Gastroenterology 2018;154:874–885

Factors Associated With Response to Teduglutide in Patients With Short-Bowel Syndrome and Intestinal Failure

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BACKGROUND & AIMS: Clinical studies showed teduglutide to increase urine production and reduce need for parenteral support volume in patients with short bowel syndrome (SBS) with intestinal failure, increasing intestinal wet weight absorption and reducing diarrhea. However, the effects of teduglutide on parenteral support vary among patients. We performed a post hoc analysis of a phase III placebo-controlled study to identify characteristics of patients in whom teduglutide has the largest effects on parenteral support volume response. **METHODS:** We collected data from 85 patients with SBS with intestinal failure, according to the European Society for Clinical Nutrition and Metabolism classification system, who received teduglutide or placebo between November 25, 2008, and January 4, 2011, at 27 sites in 10 countries. Changes in parenteral support volume were evaluated according to baseline parenteral support volume, bowel anatomy (group 1, jejunostomy/ileostomy; group 2, ≥50% colon-in-continuity without stoma; and group 3, other colon anatomies), and disease features (with inflammatory bowel disease, mesenteric vascular diseases, or other conditions). Correlation analyses were conducted using simple linear regression models, with unadjusted r^2 values reported. Two-sided t tests were used for comparisons between treatment groups. **RESULTS:** We correlated parenteral support volume reduction with teduglutide treatment and baseline parenteral support volume ($y = -0.3870x + 90.0279$, $r^2 = 0.61$; $P < .0001$). The effects of teduglutide on absolute parenteral support volume were significantly greater in group 1 patients (reduction of 919 ± 644 mL/d), not only compared with patients given placebo (reduction of 340 ± 436 mL/d; $P = .0112$) but also compared with teduglutide-treated patients in group 2 (reduction of 355 ± 306 mL/d; $P = .0066$). Teduglutide had an intermediate effect on patients in group 3. A minority of patients with SBS and inflammatory bowel diseases had colon-in-continuity (10.5% [n = 2/19]), whereas most patients with SBS and vascular or other diseases had colon-in-continuity (84.4% [n = 27/32] and 67.6% [n = 23/34], respectively). **CONCLUSIONS:** In a post hoc analysis of data from a phase III study of the effects of teduglutide on patients with SBS, we associated reduced parenteral support volume with baseline parenteral support volume, bowel anatomy, and SBS features. These findings may inform initial parenteral support volume adjustments and management of these severely disabled patients. ClinicalTrials.gov no: NCT00798967; ClinicalTrialsRegister.eu no: 2008-006193-15.

Keywords: Short-Gut Syndrome; GLP-2 Receptor Agonist; Parenteral Nutrition; IBD.

Teduglutide, a glucagon-like peptide-2 (GLP-2) analog, is a novel drug approved for the treatment of patients with short bowel syndrome (SBS) and intestinal failure (IF).[1,2] In the pivotal phase III, randomized, double-blind, placebo-controlled study (ClinicalTrials.gov, NCT00798967; ClinicalTrialsRegister.eu, 2008-006193-15), 63% of teduglutide-treated patients with IF who required parenteral support (PS; parenteral nutrition and/or intravenous fluids) ≥3 times per week for at least 12 months, had a relative reduction in their PS volume of >20% (from baseline at weeks 20 and 24) compared with 30% of patients receiving placebo ($P < .01$).[3] Due to a large variation in patient response with respect to teduglutide-induced PS volume changes, which ranged from −1993 to +329 mL/d, this study aimed to identify characteristics of individual patients with SBS who had the largest absolute teduglutide-induced PS volume reductions.

