 was a 2-year, open-label extension study that included patients from 25 centers in nine European and North American countries (ClinicalTrials.gov identifier: NCT00930644). The study protocol was reviewed and approved by the institutional review boards/independent ethics committees/research ethics boards. All patients who met the inclusion/exclusion criteria¹⁷ and

completed 24 weeks of treatment in the initial placebo-controlled study with either teduglutide or placebo were eligible to enroll (Figure 1). In addition, patients who completed the fluid optimization and stabilization phases of the initial placebo-controlled study¹⁷ to establish baseline PS requirements but were not randomized because of full study enrollment could enroll directly into STEPS-2. All patients received a daily subcutaneous injection of 0.05 mg/kg/day teduglutide for up to 24 months. The study population included three patient subgroups: those who received teduglutide in the initial placebo-controlled study and STEPS-2 (TED/TED), those who received placebo in the initial placebo-controlled study followed by teduglutide in STEPS-2 (PBO/TED), and those who received no treatment in the initial placebo-controlled study followed by teduglutide in STEPS-2 (NT/TED). Including study drug exposure during the placebo-controlled trial, total exposure to teduglutide at the end of STEPS-2 was up to 30 months for TED/TED and up to 24 months for the NT/TED and PBO/TED subgroups.

Protocol for PS adjustments. All patients enrolled in STEPS-2, including the NT/TED subgroup not randomized to treatment in the initial placebo-controlled study, had undergone a period of strict PS optimization and stabilization at the start of the initial placebo-controlled study to establish stable, minimal weekly PS volumes while maintaining appropriate hydration (i.e., urine outputs between 1 and 2 l/day).¹⁷ During the extension study, PS volume adjustments of 10–30% were made according to the placebo-controlled study algorithm¹⁷ but at less frequent intervals. Details are provided in the Supplementary Materials online (study results are also posted to the ClinicalTrials.gov website (study identifier: NCT00930644)).

Safety and efficacy measures. Clinical evaluations were performed as outlined in the Supplementary Materials. Colonoscopies were performed at the start of the initial placebo-controlled study and at the end of STEPS-2 in those patients with colons for the purpose of polyp surveillance.

Table 1 Baseline demographics and characteristics of the overall study population

Characteristic	TED/TED (n = 37)	PBO/TED (n = 39)	NT/TED (n = 12)	All Patients (N = 88)
Mean (s.d.) age, years	51.8 (12.5)	50.4 (15.9)	50.0 (13.9)	50.9 (14.2)
Mean (s.d.) body weight, kg	62.7 (12.1)	61.1 (13.2)	65.8 (12.9)	62.4 (12.6)
Mean (s.d.) BMI, kg/m ²	22.3 (3.3)	22.0 (3.2)	22.9 (3.9)	22.3 (3.3)
Men, n (%)	18 (49)	17 (44)	6 (50)	41 (47)
<i>Reason for resection, n (%)</i>				
Vascular disease	12 (32)	15 (38)	2 (17)	29 (33)
Crohn's disease	8 (22)	7 (18)	1 (8)	16 (18)
Volvulus	3 (8)	6 (15)	2 (17)	11 (13)
Injury	4 (11)	3 (8)	0	7 (8)
Cancer	1 (3)	2 (5)	0	3 (3)
Other	9 (24)	6 (15)	7 (58)	22 (25)
Colon-in-continuity, n (%)	24 (65)	23 (59)	7 (58)	54 (61)
Mean (s.d.) percentage of colon remaining	55 (21)	70 (27)	60 (37)	63 (27)
Median (range) estimated remaining small intestine, ^a cm	60.0 (20–250)	43.0 (5–170)	45.0 (15–150)	50.0 (5–250)
Stoma, n (%)	17 (46)	14 (36)	5 (42)	36 (41)
Mean (range) time since start of PS dependence, years	7.0 (1.0–24.7)	6.0 (1.0–25.8)	6.2 (1.1–20.8)	6.4 (1.0–25.8)

BMI, body mass index; NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids); TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2.

^aIncludes only patients with known residual small intestine length.

Patients were evaluated for antibodies to teduglutide and plasma citrulline levels, as described in the Supplementary Materials.

Efficacy end points included the change in PS volume from baseline, the percentage of patients achieving a response ($\geq 20\%$ reduction in PS volume from baseline), duration of response, reduction in days of PS per week, and the number of patients who achieved independence from PS.

