

# 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  $\geq 10\%$ . 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  $4.4 \pm 3.8$  L/wk (baseline  $12.9 \pm 7.8$  L/wk) compared with  $2.3 \pm 2.7$  L/wk (baseline  $13.2 \pm 7.4$  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,<sup>1,2</sup> 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).<sup>3,4</sup> 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.

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**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 <sup>2</sup>                                                                                                                     |
| PS required $\geq 3$ 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 $\geq 12$ 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,<sup>5,6</sup> stimulates intestinal blood flow,<sup>7</sup> increases intestinal barrier function,<sup>8</sup> and enhances nutrient and fluid absorption in preclinical and clinical models.<sup>9-12</sup>

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 ( $\sim 700$  to  $1000$  g/d) and energy ( $\sim 1$  MJ/d) after treatment with GLP-2 and teduglutide.<sup>10,11,13,14</sup> 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.<sup>12</sup> 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 electrolyte needs because of ongoing malabsorption. The proto-

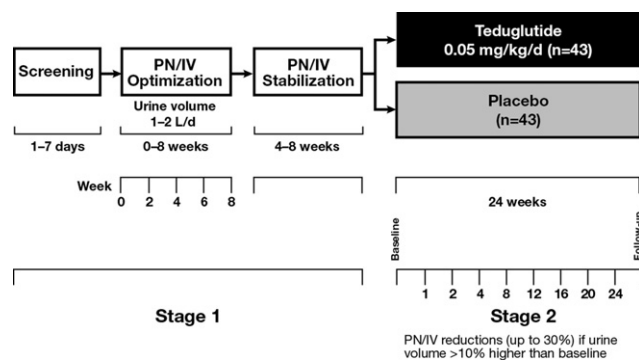
col did not specify whether previous attempts at weaning had to be made.

Inclusion and exclusion criteria are listed in Table 1. 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 ( $\sim 1.5$  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

**Figure 1.** Study design.

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

| Urine output <sup>a</sup>                           | PN/IV action                                                                                                 |
|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <1.0 L/d or target based on stabilized urine output | Increase PN/IV by $\geq 10\%$ (wk 2) or to previous level                                                    |
| $\geq 1.0$ 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                                                                                                  |
| $\geq 10\%$ increase over baseline                  | Reduce PS by $\geq 10\%$ of stabilized baseline level up to a clinically appropriate amount (maximum of 30%) |

<sup>a</sup>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 osmolality 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 ( $\leq 6$  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,  $\pm 3$  days) for hydration and nutrition. PS was adjusted in targeted increments of  $\geq 10\%$  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  $\pm 25\%$  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 randomized.

### Efficacy and Safety

During the treatment period, PS adjustments were targeted to be  $\geq 10\%$  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.<sup>12</sup>

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),<sup>15</sup> and change in the fluid composite effect (FCE).<sup>12</sup> The FCE is a putative measure of

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<sup>12</sup> ( $\alpha = .05$ , 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 ( $\leq 6$  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  $19 \pm 23$  days for the teduglutide group and  $23 \pm 24$  days for the placebo group. No patients were weaned off PS during the optimization period.

### 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  $\pm$  SD PS volume reduction in the teduglutide group was  $4.4 \pm 3.8$  L/wk from a baseline of  $12.9 \pm 7.8$  L/wk vs  $2.3 \pm 2.7$  L/wk from a baseline of  $13.2 \pm 7.4$  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  $32\% \pm 19\%$  in the teduglutide group vs  $21\% \pm 25\%$  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  $\geq 2$  days off]) than in the placebo group (23%,  $n = 9/39$ ; [6 with 1 day off; 3 with  $\geq 2$  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  $\pm$  SD reduction in the teduglutide group was  $5.4 \pm 6.0$  L/wk vs  $1.1 \pm 4.3$  L/wk in the placebo group ( $P < .0006$ ).

