CLINICAL—ALIMENTARY TRACT

Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure

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BACKGROUND & AIMS: Teduglutide, a glucagon-like peptide 2 analogue, might restore intestinal structural and functional integrity by promoting growth of the mucosa and reducing gastric emptying and secretion. These factors could increase fluid and nutrient absorption in patients with short bowel syndrome with intestinal failure (SBS-IF). We performed a prospective study to determine whether teduglutide reduces parenteral support in patients with SBS-IF. **METHODS:** We performed a 24-week study of patients with SBS-IF who were given subcutaneous teduglutide (0.05 mg/kg/d; n = 43) or placebo (n = 43) once daily. Parenteral support was reduced if 48-hour urine volumes exceeded baseline values by ≥10%. The primary efficacy end point was number of responders (patients with >20% reduction in parenteral support volume from baseline at weeks 20 and 24). **RESULTS:** There were significantly more responders in the teduglutide group (27/43 [63%]) than the placebo group (13/43 [30%]; $P = .002$). At week 24, the mean reduction in parenteral support volume in the teduglutide group was 4.4 ± 3.8 L/wk (baseline 12.9 ± 7.8 L/wk) compared with 2.3 ± 2.7 L/wk (baseline 13.2 ± 7.4 L/wk) in the placebo group ($P < .001$). The percentage of patients with a 1-day or more reduction in the weekly need for parenteral support was greater in the teduglutide group (21/39 [54%]) than in the placebo group (9/39 [23%]; $P = .005$). Teduglutide increased plasma concentrations of citrulline, a biomarker of mucosal mass. The distribution of treatment-emergent adverse events that led to study discontinuation was similar between patients given teduglutide (n = 2) and placebo (n = 3). **CONCLUSIONS: Twenty-four weeks of teduglutide treatment was generally well tolerated in patients with SBS-IF. Treatment with teduglutide reduced volumes and numbers of days of parenteral support for patients with SBS-IF.**

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Short bowel syndrome (SBS) results from surgical resection, congenital defect, or disease associated loss of absorption. The concomitant malabsorptive spectrum of SBS is wide, and patients with SBS are heterogeneous because of large variations in remnant bowel anatomy and function. Patients with intestinal insufficiency are able to compensate for their malabsorption by physiologic or pharmacologic adaptation,[1,2] whereas supplemental parenteral support (PS; parenteral nutrition and/or intravenous [PN/IV] fluids) is required to maintain fluid, electrolytes, trace elements, vitamins, and nutrient balances in patients with SBS with intestinal failure (SBS-IF).[3,4] Treatments aim to maximize remnant intestinal absorptive capacity; to minimize the symptoms of malabsorption; and to avoid, minimize, or eliminate the need for PS, thereby alleviating the daily burden of this debilitating condition. Hormonal therapies focusing on enhancing the structural and functional integrity of the remaining intestine are emerging. Glucagon-like peptide 2 (GLP-2), a peptide secreted from the intestinal L cells after food ingestion, ameliorates the pathophysiologic consequences of SBS. GLP-2 administration inhibits gastric acid secre-

Abbreviations used in this paper: AE, adverse event; FCE, fluid composite effect; GLP-2, glucagon-like peptide 2; IF, intestinal failure; PN/IV, parenteral nutrition and/or intravenous; PS, parenteral support; SBS, short bowel syndrome; TEAE, treatment-emergent adverse event.