Data analysis. The primary patient population for all analyses was the intent-to-treat population, defined as all patients who signed informed consent. The safety population included all patients who received at least one dose of study drug. For safety analyses, patients with no previous exposure to teduglutide (PBO/TED and NT/TED subgroups) were combined. For efficacy analyses, data for each subgroup were considered separately because patients in the NT/TED subgroup were not randomized in the initial 24-week placebo-controlled study and therefore did not participate in that study's regimented, regularly scheduled study visits, including the protocol-driven efforts at PS reduction.

Treatment-emergent AEs (TEAEs) were coded using the Medical Dictionary for Regulatory Activities and summarized using descriptive statistics. TEAEs were categorized as related to treatment if a causal relationship to the study drug could not be ruled out. Onset of TEAEs was based on the study period of STEPS-2, regardless of treatment in the initial placebo-controlled study. Missing safety parameters were not imputed.

Descriptive statistics summarized the change from baseline in efficacy variables at each time point. The study was not sufficiently powered to determine the statistical significance of safety or efficacy end points. Baseline was determined by the initial exposure to teduglutide. Therefore, baseline was considered the last visit before teduglutide treatment in the initial placebo-controlled study for TED/TED and the last visit before teduglutide treatment in STEPS-2 for PBO/TED and NT/TED.¹⁷ Weekly PS volume was calculated from the 2-week

interval before a visit based on patient diary entries. Missing PS volumes from patient diaries were not imputed, and a maximum of five missing days from each 2-week interval was allowed; otherwise, the interval was classified as missing.

RESULTS

Patients. Of the 78 patients who completed the initial placebo-controlled study and were eligible for STEPS-2, 76 enrolled in the extension ($n = 37$ TED/TED; $n = 39$ PBO/TED). An additional 12 patients who were screened and optimized in the placebo-controlled study but not randomized were enrolled directly in STEPS-2. Of the 88 patients enrolled in STEPS-2, 65 (74%) completed the study ($n = 30/37$ TED/TED; $n = 29/39$ PBO/TED; $n = 6/12$ NT/TED). In the TED/TED subgroup, seven patients discontinued because of AEs ($n = 4$; three were TEAEs, described below, and one was an ongoing event (non-treatment-emergent AE) that originated during the initial placebo-controlled study), patient decision ($n = 2$), and death ($n = 1$; case of catheter-related sepsis described below). In the combined NT/TED and PBO/TED subgroups, 16 patients discontinued because of AEs ($n = 12$), patient decision ($n = 2$), or investigator decision ($n = 2$). Patient characteristics and demographics (Table 1) were similar among the three subgroups.

All 88 patients who signed the consent form received at least one dose of teduglutide; therefore, the safety and intent-to-treat populations were identical. Of the 88 patients, 81 (92%) received $\geq 80\%$ of planned doses: 32/37 (87%) in TED/TED and 49/51 (96%) in the combined NT/TED and PBO/TED subgroups.

Safety and tolerability. TEAEs were reported in 84/88 (95%) patients; 46 patients (52%) had TEAEs that were considered treatment related. Most patients experienced TEAEs that were mild or moderate in severity. The most common TEAEs are listed in Table 2.

Treatment-emergent serious AEs (TESAEs) occurred in 56/88 (64%) patients (Table 3): 24 (65%) in TED/TED and

Table 2 Treatment-emergent adverse events occurring in $\geq 10\%$ of study patients

Adverse event, <i>n</i> (%)	All patients, <i>N</i> = 88
Abdominal pain	30 (34)
Catheter sepsis	25 (28)
Episodes of weight decrease	22 (25)
Asthenic conditions	20 (23)
Febrile disorders	18 (20)
Nausea	17 (19)
Urinary tract infections	16 (18)
Catheter site-related reactions	15 (17)
Upper respiratory tract infections	15 (17)
Abdominal distension	14 (16)
Diarrhea	13 (15)
Musculoskeletal pain	13 (15)
Gastrointestinal stoma ^a complications	12 (33)
Dehydration	12 (14)
Fluid overload	12 (14)
Headaches	10 (11)
Hypersensitivity	9 (10)
Muscle spasms	9 (10)
Flatulence	9 (10)
Vomiting	9 (10)

^aOnly among patients with stoma (*n* = 36).