GLP-2 receptor activation is known to prompt the induction of crypt cell proliferation and prevention of enterocyte apoptosis,[4] leading to expansion of the epithelial surface area and morphologic adaptation. However, receptor activation also inhibits gastric acid secretion and gastric emptying,[5,6] stimulates intestinal blood flow,[7–9] increases intestinal barrier function,[10] opposes inflammatory insults,[11,12] and enhances nutrient and fluid absorption.[13–15]

Theoretically, the teduglutide-induced amelioration of the pathophysiologic manifestations of intestinal resection contributing to the malassimilation would be more pronounced in SBS–IF with an attenuated endogenous postprandial GLP-2 secretion mainly seen in jejunostomy SBS–IF.[16] In contrast, in patients with SBS–IF with a

Abbreviations used in this paper: **ANCOVA, analysis of covariance; FCE, fluid composite effect; GLP-2, glucagon-like peptide-2; IBD, inflammatory bowel disease; IF, intestinal failure; PS, parenteral support; SBS, short bowel syndrome; Vasc, mesenteric vascular disease.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2017.11.023

EDITOR'S NOTES

BACKGROUND AND CONTEXT

The glucagon-like peptide-2 analog, teduglutide, reduces parenteral support (PS) volumes in patients with short bowel syndrome–intestinal failure (SBS–IF). Because of patient and treatment-effect heterogeneity, further analyses are critical for individualized patient care.

NEW FINDINGS

Baseline PS volume strongly correlated with teduglutide-associated PS volume reductions. Thus, in absolute terms, SBS–IF patients with pronounced malabsorption and high fecal losses are likely to benefit the most from teduglutide treatment.

LIMITATIONS

Because data are derived from a post hoc analysis, no final conclusions can be drawn regarding clinical outcome, and randomized clinical trials are necessary to corroborate the findings.

IMPACT

The findings may permit better individualization of initial PS volume adjustments, thereby allowing patients to obtain clinical benefits from teduglutide more rapidly while potentially alleviating fluid accumulation side effects.

preserved terminal ileum and colon-in-continuity, who have an elevated endogenous postprandial GLP-2 secretion, teduglutide effects would theoretically be less pronounced.[17] However, the preexisting condition leading to SBS–IF and the severity of IF could also influence the effect of teduglutide.

Therefore, the aim of the current post hoc analysis was to explore whether predictors of response regarding absolute PS volume reduction in relation to teduglutide treatment could be identified when grouping patients with SBS–IF according to the principles set forth in the recent European Society for Clinical Nutrition and Metabolism (ESPEN)-endorsed classifications.[18] Based on absolute PS volume needs at baseline, the patients with IF were aligned in the spectrum from borderline toward intestinal insufficiency across various degrees of IF.[19] Separately, they were grouped either according to bowel anatomy based on the absence or presence of a stoma and/or a significant amount of colon-in-continuity (≥50%), or according to a diagnosis classification based on the original disease that caused the intestinal resection (eg, mesenteric vascular disease [SBS–Vasc], inflammatory bowel disease [SBS–IBD], or other conditions). This allowed for the comparison of absolute PS reductions in relation to teduglutide treatment in these distinct pathophysiologic SBS–IF phenotypes.

Methods

Patients and Study Design

Details regarding the key inclusion and exclusion criteria, as well as a thorough description of the study design, have been published previously.[3] In summary, after screening, eligible patients underwent a PS optimization period to achieve a stable target urine output between 1.0 and 2.0 L per day. Eighty-six patients were randomized in a 1:1 ratio to teduglutide 0.05 mg/kg per day or placebo given subcutaneously once daily. All patients were required to record PS volume, 48-hour oral fluid intake, and urinary output at baseline and before the post-randomization evaluations. These visits were scheduled at weeks 1, 2, 4, 8, 12, 16, 20, and 24. Reductions in PS volumes by 10% to 30% of baseline levels were allowed if the 48-hour urinary volumes exceeded the baseline values by >10%. Oral intakes during the 48-hour balances were intended to be constant. Interim safety evaluations, including body weight and laboratory tests, 1 week after PS reductions ensured that PS reductions were well tolerated. The study was conducted in accordance with the applicable International Conference on Harmonisation Guidelines, Good Clinical Practice, and the Declaration of Helsinki. The study protocol was approved by local institutional review boards or medical ethics committees.