Teduglutide resulted in a significant increase in plasma citrulline concentration from baseline levels. At baseline, mean  $\pm$  SD plasma citrulline concentration values were  $18.4 \pm 9.5$   $\mu\text{mol/L}$  and  $17.5 \pm 9.0$   $\mu\text{mol/L}$  in the teduglutide and placebo groups, respectively. At 24 weeks, the mean  $\pm$  SD increase over baseline in plasma citrulline concentration was  $20.6 \pm 17.5$   $\mu\text{mol/L}$  in the teduglutide group vs  $0.7 \pm 6.3$   $\mu\text{mol/L}$  in the placebo group ( $P \leq .0001$ ). Over 24 weeks, patients receiving teduglutide had a nonsignificant increase in body weight of  $1.0 \pm 3.7$  kg compared with baseline ( $P = .10$ ), whereas patients receiving placebo had a decrease in body weight of  $-0.6 \pm 2.8$  kg ( $P = .20$ ).

**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 <sup>a</sup>  |
| Range                                                                            | 18–82            | 22–78                              | 18–82            |                    |
| BMI, mean (SD), kg/m <sup>2</sup>                                                | 22.3 (3.1)       | 22.5 (3.2)                         | 22.4 (3.1)       | .759 <sup>a</sup>  |
| 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 <sup>b</sup>  |
| Cause of major intestinal resection, n (%)                                       |                  |                                    |                  |                    |
| Vascular disease                                                                 | 16 (37)          | 13 (30)                            | 29 (34)          |                    |
| Crohn's disease                                                                  | 8 (19)           | 10 (23)                            | 18 (21)          | .694 <sup>b</sup>  |
| 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 <sup>b</sup>  |
| 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 <sup>a</sup>  |
| 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 <sup>a</sup>  |
| 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 <sup>a</sup>  |
| n                                                                                | 22               | 25                                 | 47               |                    |
| Median                                                                           | 32.5             | 50                                 | 38               |                    |
| Range                                                                            | 5–100            | 15–140                             | 5–140            |                    |
| Remnant colon, n (%)                                                             |                  |                                    |                  | .019 <sup>b</sup>  |
| >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 <sup>a</sup>  |
| 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 <sup>a</sup>  |
| 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 <sup>a</sup>  |
| 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 <sup>c</sup> |
| 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      |                    |

Table 3. Continued

|                             | Placebo (n = 43) | Teduglutide, 0.05 mg/kg/d (n = 43) | Overall (N = 86) | P value |
|-----------------------------|------------------|------------------------------------|------------------|---------|
| Concomitant medication      |                  |                                    |                  |         |
| Antidiarrheals, n (%)       | 16 (37)          | 22 (51)                            | 38 (44)          |         |
| Antisecretory agents, n (%) | 22 (51)          | 25 (58)                            | 47 (55)          |         |

BMI, body mass index.

<sup>a</sup>P value is calculated using the general linear model method, with corresponding variables as dependent variables and treatment group as the independent variable.

<sup>b</sup>P value is based on the  $\chi^2$  contingency table using the exact method.

<sup>c</sup>P values for overall treatment comparisons are based on the Fisher exact test for categorical variables and on a 1-way analysis of variance with effect for treatment for continuous variable.

### Safety and Tolerability

The safety population consisted of 85 patients who received  $\geq 1$  doses of study drug. Total exposure to study drug was similar in the 2 study groups. There were no deaths during the study. The number of patients with AEs, serious AEs, treatment-emergent AEs (TEAEs), or discontinuations due to treatment-emergent serious AEs was comparable between treatment groups. Treatment-emergent serious AEs were reported by 27 patients (15/42 patients [36%] vs 12/43 patients [28%] in the teduglutide group vs placebo group, respectively). Sixty-nine patients were reported to have  $\geq 1$  TEAEs during the study (35/42 [83%] vs 34/43 [79%]). Five patients were reported to have experienced TEAEs leading to discontinuation during the study (2/42 [5%] vs 3/43 [7%]); none were serious.

The most frequently reported TEAEs in the teduglutide group were of gastrointestinal origin, such as abdominal pain, nausea, gastrointestinal stoma complication, or abdominal distension (Supplementary Table 2). Two treatment-emergent serious AEs reported in the teduglutide group were deemed related to the study treatment (acute cholecystitis and small intestinal stenosis); both resolved.