32 (63%) in the combined NT/TED and PBO/TED subgroups. Nine of 88 (10%) patients experienced TESAEs considered by the clinical site investigator to be related to teduglutide treatment. These were gastrointestinal stoma complications and abdominal pain (*n* = 2 for each), and exacerbation of Crohn's disease, intestinal obstruction, injection site hematoma, cholecystitis, portal hypertension, blood bilirubin increased, metastatic neoplasm (case history for patient with metastatic adenocarcinoma described below), and hypertension (*n* = 1 for each). Weight loss was not reported as a serious AE (SAE) in any patient.

Three deaths occurred during the study. A 70-year-old man in the TED/TED subgroup with SBS as a result of major intestinal resection secondary to mesenteric artery embolism was hospitalized with catheter-related sepsis and urinary tract infection following 28 months of teduglutide. The patient died 15 days after hospitalization, despite empiric antibiotic treatment. Sepsis in this patient was considered unrelated to teduglutide, and no change was made to his teduglutide treatment regimen during these events. A 48-year-old man in the NT/TED subgroup was diagnosed with metastatic adenocarcinoma to the liver of unconfirmed origin 11 months after starting teduglutide treatment. This patient had a history of Hodgkin's disease treated with chemotherapy and abdominal radiation two decades before receiving teduglutide. The investigator considered the patient's prior Hodgkin's disease and treatment course of chemotherapy and radiotherapy to be risk factors for neoplasm; however, the event was reported as treatment related. Six months before starting teduglutide therapy, the patient had undergone a computed tomography (CT) of the abdomen, which showed liver enlargement. A subsequent review of this CT and a second CT scan performed after initial back pain symptom onset (almost 11 months after teduglutide initiation) revealed a focal lesion in the liver that had not been reported on the initial CT. Teduglutide was discontinued (13 days before death) and a biopsy of the liver lesion (8 days before death) revealed

Table 3 Treatment-emergent serious adverse events by system organ class and preferred term occurring in ≥ 2 patients

System organ class preferred term, <i>n</i> (%)	All patients <i>N</i> = 88 ^a
Infections and infestations	34 (39)
Central line infection	8 (9)
Catheter bacteremia	4 (5)
Catheter sepsis	4 (5)
Sepsis	4 (5)
Catheter-related infection	3 (3)
Pneumonia	3 (3)
Urinary tract infection	3 (3)
Catheter site infection	2 (2)
Gastroenteritis	2 (2)
Gastrointestinal disorders	9 (10)
Crohn's disease	2 (2)
General disorders and administration site conditions	8 (9)
Pyrexia	5 (6)
Injury, poisoning, and procedural complications	8 (9)
Gastrointestinal stoma complication ^b	2 (6)
Vascular disorders	6 (7)
Subclavian vein thrombosis	2 (2)
Investigations	2 (2)
Blood bilirubin increased	2 (2)

^aIntent-to-treat population.

^bOnly among patients with stoma (*n* = 36).

metastatic adenocarcinoma with primary tumor likely to be located in the gastrointestinal tract (precise location unknown). A 64-year-old man in the PBO/TED subgroup was diagnosed with non-small-cell lung cancer 3 months after starting teduglutide. This patient had an extensive smoking history (about 30 cigarettes per day for about 30 years). In addition, during his career as a technician, the patient had been exposed to asbestos for an unknown period of time. Teduglutide was discontinued upon diagnosis (5 months before death), and the event was considered unrelated to the study drug. A third patient was diagnosed with cancer during STEPS-2. A 74-year-old man in the TED/TED subgroup with a history of smoking (10 cigarettes per day for 5 years and stopped approximately 25 years ago) was diagnosed with lung squamous cell carcinoma more than 1 year after starting teduglutide and withdrew from the study. The event was not considered related to teduglutide and was ongoing as of last follow-up.

Fifty patients underwent 51 colonoscopies during or as follow-up for the STEPS-2 study. Gastrointestinal polyps were reported in nine patients (*n* = 3 TED/TED; *n* = 6 PBO/TED) within or at the end of the 24-month treatment period with teduglutide. Of these nine patients, two had polyps at baseline. Histopathology classifications were adenoma (*n* = 5), hyperplastic polyp (*n* = 1), and rectal inflammatory polyp (*n* = 1) and unclassified (*n* = 2; colonoscopies were done outside of the study procedures). There were no cases of intestinal dysplasia or malignancy.