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
SBS resulting from intestinal failure caused by a major intestinal resection (eg, injury, cancer, Crohn's disease, vascular disease, volvulus)	Cancer within last 5 y
At least 12 continuous months of PS dependency (PN and/or IV fluids) before signing informed consent	Body mass index <15 kg/m^2
PS required ≥3 times weekly to meet caloric, fluid, or electrolyte needs	Inflammatory bowel disease on immunosuppressant therapy that has been introduced or changed within last 3 mo or treatment with biologics within last 6 mo
Patients with Crohn's disease had to be in clinical remission for ≥12 wk before dosing	Previous use of teduglutide
	Previous use of native GLP-2 or human growth hormone within 6 mo before screening
	>4 SBS-related hospital admissions within 12 mo or hospital admission within 30 d before screening

tion and motility,[5,6] stimulates intestinal blood flow,[7] increases intestinal barrier function,[8] and enhances nutrient and fluid absorption in preclinical and clinical models.[9-12]

Teduglutide, a dipeptidyl-peptidase degradation-resistant GLP-2 analogue, has been demonstrated to enhance structural and functional integrity of the remaining intestine in SBS. Open-label, uncontrolled studies in adult patients with SBS have suggested clinically meaningful reductions of fecal excretions of wet weight (~700 to 1000 g/d) and energy (~1 MJ/d) after treatment with GLP-2 and teduglutide.[10,11,13,14] A recently published, randomized, placebo-controlled phase 3 study investigated whether teduglutide, by increasing intestinal absorption, could facilitate PS reductions in patients with SBS-IF.[12] Contrary to the expectations of a dose response, a 0.10-mg/kg/d dosage did not meet the primary end point of PS reduction, but significant findings from the ad hoc analysis of a 0.05-mg/kg/d dosage in that study suggested that these differences could be explained by the limitation of PS volume reductions to no more than 10% of baseline levels, beginning only at the fourth week of dosing, along with a trend toward larger baseline PS volume requirements in the 0.10-mg/kg/d group. Therefore, the primary objective of this study, the largest double-blind, randomized, placebo-controlled trial performed in patients with SBS-IF, was to evaluate whether teduglutide at the 0.05-mg/kg/d dosage and with a protocol allowing for earlier (ie, at second week of dosing) and more aggressive PS reductions of 10% to 30% of baseline levels of PN/IV fluid could reduce PS volume in these patients.

Materials and Methods

All authors had access to the study data and have reviewed and approved the final manuscript.

Patients

After receiving approval from local institutional review boards or medical ethics committees, centers screened patients of both sexes who were 18 years of age or older and who had a history of SBS that resulted in a dependency on PS for a period of at least 12 months before the start of the study. PS dependency was defined as at least 12 continuous months of PS required at least 3 times weekly to meet their caloric, fluid, or

col did not specify whether previous attempts at weaning had to be made.

Inclusion and exclusion criteria are listed in . Although patients with neoplasms could be included in the study, patients with ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis were excluded, along with any condition or circumstance that, in the investigator's opinion, put the patient at undue risk or jeopardized the integrity of the study results, including the presence of any of the excluded disease states described in the Supplementary Materials (Supplementary Table 1).

Patients were not categorized by whether they were receiving parenteral nutrition vs intravenous fluids alone. Throughout the study, patients were requested to maintain habitual diet and fluids, and no new medications were started or ongoing treatments changed during the stabilization period or throughout the 24-week treatment period unless deemed medically necessary. Patients who completed the 24-week treatment period were offered entry into an open-label extension study, the results of which will be the subject of a separate report.

Study Design

In this multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2-stage, phase 3 study (Figure 1), patients were recruited from 27 sites in 10 countries across Europe and North America. Stage 1 consisted of a screening visit and optimization and stabilization periods. After screening, eligible patients underwent a PS optimization period, if needed, of up to 8 weeks to achieve a stable target urine output of 1.0 to 2.0 L/d. This range, at the higher end of normal output (~1.5 L/d), was considered to minimize the risk for dehydration-related complications (eg, renal calculi) without provoking hyperhydration in a population that is prone to diarrhea and