No major findings were reported in the laboratory/chemistry or hematology tests of the teduglutide-treated vs placebo patients. Six patients from the teduglutide group and none from the placebo group developed anti-teduglutide antibodies after the start of study drug. An-

tibodies were non-neutralizing and without evidence of decreased effect on PS volume reduction or evidence of systemic hypersensitivity or other clinically significant sequelae.

### Discussion

In this phase 3 study, teduglutide met the primary efficacy end point, defined as the percentage of patients who achieved a 20% to 100% reduction in weekly PS volume at weeks 20 and 24 compared with baseline. There were 27/43 (63%) responders in the teduglutide group and 13/43 (30%) in the placebo group ( $P = .002$ ). When addressing the proabsorptive effects of teduglutide, improvements in intestinal fluid absorption under ideal circumstances should be counterbalanced by equivalent PN/IV volume reductions.

One of the observations in the previous phase 3 study was that, in addition to significant reductions in PS volume in patients assigned to teduglutide 0.05 mg/kg/d (and nonsignificant reductions in those receiving the 0.10-mg/kg/d dosage), there were also small decreases in PS volume in patients randomized to placebo.<sup>12</sup> This suggests that appropriate day-to-day fluid management with strict adherence to the weaning algorithm can have an intrinsic benefit and that treatment with teduglutide 0.05 mg/kg/d provides an important additional benefit.

Compared with the previous phase 3 study, this study protocol allowed earlier (after 2 weeks vs 4 weeks) and more aggressive (10%–30% vs 10%) PS volume reductions.<sup>12</sup> This was intended to minimize fluid accumulation (edema), reductions in oral intake, and increases in urine production encountered in the previous phase 3 study in relation to treatment with teduglutide 0.10 and 0.05 mg/kg/d, which negatively affected the primary study end point.<sup>12</sup>

At week 24, after these protocol adjustments, a larger mean PS volume reduction, of  $4.4 \pm 3.8$  L/wk (32% change from baseline mean of 12.5 L/wk) was observed compared with a reduction of  $2.5 \pm 2.3$  L/wk (27% change from baseline mean of 9.6 L/wk) in the teduglutide 0.05-mg treatment group in the previous study, which might explain this study's higher responder rate. In this study, the effects of teduglutide on PS volume reduction more closely reflected the FCE ( $5.4 \pm 6.0$  L/wk). The FCE