Teduglutide-specific antibodies were detected in 37/87 patients (43%; *n* = 18/37 (49%) TED/TED and *n* = 19/50 (38%) combined NT/TED and PBO/TED) during STEPS-2. No neutralizing antibodies to teduglutide were detected. Clinical parameters, including weekly PS volume, duration of

Table 4 Parenteral support volume reductions

	All patients ^a (N = 88)			Completers (n = 65)		
	TED/TED (n = 37)	PBO/TED (n = 39)	NT/TED (n = 12)	TED/TED (n = 30)	PBO/TED (n = 29)	NT/TED (n = 6)
Baseline PS requirement, l/week ^b	12.3	11.4	14.2	12.4	10.4	12.8
Clinical response, ^c n (%) ^d	33 (89)	18 (46)	6 (50)	28 (93)	16 (55)	4 (67)
Mean PS reduction from baseline, l/week (s.d.)	6.8 (4.9)	2.9 (3.9)	3.3 (3.7)	7.6 (4.9)	3.1 (3.9)	4.0 (2.9)
Percentage reduction ^e	59	25	19	66	28	39

ITT, intent-to-treat; NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids); TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2.

^aLast dosing visit in the ITT population.

^bLast dosing visit population is n = 36, n = 36, n = 10, respectively. Baseline determined by start of teduglutide treatment: at randomization in the initial placebo-controlled study for TED/TED patients (30 months of teduglutide treatment) and at start of STEPS-2 for PBO/TED and NT/TED patients (24 months of teduglutide treatment).

^c20–100% PS volume reduction from baseline.

^dLast dosing visit ITT population is n = 37, n = 39, n = 12, respectively.

^eLast dosing visit ITT population is n = 36, n = 36, n = 10, respectively.

response, plasma citrulline levels, or occurrence of AEs related to immunogenicity, were similar between antibody-positive and antibody-negative patients.

Vital signs were stable during the study. Despite decreases in PS volume throughout the study, mean body weight and body mass index remained constant (mean ± s.d. at end of treatment: -0.4 ± 5.0 kg and -0.2 ± 1.7 kg/m², respectively). No substantial shifts occurred in plasma calcium, magnesium, or phosphate (Supplementary Table S1). Mean albumin levels remained stable; mean liver enzyme levels either numerically decreased or remained near baseline (Supplementary Table S2). In the subset of patients who showed ≥ 50% reduction from baseline in their PS volume requirements at month 24, all mean liver enzymes numerically declined by month 1 and month 24. There were no changes from baseline in kidney function tests, including plasma creatinine levels.

Efficacy. PS volume reductions were observed across all subgroups (Table 4), with the greatest reductions seen in the subgroup with the longest duration of exposure to teduglutide, TED/TED. In the intent-to-treat population (N = 88), 89% of the TED/TED (n = 33/37), 46% of the PBO/TED (n = 18/39), and 50% of the NT/TED (n = 6/12) subgroups achieved a clinical response, defined as a ≥ 20% reduction in PS volume from baseline at the last visit. Mean reductions in PS volume from baseline to the last dosing visit in the intent-to-treat population were 6.8 l/week (–59%) for TED/TED (n = 36), 2.9 l/week (–25%) for PBO/TED (n = 36), and 3.3 l/week (–19%) for NT/TED (n = 10).

Among those who completed STEPS-2, 28/30 (93%) TED/TED patients, 16/29 (55%) PBO/TED patients, and 4/6 (67%) NT/TED patients achieved a clinical response (Table 4). Response to teduglutide was maintained over long-term treatment. In the TED/TED subgroup, 21/22 patients (95%) who achieved a clinical response with teduglutide during the initial placebo-controlled study maintained a ≥ 20% PS volume reduction after a further 24 months of continuous treatment in STEPS-2. PS volume requirements decreased progressively over the course of up to 30 months of treatment (Figure 2a). These mean reductions in prescribed PS volume

translated into at least one additional day per week free from infusion for 38/65 patients who completed 24 months of treatment (Figure 2b).

In addition, 13 patients obtained enteral autonomy and independence from PS during STEPS-2 (n = 10 TED/TED; n = 2 PBO/TED; n = 1 NT/TED; Figure 2b). Demographic and disease characteristics varied widely among these patients: baseline PS volume ranged from 3.5 to 13.4 l/week; nine patients had colon-in-continuity; and five patients had a stoma (three with jejunostomy and two with colonostomy). Independence from PS occurred after teduglutide treatment ranging from 28 to 127 weeks and after up to 15.5 years of PS dependence. The patient who obtained enteral autonomy after 15.5 years of PS dependence was a 63-year-old man with SBS as a result of mesenteric thrombosis who had colon-in-continuity and 26 cm of small bowel remaining. He had a baseline PS requirement of 13.4 l/week and had been receiving teduglutide for 115 weeks as of his first visit off of PS.