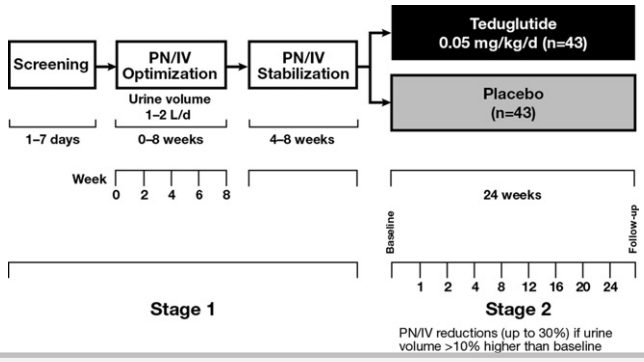

Table 2. PN/IV Adjustments Based on 48-Hour Urinary Output

Urine output[a]	PN/IV action
<1.0 L/d or target based on stabilized urine output	Increase PN/IV by ≥10% (wk 2) or to previous level
≥1.0 L/d but less than baseline	If patient is dehydrated or inadequately nourished, increase PS; if not, maintain PS
0% to <10% increase over baseline	Maintain PS
≥10% increase over baseline	Reduce PS by ≥10% of stabilized baseline level up to a clinically appropriate amount (maximum of 30%)

[a]Baseline urine output is the urine volume obtained during the stabilization period before initiating treatment.

dehydration. All patients then underwent a 4- to 8-week stabilization period during which PS usage was to match prescribed PS, and oral fluid intake and urine volume could not deviate >25% from the optimized levels. Although the osmolarity and oral intake were not strictly controlled, patients were asked to keep intake as constant as possible. Patients who were not stable could repeat stage 1 once.

Stage 2 began when the patients demonstrated PS volume stability. Eighty-six patients were randomized in a 1:1 ratio to placebo or teduglutide 0.05 mg/kg/d (administered once daily subcutaneously into the abdomen, thigh, or arm, at approximately the same time each day) for 24 weeks (Figure 1). Randomization was performed according to a computer-generated interactive response system and was stratified at 2 levels of baseline PS volume (≤6 or >6 L/wk). The postrandomization study evaluations and visits were scheduled at weeks 1, 2, 4, 8, 12, 16, 20, and 24.

All patients were required to record PS volume, 48-hour oral fluid intake and urinary output, and study drug dosing information in an electronic diary. PS volume was recorded daily and 48-hour oral fluid intake and urinary output was recorded during the optimization and stabilization periods and at weeks 2, 4, 8, 12, 16, 20, and 24 during the treatment period. If there was a change in oral intake, the clinician considered whether to adjust PS volume. Attempts to reduce PS volume were made at every visit before week 24.

Optimization and Stabilization

During the optimization period, patients were assessed at planned intervals (weeks 2, 4, 6, and 8, ±3 days) for hydration and nutrition. PS was adjusted in targeted increments of ≥10% of the volume at the previous visit. Immediately before each scheduled visit, 48-hour oral fluid intake and urine output were measured. The measurement included 1 day on and 1 day off PS, unless the PS was infused daily. Blood and urine samples were collected at each visit to evaluate hydration and nutrition. A targeted urine output of 1.0 to 2.0 L/d was used to determine if patients required optimization or could enter the stabilization period.

Stability was defined as actual PS usage matching the prescribed PS, baseline 48-hour oral fluid intake and urine output volumes within ±25% of the respective 48-hour volumes, and urine output volume of 2 to 4 L per 48 hours. No further PS adjustments were permitted during the stabilization period.

The purpose of the PS optimization period was to ensure that all patients received and tolerated a stable minimal level of PS before treatment, with adequate hydration as indicated by urine output. Patients who failed to remain stable for at least 4 consecutive weeks immediately before randomization were to start the optimization period again. Those patients who failed to stabilize after 2 attempts could not proceed and were not ran-

Efficacy and Safety

During the treatment period, PS adjustments were targeted to be ≥10% but <30% of stabilized PS level. Patients were required to remain compliant with the prescribed PS throughout the study, with all adjustments based on the actual PS volume infused. Patients were assessed at planned intervals (baseline and weeks 2, 4, 8, 12, 16, and 20) for hydration and nutrition. Before all scheduled visits, 48-hour oral fluid intake and urinary output measurements were taken and included 1 day on and 1 day off PS, unless the PS was infused daily.