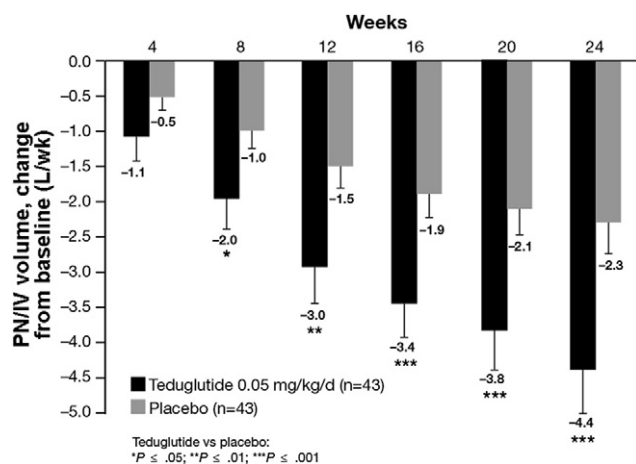
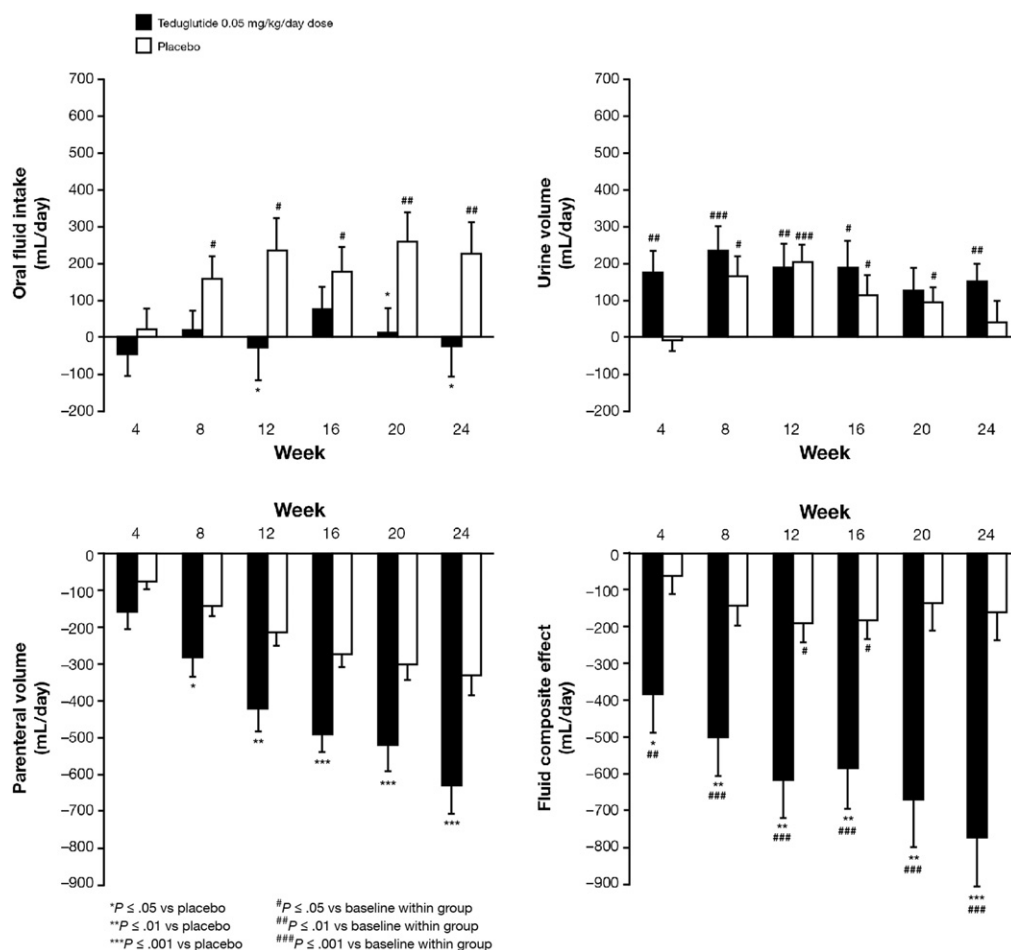


Figure 2. Mean (SE) absolute reduction in parenteral support.



**Figure 3.** Summary of changes in (upper left panel) oral fluid intake, from baseline mean, 1888 (SD 883) mL/d for teduglutide, 1637 (603) mL/d for placebo; (upper right panel) urine volume, from baseline mean 1350 (216) mL/d for teduglutide, 1372 (269) mL/d for placebo; (lower left panel) par-enteral volume, from baseline mean 1777 (1096) mL/d for teduglutide, 1899 (1077) mL/d for placebo; and (lower right panel) fluid composite effect, from baseline mean 2317 (1651) mL/d for teduglutide, 2176 (1270) mL/d for placebo. Mean (SE) values for changes are shown.

at week 24 was in the same magnitude in both studies ( $4.4 \pm 7.3$  L/wk).

The high placebo response in this study (30% vs 5% in the previous study) might be explained by addressing the components of the FCE (Figure 3). In the previous study, at week 24, patients receiving placebo had no significant changes in the oral fluid intake or urine output volume during 48-hour measurements. Therefore, the PS volume reduction ( $0.9 \pm 1.4$  L/wk) was in the same magnitude as the FCE ( $0.8 \pm 6.2$  L/wk) in the previous study. In the current study, where protocol modifications encouraged earlier and more aggressive PS reductions, significantly larger PS reductions were also achieved in patients receiving placebo ( $2.3 \pm 2.7$  L/wk), but subsequently these patients had to increase their oral fluid intake significantly ( $1.6 \pm 3.6$  L/wk;  $P = .009$ ) to maintain urine production and hydration constant (Figure 3).