The onset to clinical response in PS volume reductions was delayed in some patients. Of eight patients in the TED/TED group who were nonresponders in the placebo-controlled study and completed STEPS-2, seven (88%) achieved a clinical response in STEPS-2. At baseline, these seven “slow responders” had a mean weekly PS volume requirement of 12.7 (range, 3.5–26.6) l/week, and had been dependent on PS for 1.1–9.8 years. In addition, all seven slow responders had colon-in-continuity; remnant small bowel lengths ranged from 30 to 120 cm. Causes of SBS in these patients were vascular disease (n = 4), strangulated small intestine (n = 1), injury (n = 1), and Crohn’s disease (n = 1). The slow responders achieved PS volume reductions of 3.1–16.6 l/week (percentage reduction of 29–100%) over 24–104 weeks of treatment with teduglutide. Three of these seven patients achieved complete independence from PS. The single nonresponding patient, who failed to obtain the protocol-defined clinical response with teduglutide in either initial placebo-controlled study or STEPS-2, experienced a 17% reduction from baseline in weekly PS volume during the extension study.

Mean plasma citrulline levels increased numerically in all study subgroups. Mean baseline values were 18.4 μM for

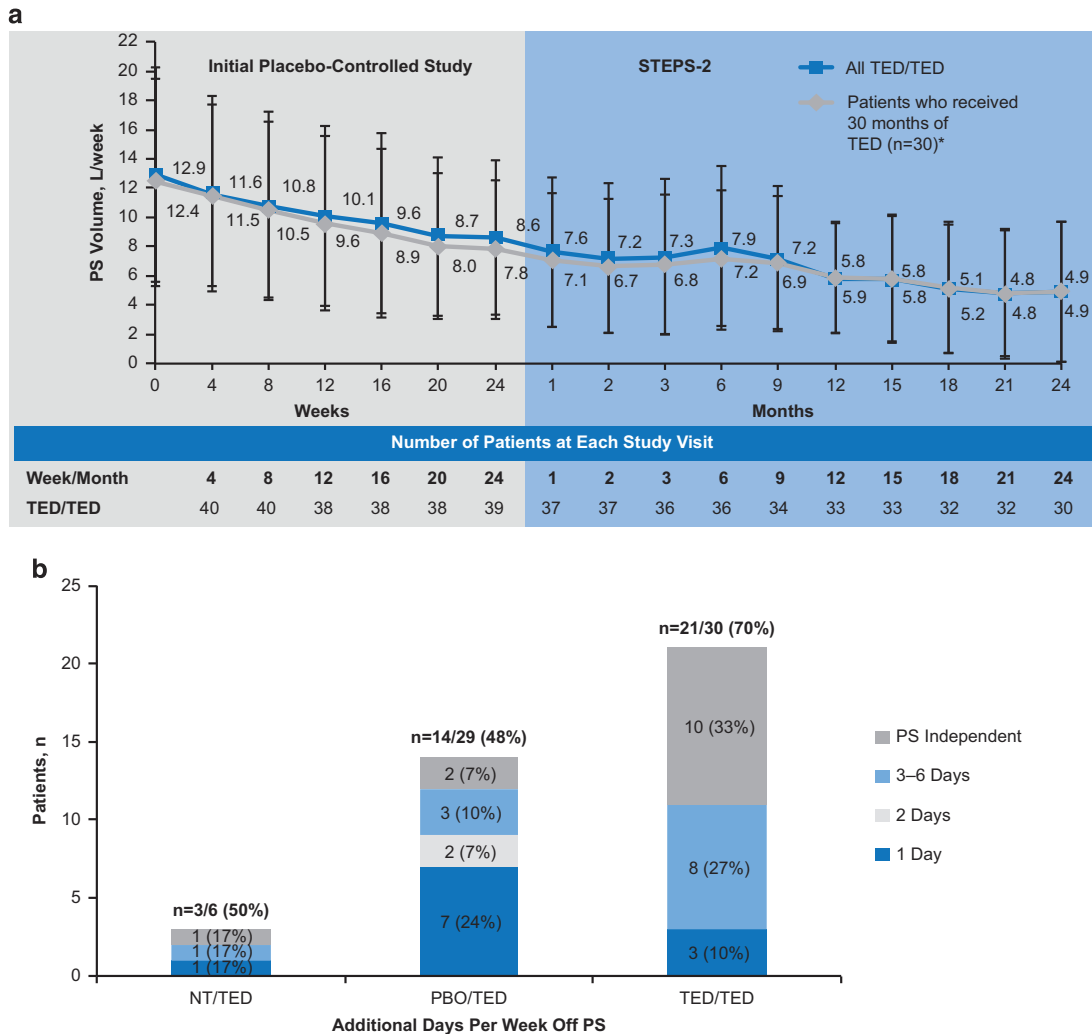


Figure 2 PS reductions in patients with SBS who received long-term teduglutide treatment. (a) Time course of mean PS requirements among patients who received teduglutide for up to 30 months. Squares represent the ITT TED/TED data set (table below figure has the number of patients corresponding to each time point), and diamonds represent the data set from the 30 TED/TED patients who completed the study. Error bars represent s.d. (b) Additional days per week off PS from baseline, including complete independence (7 days), with long-term teduglutide treatment. *Represents data for only those patients who completed 30 months of treatment with teduglutide. ITT, intent-to-treat; NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids); SBS, short bowel syndrome; TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2.

TED/TED, $16.7 \mu\text{M}$ for PBO/TED, and $17.3 \mu\text{M}$ for NT/TED subgroups. At month 24, mean \pm s.d. plasma citrulline rose to $32.7 \pm 23.1 \mu\text{M}$ (+71%) in the TED/TED subgroup, to $25.9 \pm 25.4 \mu\text{M}$ (+42%) in the PBO/TED subgroup, and to $19.5 \pm 9.1 \mu\text{M}$ (+29%) in the NT/TED subgroup.