Reductions in PS volumes by 10% to 30% of baseline PS levels were allowed if the 48-hour urinary volumes exceeded the baseline values by >10%. Oral intake during these 48-hour balances was to be constant. Determination of the amount of PS volume reduction was based on 48-hour urinary output, according to the algorithm described in . The decision of whether to stop a day of PS, reduce the percentage volume of all days that PS was administered, or change the relative PN/IV constituents of the PS or whether total PS weaning was possible was based on the investigator's clinical judgment and the personal preference of the patient.

Interim safety evaluations 1 week after PS reductions ensured that PS reductions were well tolerated. This assessment of nourishment and hydrational status was based on repeated 48-hour urine collections and a clinical evaluation that included clinical signs and symptoms of dehydration, change in body weight, reviews of the recorded oral fluid intake, blood samples (hematocrit, creatinine, blood urea nitrogen), and urine sodium. Because the injection site reactions or stomal changes that are known to occur with GLP-2 and teduglutide might have unblinded the observer, the clinician assessing and adjusting PS volume was required to be different from the one conducting the physical examination and assessing safety. If the reduced PS volume was well tolerated, the new weekly PS volume was maintained until the next visit; if not, the previously tolerated PS volume was resumed. Patients could be rechallenged at the next visit if adequate hydration and nutrition requirements were met.

The primary efficacy end point was the percentage of patients who demonstrated a response at week 20 and maintained that response at week 24 (responder). A response at a given visit was defined as the achievement of a 20% to 100% reduction from baseline in weekly PS volume. The secondary efficacy end points included the percentage and absolute change in PS and the number of patients who stopped PS and their time of discontinuation.[12]

Exploratory end points included response by visit, reduction in days on PS, change from baseline in plasma concentrations of citrulline (an amino acid produced by enterocytes and used here as a biomarker of remnant enterocyte mass)[15] and change in the

the combined effects of teduglutide on intestinal fluid absorption, that is, not only on PS volume reduction, but also on the ability to reduce oral fluid intake and increase urine output volume. The FCE was a summation of the increase in urine production, reduction in PN/IV volume, and reduction in oral fluid intake (L/wk), calculated as a baseline measurement of the individual components. The FCE was also calculated for each scheduled postbaseline visit using the following equation: reduction in PS volume (L/wk) + reduction in oral fluid intake volume (L/wk) + increase in urine output volume (L/wk).

Clinical evaluations (vital signs, physical examinations, and electrocardiograms), adverse event (AE) monitoring, and laboratory tests (hematology, serum chemistries, and urinalysis) were assessed. Safety assessments also included body weight, 48-hour urine output, antibodies to teduglutide, and any required endoscopic evaluations. In patients with colon, a baseline colonoscopy was required for inclusion to rule out the presence of polyps or active intestinal disease.

Statistical Analysis

Eighty-six patients were randomized in a 1:1 ratio to detect differences in responder rates between teduglutide 0.05 mg/kg/d and placebo groups of 35% vs 6%, respectively, based on the response rates reported in the earlier phase 3 study[12] (α = .05, 2-sided test and power = 90%). Grounded on these assumptions, nQuery Advisor (version 6.0, Statistical Solutions, Saugus, MS) based on Fisher exact test was used to calculate the power.

The number and percentage of responders are presented here by treatment group. The intent-to-treat analysis compared the event rates for the 2 treatment groups using the Cochran-Mantel-Haenszel test statistics adjusted for the randomization stratification variable (≤6 or >6 L/wk of PS volume at baseline). The percentage and absolute change in PS volume from baseline to the last dosing visit as well as all scheduled visits starting at week 4 are presented by treatment group using descriptive statistics. Treatment group differences were compared using an analysis of covariance model with effects for treatment and baseline PS volume, with the potential for the interaction of the 2 variables also included as an effect. Safety analyses were descriptive.