At week 24, the FCE was  $1.1 \pm 4.3$  L/wk in this study in the patients receiving placebo, which closely reflected findings in the first phase 3 study. In addition, because the oral fluid intake and urine output were not constant over time, the observed effects of teduglutide on absolute and relative PS volume reduction might imprecisely estimate the true effect of teduglutide on intestinal fluid absorption. Therefore, the FCE might better illustrate the summarized effects of teduglutide as also demonstrated

in the 3-week, phase 2, metabolic balance study in patients with SBS, in which fecal wet weight excretion was reduced from baseline by  $711 \pm 734$  g/d ( $P = .001$ ) and intestinal wet weight absorption was increased by  $743 \pm 477$  g/d ( $P < .001$ ).<sup>11</sup> Although FCE is not a standard measure, it can be of value in the clinical assessment of patients with SBS as another potential indicator, along with urine output alone or determination of enteral balance (ie, oral fluid intake minus stool volume) when making weaning decisions.

The PS volume reductions from baseline of  $32\% \pm 19\%$  ( $4.4 \pm 3.8$  L/wk) demonstrated in this study provide correspondingly less time connected to the central line, if the infusion rate is the same. Because patients with SBS can spend up to 16 hours per day connected to the central line, this will liberate considerable time for unhindered daytime activities or undisturbed sleep.<sup>16</sup> It is appealing that significantly more patients treated with teduglutide had at least 1 day off PS compared with patients treated with placebo (54% vs 23%;  $P = .005$ ). Although an assessment of quality-of-life measures was beyond the scope of this study, PS therapy might negatively impact a variety of physical and psychosocial factors, including restriction of daily activities and the potential for sleep alteration. Because SBS-IF is a complex disease, PS reduction alone

might not capture all the factors that affect quality of life in these patients.

When introducing teduglutide in current treatment practice, the clinical meaningfulness and implications of the observed effects should be balanced against treatment-related AEs and possible unfavorable effects of long-term treatment. In this study, teduglutide was well tolerated. Only 2/42 (5%) patients in the teduglutide group vs 3/43 (7%) in the placebo group experienced TEAEs leading to discontinuation within the 24 weeks of treatment (see Supplementary Materials for details on patients withdrawn because of AEs considered related to treatment). In general, the tolerability profile resembles findings from the previous phase 3 study.<sup>12</sup> The presence of antibodies to teduglutide did not appear to have any clinical significance, and there were no differences in efficacy parameters in patients with or without anti-teduglutide antibodies; importantly, no neutralizing antibodies were detected (see Supplementary Materials for additional discussion of antibody assays).

The preponderance of gastrointestinal effects is not surprising in view of the effects of teduglutide. Adverse effects are mainly related to either the proabsorptive and intestinotrophic effects of teduglutide or insufficient PS weaning. In patients with SBS, symptoms such as abdominal pain, nausea, vomiting, and abdominal distension are also known to arise when reducing diarrhea with antidiarrheal medications. Intestinal epithelial hyperplasia can lead to small intestinal obstruction; it is possible that the AE of small intestinal stenosis observed in this study might have developed as a consequence of underlying luminal compromise that the investigator was unaware of before the patient's entry into the study. Patients with signs and symptoms of small bowel obstruction would need to be further evaluated before initiating treatment with teduglutide.

Ten patients in the teduglutide group experienced stoma changes; however, enlargement of the stoma nipple size is an expected effect of teduglutide.<sup>11</sup> With proper patient information and guidance to adjust and enlarge the hole in the stoma pad, discomfort in relation to the protruding stoma nipple can be reduced. Decreased fluid output from a stoma could result in less peristomal skin breakdown. However, this was not investigated in this study.

Increased intestinal fluid absorption, which is desirable in the majority of patients with SBS, could cause concern in patients with latent or overt cardiac decompensation, if PS is not weaned accordingly. The presence of edema and dyspnea can be signs of insufficient PS weaning; however, PS reduction that is too aggressive can cause signs of dehydration, such as headache, decreased weight, and muscle spasms.

Considering the intestinotrophic effect of teduglutide reflected in increases in plasma citrulline concentration and based on preclinical findings, it cannot be excluded that long-term treatment with teduglutide can promote growth of existing tumors in patients with SBS-IF.<sup>17</sup> Can-

cer surveillance colonoscopies are relevant in patients with a preserved colon.