In the current exploratory analyses, the patients were primarily categorized according to the severity of IF based on the need for PS volume at baseline. Subsequently, patients were classified according to bowel anatomy as follows: patients with SBS–IF with a jejunostomy or ileostomy (group 1), patients with SBS–IF with ≥50% of colon-in-continuity and no stoma (group 2), and other colon anatomies (<50% colon or with colostomy, group 3). Finally, patients were classified according to the underlying condition that caused IF: SBS–IBD, SBS–Vasc, and other conditions (Other). Thus, the entire study population was stratified 3 times by baseline PS volume, by bowel anatomy, and by diagnosis to create 3 distinct analysis populations (ie, an individual patient was independently assigned to each analysis population based on the stratification criteria of PS volume, bowel anatomy, or etiology). Reduction in PS volume, reduction in oral fluid intake, increase in urine volume, and the fluid composite effect (FCE), which represents the sum of these positive combined effects, were evaluated according to these patient classifications.

Statistical Analysis

The intent-to-treat population consisted of 86 randomized patients. One patient was randomized but discontinued before the first dose and did not undergo any study assessments. This patient was excluded from the current post hoc analysis, yielding an analysis population of 85.

Correlation analyses were conducted using simple linear regression models; unadjusted r^2 values are reported. Two-sided t tests for 2 independent mean differences were used for comparisons between patients receiving teduglutide vs those receiving placebo. Generalization of P value interpretations may be limited because of the small size of the analysis groups. Two analysis of covariance (ANCOVA) models were evaluated, using treatment arm (teduglutide or placebo) as the independent variable and change in PS at week 24 as the dependent variable. In the first model, covariates were baseline PS volume and remaining small bowel length. In the second model, covariates were baseline PS volume, remaining small bowel length, and diagnosis classification. SAS version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses. All authors had access to the study data and reviewed and approved the final manuscript.

Results

In the overall SBS–IF patient population receiving teduglutide, the average absolute PS volume reduction was

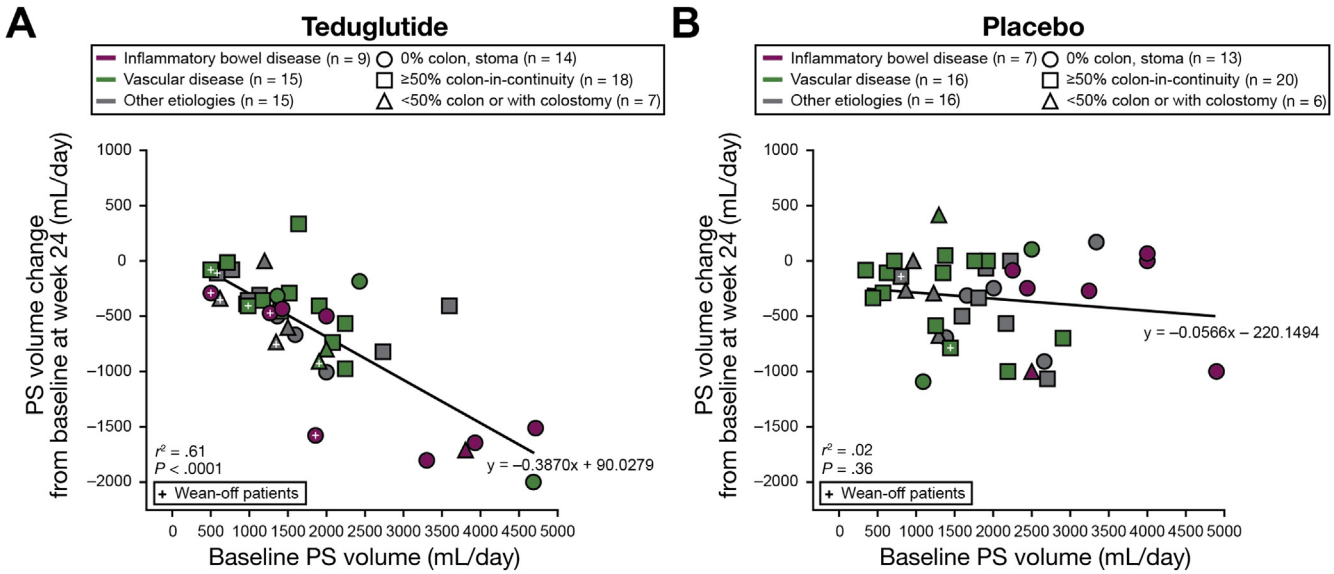

Figure 1. Absolute PS volume reduction at week 24 vs baseline PS volume in patients treated with teduglutide (*A*) or placebo (*B*). + symbol represents patients who became PS independent by the end of the 2-year, open-label extension of this phase III study (NCT00930644; EudraCT 2009–011679–65).