Results

Patients

From November 2008 to January 2011, one hundred and thirty-two patients who signed informed consent forms were screened, 86 were randomized, and 78 completed the dosing period (Supplementary Figure 1). There were no significant differences between treatment groups regarding demographic characteristics and medications at baseline (Table 3). A total of 39 patients (17 in the teduglutide group and 22 in the placebo group) required optimization of PN/IV volume before entering the stabilization period; 26 patients in the teduglutide group and 21 in the placebo group went directly from screening to stabilization. However, 12 of these (6 in each group) failed to remain stable for a full 4-week period and required a return to the optimization period. Overall, mean time spent in the optimization stage was 19 ± 23 days for the teduglutide group and 23 ± 24 days for the placebo group. No patients were weaned off PS during the opti-

Efficacy

Primary efficacy end point. The primary efficacy end point was the responder rate. There were 27/43 (63%) responders in the teduglutide group and 13/43 (30%) in the placebo group (P = .002). Small bowel length did not appear to be a predictor of response. Responder rate was higher for patients without colon in continuity (compared with patients with colon in continuity); however, findings did not achieve statistical significance.

Secondary end points. At all visits, change from baseline in actual PS volume was greater in the teduglutide group than in the placebo group (Figure 2). At Week 24, the mean ± SD PS volume reduction in the teduglutide group was 4.4 ± 3.8 L/wk from a baseline of 12.9 ± 7.8 L/wk vs 2.3 ± 2.7 L/wk from a baseline of 13.2 ± 7.4 L/wk in the placebo group. The difference in absolute change between the treatment groups was statistically significant at week 8 (P = .011) and remained significant through week 24 (P < .001). The percentage reduction in actual PS volume at week 24 was 32% ± 19% in the teduglutide group vs 21% ± 25% in the placebo group. The difference in percentage change between the treatment groups was significant at week 12 (P = .028) and remained significant through week 24 (P = .030). No patients were completely weaned from PS at week 24.

Selected exploratory end points. The percentage of patients with response (20%−100% PS reduction vs baseline) was higher in the teduglutide group than in the placebo group at all visits. At week 24, 30/39 teduglutide patients (77%) demonstrated response vs 18/39 placebo patients (46%; P = .01). The percentage of patients with a 1-day or more reduction in weekly actual PS use at week 24 was higher in the teduglutide group (54%, n = 21/39 [13 with 1 day off; 8 with ≥2 days off]) than in the placebo group (23%, n = 9/39; [6 with 1 day off; 3 with ≥2 days off]; P = .005).

Oral fluid intake was significantly higher in patients receiving placebo compared with those receiving teduglutide at weeks 12, 20, and 24 (Figure 3). At all visits, greater reduction in FCE was seen in the teduglutide group than in the placebo group. At week 24, the mean ± SD reduction in the teduglutide group was 5.4 ± 6.0 L/wk vs 1.1 ± 4.3 L/wk in the placebo group (P < .0006).

Teduglutide resulted in a significant increase in plasma citrulline concentration from baseline levels. At baseline, mean ± SD plasma citrulline concentration values were 18.4 ± 9.5 0 μmol/L and 17.5 ± 9.0 μmol/L in the teduglutide and placebo groups, respectively. At 24 weeks, the mean ± SD increase over baseline in plasma citrulline concentration was 20.6 ± 17.5 μmol/L in the teduglutide group vs 0.7 ± 6.3 μmol/L in the placebo group (P ≤ .0001). Over 24 weeks, patients receiving teduglutide had a nonsignificant increase in body weight of 1.0 ± 3.7 kg compared with baseline (P = .10), whereas patients receiving placebo had a decrease in body weight of −0.6 ± 2.8