This study did not include any follow-up to assess the duration of effect of teduglutide after discontinuation. However, there is evidence that some patients experience nearly immediate increases in their need for PS when teduglutide is discontinued, and that others maintain PS reductions for up to 1 year. These observations underscore the importance of individualized treatment in this heterogeneous population.

It is noteworthy that even in dedicated centers managing to recruit patients for this study, the numbers of patients receiving adequate conventional antidiarrheal and antisecretory medication seems low (Table 3). In general, it is prudent to use these conventional therapies before additional therapies are considered. This study also does not answer the question of whether there might be a benefit to initiating teduglutide therapy earlier in the course of SBS, for example, immediately after resection or concurrent with the beginning of enteral or oral feeding when enteral GLP-2 receptors are up-regulated.<sup>18,19</sup> Limitations of the study design are addressed in further detail in the Supplementary Materials.

In conclusion, in a 24-week study, teduglutide was safe and well tolerated, facilitated reduction in PS volume, and provided days off PS in patients with SBS-IF. In this relatively rare and heterogeneous condition, teduglutide can reduce malabsorption-related consequences (eg, diarrhea, large stomal output, stomal problems, fecal incontinence, meteorism, abdominal pain), PS-related inconveniences (eg, time spent connected to PS, social isolation, disturbed sleep, altered body image), and potentially life-threatening complications (eg, catheter-related sepsis, central venous thrombosis, and IF-associated liver disease). Based on the findings of this study, teduglutide could positively add to the limited treatment armamentarium.

## Appendix

The participating investigators for this study were as follows: C. Compher, University of Pennsylvania School of Nursing, Philadelphia, PA; D. Kirby, Cleveland Clinic, Cleveland, OH; T. Ziegler, Atlanta Clinical and Translational Science Institute, Atlanta, GA; K. Fujioka, Scripps Clinical Research Services, LaJolla, CA; K. Olden, Washington Hospital Center, Washington, DC; J. Allard, Toronto General Hospital, University Health Network, Toronto, ON, Canada; K. Jeejeebhoy, Polyclinic Family and Specialty Medicine Facility, North York, ON, Canada; D. Armstrong, Hamilton Health Sciences Corporation, Hamilton, ON, Canada; L. Gramlich, GI Research, Edmonton, AB, Canada; S. Rudzki, Samodzielny Publiczny Szpital, Lubin, Poland; K. T. Urbanowicz, Wojewódzki Szpital Specjalistyczny, Olsztyn, Poland; M. Kunecki, Wojewódzki Specjalistyczny Szpital, Łódź, Poland; S. Schneider, Hôpital de l'Archet, Nice, France; H. G. Lamprecht, Medizinische Klinik, Universitätsklinikum Tübingen, Tübingen,

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## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at <http://dx.doi.org/10.1053/j.gastro.2012.09.007>, and at <http://dx.doi.org/10.1053/j.gastro.2012.09.007>.

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## Conflicts of interest

The authors disclose the following: Palle B. Jeppesen, Marek Pertkiewicz, Bernard Messing, Kishore Iyer, Douglas L. Seidner, Stephen J. D. O'Keefe, and Alastair Forbes have served on the advisory board of and as consultants for NPS Pharmaceuticals. Hartmut Heinze is an employee at Nycomed GmbH and Bo Joelsson is an employee at NPS Pharmaceuticals.

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### ***Narratives of Patients Discontinuing Study Because of an Adverse Event Considered Related to Treatment***

**Patient 1.** This patient was a 60-year-old white woman whose SBS resulted from a major intestinal resection 10 years earlier due to radiation enteritis. Four hours after her first dose of teduglutide 0.05 mg/kg/d, she experienced intermittent abdominal pain and nausea. Both events were deemed mild in severity and related to the study drug, which was continued. After 12 days on teduglutide, the patient experienced abdominal distension, which became severe 9 days later; this event also was deemed related to study drug. One week later, after a month of treatment, the study drug was permanently discontinued. All events resolved within 3 days of discontinuation.