DISCUSSION

Data from the open-label, 24-month STEPS-2 study support the overall safety conclusion that long-term treatment with teduglutide is well tolerated and that efficacy is maintained or enhanced. Most patients completed the study, suggesting that teduglutide was generally well tolerated. Many of the observed AEs were consistent with the known mechanism of action of teduglutide or the underlying condition of SBS or were complications associated with PS. As in the placebo-

controlled studies, gastrointestinal-related AEs were frequent, with abdominal pain being the most commonly reported AE during the study.^{17,21} This was as anticipated because gastrointestinal symptoms are a typical manifestation of SBS itself.²² In addition, long-term use of narcotic agents, which are often prescribed to decrease intestinal motility in SBS, is associated with gastrointestinal complaints, including abdominal pain, constipation, bloating, nausea, and vomiting.^{15,23} Catheter sepsis was also a common AE, and catheter-related complications were among the most common SAEs. Although catheter-related SAEs in this study were not considered to be related to teduglutide, these events underscore the prevalence of catheter-related complications and the importance of meticulous catheter care for patients who require chronic PS.

Three cases of cancer were reported during the study. Two patients with significant smoking histories were diagnosed

with lung cancer, and one patient with a history of Hodgkin's disease treated with chemotherapy and radiotherapy developed metastatic adenocarcinoma. Each of these patients had a significant risk factor for malignancy. The causal link between smoking and lung cancer has been well established.²⁴ Similarly, survivors of Hodgkin's disease are at increased risk of secondary cancers, which are the leading cause of death in this population.^{25,26} However, because a causal relationship with teduglutide treatment and the case of metastatic adenocarcinoma could not be ruled out, that event was reported as treatment related. Neither of the other two cancer cases was considered related to teduglutide. Nonetheless, because teduglutide is an intestinotrophic hormone, treated patients should be monitored for signs of intestinal neoplasia, and use of teduglutide should be discontinued if neoplasm is detected. Furthermore, continued clinical assessment of risk of teduglutide with regard to neoplastic growth is warranted.