Table 3. Demographic Characteristics and Medication at Baseline

	Placebo (n = 43)	Teduglutide, 0.05 mg/kg/d (n = 43)	Overall (N = 86)	*P* value
Age, mean (SD), *y*	49.7 (15.6)	50.9 (12.6)	50.3 (14.1)	.694[a]
Range	18–82	22–78	18–82	
BMI, mean (SD), *kg/m²*	22.3 (3.1)	22.5 (3.2)	22.4 (3.1)	.759[a]
n	43	42	85	
Range	17.5–28.6	17.6–9.8	17.5–29.8	
Women, n (%)	24 (56)	22 (51)	46 (54)	.829[b]
Cause of major intestinal resection, n (%)				
Vascular disease	16 (37)	13 (30)	29 (34)	
Crohn's disease	8 (19)	10 (23)	18 (21)	.694[b]
Volvulus	6 (14)	3 (7)	9 (11)	
Injury	4 (9)	4 (9)	8 (9)	
Cancer	2 (5)	1 (2)	3 (4)	
Other	7 (16)	12 (28)	19 (22)	
Intestinal anatomy or remnant small bowel length unknown, n	3	3	6	
Patients with stoma, n	17	21	38	
Types of stoma, n *(%)*				.100[b]
Jejunostomy	5 (29)	11 (52)	16 (42)	
Ileostomy	9 (53)	6 (29)	15 (40)	
Colostomy	1 (6)	4 (19)	5 (13)	
Other (duodenostomy; jejunostomy + ileostomy)	2 (12)	0 (0)	2 (5)	
Colon in continuity, n *(%)*	23 (54)	26 (61)	49 (57)	
Overall remnant small bowel length, mean (SD), *cm*	68.7 (63.9)	84.4 (64.6)	76.5 (64.4)	.277[a]
n	40	40	80	
Median	48.0	70.0	57.5	
Range	5–343	15–250	5–343	
Remnant small bowel length in patients with jejunostomy/ileostomy, mean (SD), *cm*	122.8 (81.6)	137.7 (70.9)	130.8 (75.0)	.608[a]
n	13	15	28	
Median	130	120	125	
Range	40–343	45–250	40–343	
Remnant small bowel length in patients with colon in continuity, mean (SD), *cm*	43.3 (31.5)	52.4 (31.8)	48.1 (31.6)	.332[a]
n	22	25	47	
Median	32.5	50	38	
Range	5–100	15–140	5–140	
Remnant colon, n *(%)*				.019[b]
>25%−50%	5 (12)	14 (33)	19 (22)	
>50%−75%	8 (19)	6 (14)	14 (16)	
>75%−100%	10 (23)	3 (7)	13 (15)	
Time since last small bowel resection, mean, *y*	7.9	6.9	7.4	
n	43	42	85	
<1	0	1	1	
≥1 to <2	6	7	13	
≥2 to <5	17	15	32	
≥5	20	19	39	
Time receiving PS, mean (SD), *y*	5.9 (5.7)	6.8 (6.3)	6.3 (6.0)	.504[a]
Median	3.9	3.6	3.9	
Range	1.0–25.8	1.0–24.7	1.0–25.8	
Parenteral volume, mean (SD), *mL/d*	1929 (1026)	1844 (1057)	1887 (1036)	.707[a]
Median	1771	1714	1764	
Range	514–5000	124–4714	124–5000	
Time receiving PS, mean (SD) *d/wk*	5.9 (1.5)	5.6 (1.7)	5.8 (1.6)	.388[a]
Median	7.0	7.0	7.0	
Range	3.0–7.0	3.0–7.0	3.0–7.0	
Parenteral volume stratification				1.000[c]
Parenteral volume ≤6 L/wk, n (%)	7 (16)	8 (19)	15	
Receiving PS 3/4/5/6/7 d/wk, n	4,1,0,1,1	7,0,1,0,0	11,1,1,1,1	
Parenteral volume >6 L/wk, n (%)	36 (84)	35 (81)	71	
Receiving PS 3/4/5/6/7 d/wk, n	2,2,2,6,24	3,4,2,4,22	5,6,4,10,46	

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