**Patient 2.** This patient was a 37-year-old white man whose SBS resulted from major intestinal resection 10 years earlier due to Crohn's disease. He was randomized to 0.05 mg/kg/d teduglutide and, after 3 days of taking the study drug, he experienced intermittent abdominal pain deemed severe in intensity and related to teduglutide use. Administration of teduglutide was discontinued, and the event resolved within 3 days. The patient was withdrawn from the study.

### ***Weaning Failure***

Of 13/86 patients (15%) who failed an attempt at weaning, only 1 (randomized to placebo) also failed a second attempt. This patient's baseline PS volume was 24.5 L/wk, and the first attempt was to reduce the volume by 3.5 L/wk to 21 L/wk (ie, 14.28% of the PS volume, consistent with the per-protocol targeted reductions of  $\geq 10\%$  of PS volume at previous visit). The patient was not able to tolerate this reduction and the initial PS volume of 24.5 L/wk was resumed. A second attempt was then made (at the next visit) to reduce the prescribed PS volume by 2.45 L/wk (ie, 10% reduction from the current prescribed volume) to 22.05 L/wk. This reduction was also not tolerated and the patient remained at the initial prescribed PS volume of 24.5 L/wk for the duration of the study.

### ***Antibody Assay Strategy***

Teduglutide is an analogue of native human GLP-2 produced by recombinant DNA technology that differs from the native 33-amino acid GLP-2 only by the substitution of the amino acid glycine for alanine at position 2.<sup>1,2</sup> Consequently, the likelihood for cross reactivity with native GLP-2 can be high. (As noted in the inclusion/exclusion criteria, all patients participating in this study were required to be treatment-naïve to teduglutide.)

The immunogenicity assay strategy used in the teduglutide clinical development program was designed to examine the risk of immunogenicity to either teduglutide

drug product or its process impurities in treated patients. Immunogenicity antibody binding assays were developed and validated in accordance with current literature recommendations and "guidance for industry" documents, that is, the Food and Drug Administration's *Draft Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins* (December 2009) and the European Medicines Agency's *Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins* (January 2007).

The Meso Scale Discovery method was used for the detection of anti-teduglutide antibodies. The neutralizing antibody assay was based on a functional adenosine 3',5'-cyclic monophosphate accumulation assay, which is consistent with the known activation of the GLP-2 receptor to GLP-2 and its analogues. Antibody assays were conducted at baseline, week 12, and week 24 or end of treatment; the 6 positive results were detected at week 24.

No factors predisposing patients to the development of antibodies have been identified.

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### ***Limitations of the Study Design***

Due to the rare nature of the condition and challenges in conducting a clinical trial of this nature in an outpatient setting, certain questions about the optimal use of teduglutide in patients with SBS remain unanswered by this study.

One limitation is that the study was not designed to stratify patients according to whether they were receiving intravenous fluids and electrolytes alone. Because these data were not collected, it is not known whether such patients might have a different response to teduglutide therapy than patients who require PN. Although some patients were receiving PN only and others receiving IV only at baseline, the investigators had the option to change the constituents of PS throughout the study, according to individual patients' clinical needs. The study also did not require patients to document details of dietary intake, such as use of oral rehydration solutions, so it is not possible to determine whether this might have resulted in any differences in response.

This study also did not elucidate whether the timing of teduglutide dosing (ie, pre- or postprandial) had an impact on efficacy. Given that native GLP-2 inhibits gastric motility,<sup>1</sup> it is possible that teduglutide might elicit early satiety. In that case, the beneficial effect on absorption of nutrients and/or fluids could, hypothetically, be slightly

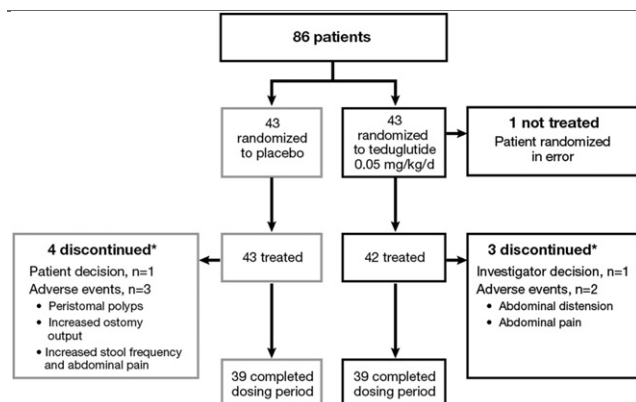
diminished by a subsequent decline in oral intake. In this study, although instructions to the investigators included the suggestion that the dose be administered at approximately the same time each day, there was no requirement regarding timing relative to meals. Thus, it was not possible to analyze the data to determine if there was any difference in response relative to timing of the dose.