Gastrointestinal polyps were reported in 9 of 51 (18%) patients who received colonoscopies. This prevalence rate is in line with recommended target adenoma detection rate for first-time colonoscopies ($\geq 15\%$ and $\geq 25\%$ for women aged ≥ 50 years and men aged > 50 years, respectively).²⁷ Furthermore, none of the seven biopsied polyps were malignant. Although the ideal schedule for colonoscopy surveillance of teduglutide-treated patients has yet to be determined, these findings support the recommendation to monitor patients receiving teduglutide with regular colonoscopies.²⁸

The nutrition and hydration status of teduglutide-treated patients was conserved in this study, despite PS volume reductions. Some patients experienced episodes of decreased weight during the study, which were reported as AEs. However, mean weight among the study group as a whole remained constant, suggesting that weight loss in individual patients was transient. Furthermore, mean body mass index did not change over the course of the study, which may indicate that weight fluctuations resulted from fluid effects. Mean kidney function tests and electrolyte levels were also stable. Mean albumin levels remained steady between baseline and end of treatment. This observation suggests that hydration and nutrition status was generally stable,²⁹ even though patients were challenged with reduction or elimination of PS. Mean liver enzyme values either numerically decreased or remained constant during this study. The most dramatic decreases were observed among the subset of patients with $\geq 50\%$ reduction in PS volume requirements; this is a notable finding, considering that liver disease is a life-threatening complication of chronic PS.³⁰

In this study, long-term teduglutide treatment for up to 2 years, or up to 30 months for a subset of the study population, was associated with continued efficacy as reflected by continued reductions in PS volume, a gain in number of days off PS per week, and achieving complete independence from PS. One of the greatest values associated with teduglutide is the potential to eliminate the need for PS in some patients. Complete enteral autonomy eradicates the risks associated with catheter dependence and chronic PS infusion.⁷ However, PS reductions that permit partial weaning and gaining additional days off PS are also powerful, with the potential to increase quality of life and reduce PS-associated complications. Indeed, among

patients with SBS-IF, decreases in PS requirements are associated with significantly higher scores on an SBS-specific quality-of-life instrument.³¹

The results of this long-term study demonstrate the durability of the effects of teduglutide. Almost all patients (21/22) in the TED/TED subgroup who achieved a clinical response ($\geq 20\%$ reduction from baseline in weekly PS volume at Weeks 20 and 24) with teduglutide in the initial placebo-controlled study maintained their response after an additional 24 months of treatment. In addition, a progressive increase in clinical benefit was observed with long-term teduglutide treatment. Mean PS volume requirements declined steadily over 30 months of treatment among patients who received teduglutide in both the initial 24-week placebo-controlled study and the STEPS-2 extension study. Furthermore, the percentage of patients achieving additional days off PS increased with longer treatment time; among teduglutide-treated patients who completed 30 months of treatment in the initial placebo-controlled study and STEPS-2, 60% (18/30) achieved a ≥ 2 -day reduction in PS infusions per week compared with 21% (8/39) of patients who received teduglutide for 24 weeks in the initial placebo-controlled study.¹⁷

Responses to teduglutide were observed in all 3 subgroups. The greatest improvements with teduglutide were observed in the TED/TED subgroup, which received the longest duration of therapy (up to 30 months). Nevertheless, PBO/TED and NT/TED patients, who initiated teduglutide during STEPS-2 for a total of up to 24 months of treatment, also incurred clinical benefits (e.g., response rates of 55 and 67% and mean PS volume decreases of 3.1 and 4.0 l/week, respectively, for study completers). Protocol differences between the 2 studies may account for some of the variation in response among treatment subgroups. The initial placebo-controlled study, which was designed to assess the efficacy of teduglutide relative to placebo, implemented a stricter protocol for PS weaning than did the extension study, which was designed to provide long-term, open-label safety and efficacy data, with less frequent study visits (on average, every 3 months). Although they did not receive teduglutide treatment in the initial placebo-controlled study, patients in the PBO/TED subgroup benefited from the more aggressive weaning algorithm. As a result of this intensive management, patients in the placebo group in the initial placebo-controlled study achieved a 2.3-l/week (21%) reduction in PS volume requirements at the end of that study.¹⁷ These patients, who had lower baseline PS requirements at the start of STEPS-2, achieved an additional 3.1-l/week (28%) reduction in PS volume requirements with 24 months of teduglutide during the extension study. Between Months 3 and 24 of STEPS-2, patients were evaluated for PS reductions less frequently than during the initial placebo-controlled study; this may partially explain why the response to teduglutide treatment in the NT/TED group at Month 24 was somewhat weaker than the response in the teduglutide arm in the initial placebo-controlled study at Month 6 (-4.0 vs. -4.4 l/week, respectively).¹⁷ However, the small size of the subgroups, particularly the NT/TED subgroup ($n=12$), limits the ability to draw firm conclusions from subgroup comparisons.