As noted in the Discussion of our primary report, this study also was not designed to evaluate the impact of administering teduglutide earlier or later in the course of

SBS-IF, or to assess the impact of discontinuation on patients' clinical status. Additional studies are warranted to explore these questions, as well as to determine whether there is a need for retreatment or maintenance therapy and, if so, what the optimal dose and timing of such treatment would be.

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\*All adverse events resolved after discontinuation of study drug.

**Supplementary Figure 1.** Patient disposition.

**Supplementary Table 1.** Excluded Diseases and Illnesses

| Body system      | Conditions excluded                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Related to SBS   | Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis; celiac disease; refractory or tropical sprue; pseudo-obstruction                                                                                                                                                                                                                                                         |
| Gastrointestinal | Active IBD that required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months; IBD that required chronic systemic immunosuppressant therapy for symptom control; untreated premalignant or malignant change in colonoscopy biopsy or polypectomy; intestinal or other major surgery scheduled within the time frame of the study; chronic pancreatitis or cholecystitis |
| Immune           | Compromised immune system (eg, AIDS, severe combined immunodeficiency); hypersensitivity or allergies to teduglutide or its constituents or GLP-2                                                                                                                                                                                                                                                                          |
| Psychiatric      | Alcohol or drug addiction within the previous year; major uncontrolled psychiatric illness                                                                                                                                                                                                                                                                                                                                 |
| General          | Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)                                                                                                                                                                                                                                                          |

AIDS, acquired immunodeficiency syndrome; GLP-2, glucagon-like peptide 2; IBD, irritable bowel disease.

**Supplementary Table 2.** Treatment-Emergent Adverse Events Reported in >5% of Teduglutide-Treated Patients in Safety Population<sup>a</sup>

| Adverse event                                 | Patients, n (%)      |                  |
|-----------------------------------------------|----------------------|------------------|
|                                               | Teduglutide (n = 42) | Placebo (n = 43) |
| All TEAEs                                     | 35 (83)              | 34 (79)          |
| Abdominal pain                                | 13 (31)              | 10 (23)          |
| Nausea                                        | 12 (29)              | 8 (19)           |
| Gastrointestinal stoma change <sup>b</sup>    | 10 (24)              | 3 (7)            |
| Abdominal distension                          | 9 (21)               | 1 (2)            |
| Central line systemic infections <sup>c</sup> | 7 (17)               | 7 (16)           |
| Peripheral edema                              | 7 (17)               | 2 (5)            |
| Urinary tract infection                       | 6 (14)               | 4 (9)            |
| Fatulence                                     | 5 (12)               | 3 (7)            |
| Vomiting                                      | 5 (12)               | 4 (9)            |
| Fatigue                                       | 4 (10)               | 3 (7)            |
| Pyrexia                                       | 4 (10)               | 4 (9)            |
| Diarrhea                                      | 3 (7)                | 5 (12)           |
| Weight increase                               | 3 (7)                | 3 (7)            |
| Dyspnea                                       | 3 (7)                | 0 (0)            |
| Nasopharyngitis                               | 3 (7)                | 0 (0)            |

TEAEs, treatment-emergent adverse events.

<sup>a</sup>Adverse events were spontaneously reported, obtained through nonleading questioning, or noted during examination of a patient.

<sup>b</sup>Stomal changes are complications defined as reports of swelling, growth, hypertrophy, enlargement, or increased size of stoma or stoma nipple; stomal mucosal excoriation; peristomal polyps; peristomal rash; peristomal inflammatory lesion.

<sup>c</sup>Includes catheter-related infection, central line infection, catheter sepsis, infective thrombosis, and bacteremia.