Although some patients showed an early response to teduglutide, others had a delayed response. Seven of 8 patients who did not achieve the response criteria of

$\geq 20\%$ reduction in PS in the initial placebo-controlled study showed dramatic reductions in PS with longer exposure to teduglutide in STEPS-2 (29–100% reduction in weekly PS volume after 24–104 weeks of treatment). Three of these slow responders eventually achieved enteral autonomy. The mechanisms underlying this delayed response are currently unclear. Baseline PS volume requirements were similar between the slow responders and the study population as a whole (mean of 12.7 l/week for the slow responders vs. 11.4–14.2 l/week for the 3 STEPS-2 subgroups). However, the slow responders were somewhat earlier in their postresection clinical course than the full study group (range for duration of PS dependency at baseline of 1.1–9.8 vs. 1.0–25.8 years, respectively). Therefore, the slow responders may have required additional time to achieve their full endogenous adaptive potential, which was then augmented by teduglutide treatment.⁴ Nonetheless, this finding suggests that there is no specified time at which to consider discontinuation of teduglutide for lack of efficacy. Rather, the physician should consider the patient's entire clinical picture, including hydration status, oral intake, fecal/stomal output, and time after resection when deciding whether to continue teduglutide therapy.

Efficacy and safety should be closely monitored on an ongoing basis in all patients, and clinical decisions should be guided by treatment objectives, physician judgment, and patient preferences.³² The decision of how long to continue teduglutide also should be considered in the context of recent data from a large series of adult patients with SBS ($N=268$) followed up for up to 24 years. Amiot *et al.* found that intestinal adaptation can continue for considerably longer than once thought (i.e., up to 5 years following resection); the analysis also confirmed that 10-year survival is considerably worse among patients with SBS who remain dependent on PS ($40.7\% \pm 0.5\%$) compared with those who become independent of PS ($67.0\% \pm 0.6\%$, $P < 0.001$).³³

The limitations of this study are primarily those shared by open-label observational studies. Furthermore, the study population is necessarily small, given the rarity of the condition, and heterogeneous with 3 patient subgroups who received treatment for different durations. Patient response to teduglutide appeared to vary, and thus, it is unclear how each phase of study attributed to the observed benefits of teduglutide. Because this extension study was not placebo-controlled, we cannot rule out the possibility that observed reductions in PS were partially caused by spontaneous adaptation, which has previously been documented in adults with intestinal failure after more than 5 years of PS dependence.^{33,34}

In STEPS-2, the longest and largest study yet conducted in patients with SBS-IF, long-term treatment with teduglutide resulted in sustained and continued reductions in PS requirements while overall health and nutritional status was maintained. PS volume reductions were observed in the majority of patients who completed the study, and 13 patients (20% of study completers) with varying baseline characteristics achieved enteral autonomy and independence from PS. Together, these data provide further evidence of the ability of teduglutide to enhance intestinal absorptive capacity. The most common AEs associated with teduglutide in this long-term study were consistent with the placebo-controlled trials and with the disease state of SBS-IF.^{17,21} Nonetheless,

further long-term data on safety and sustained durability of effect of teduglutide in patients with SBS-IF are warranted; the ongoing global registry study (ClinicalTrials.gov identifier: NCT01990040) will add to the accruing body of knowledge.

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CONFLICT OF INTEREST

Guarantor of the article: Lauren K. Schwartz, MD.

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O'Keefe, K. Fujioka, S.M. Gabe, G. Lamprecht, U.-F. Pape and P.B. Jeppesen were study investigators. B. Li was the lead statistician for the analysis. The study design was approved by NPS Pharmaceuticals. The authors contributed to study concept and design; study supervision, acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. All authors had access to the study data and have reviewed and approved the final manuscript and Supplementary Materials.

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NPS Pharmaceuticals. B. Li is an employee of NPS Pharmaceuticals. N.N. Youssef was an employee of NPS Pharmaceuticals at the time of study completion and drafting of the manuscript. P.B. Jeppesen received research support and was a consultant, advisory board member, and study investigator for NPS Pharmaceuticals.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Teduglutide, a glucagon-like peptide 2 analog, is an intestinotrophic agent that promotes intestinal adaptation.
- ✓ In short-term, placebo-controlled trials, teduglutide reduced PS requirements in patients with SBS-IF.

WHAT IS NEW HERE

- ✓ Long-term teduglutide treatment is associated with sustained responses and accrued benefit.
- ✓ Teduglutide-treated patients experienced continued reductions in PS over long-term treatment; some achieved PS independence.
- ✓ Overall health and nutritional status were maintained despite PS reductions.

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