–625 ± 545 mL/d at week 24 compared with baseline vs –327 ± 392 mL/d in patients receiving placebo ($P = .0072$). In patients with SBS–IF receiving placebo, the absolute overall fluid oral volume intake at week 24 compared with baseline was higher vs those receiving teduglutide (226 ± 507 mL/d vs –25 ± 520 mL/d, respectively, $P = .036$), whereas the increase in urine output at week 24 compared with baseline was numerically higher in patients receiving teduglutide (149 ± 296 mL/d) vs those receiving placebo (40 ± 359 mL/d, not significant vs baseline). Consequently, the average reduction in FCE (ie, the sum of reduction in PS volume, the reduction in oral fluid intake, and the increase in urine volume) was significantly greater at week 24 compared with baseline in patients receiving teduglutide (–769 ± 851 mL/d) vs placebo (–153 ± 619 mL/d, $P = .0006$).

When evaluating individual patient responses (Figure 1*A*), a close, linear, and significant correlation was found between absolute PS volume reduction per day in relation to teduglutide treatment and daily PS volume at baseline ($y = -0.3870x + 90.0279$, $r^2 = 0.61$, $P < .0001$). Thus, the patients with SBS–IF who required the highest PS volumes at baseline had the largest absolute effects of teduglutide on PS volume reduction. In patients receiving placebo (Figure 1*B*), no significant correlation was found between absolute daily PS volume reduction and daily PS volume at baseline ($y = -0.0566x - 220.1419$, $r^2 = 0.02$, $P = .36$).

No significant correlations were found between reductions in oral intake (Figure 2*A* and *B*) or increases in urine production (Figure 2*C* and *D*) and baseline PS volume in patients receiving either teduglutide or placebo. However, a close, linear, and significant correlation was found between the FCE in relation to teduglutide treatment (Figure 2*E*) and daily PS volume at baseline in individual patients with SBS–IF ($y = -0.4985x + 125.9660$, $r^2 = 0.39$, $P < .0001$). In patients receiving placebo (Figure 2*F*), no significant correlation was found between FCE and daily PS volume at baseline ($y = -0.0686x - 24.3763$, $r^2 = 0.01$, $P = .49$).

No correlation was found between remnant small bowel length and PS volume change from baseline at week 24 in either treatment group ($r^2 = 0.0022$ and $P = .7871$ for patients treated with teduglutide [n = 36]; $r^2 = 0.0086$ and $P = .5915$ for patients treated with placebo [n = 36]). After correcting for remaining small bowel length in an ANCOVA model, the effect of teduglutide on absolute PS volume reduction at week 24 remained statistically significant, compared with placebo treatment ($P = .0025$). To further evaluate the effects of teduglutide in patients with various anatomies, baseline patient characteristics stratified by bowel anatomy classification are provided in Table 1. In spite of widespread interpatient heterogeneity regarding baseline PS volume requirements, the patients with SBS–IF with ≥50% colon-in-continuity and no ostomy (group 2; indicated by symbol □ in Figure 1) generally required lower PS volumes at baseline compared with the jejunostomy or ileostomy patients with SBS–IF without colon-in-continuity (group 1; indicated by symbol ○ in Figure 1). In group 2 as a whole, baseline PS volume was 1506 ± 777 mL/d, whereas baseline PS volume in group 1 was 2368 ± 1273 mL/d ($P = .001$).

Table 2 provides the average bowel anatomy classification group outcomes and illustrates that in jejunostomy or ileostomy patients with SBS–IF (group 1), the absolute teduglutide-induced PS volume reductions were greater (–919 ± 644 mL/d) not only compared with placebo (–340 ± 436 mL/d, $P = .0112$) but also compared with teduglutide-treated patients with SBS–IF with ≥50% colon-in-continuity and no ostomy (group 2; –355 ± 306 mL/d, $P = .0066$). In fact, in group 2 patients with SBS–IF, the

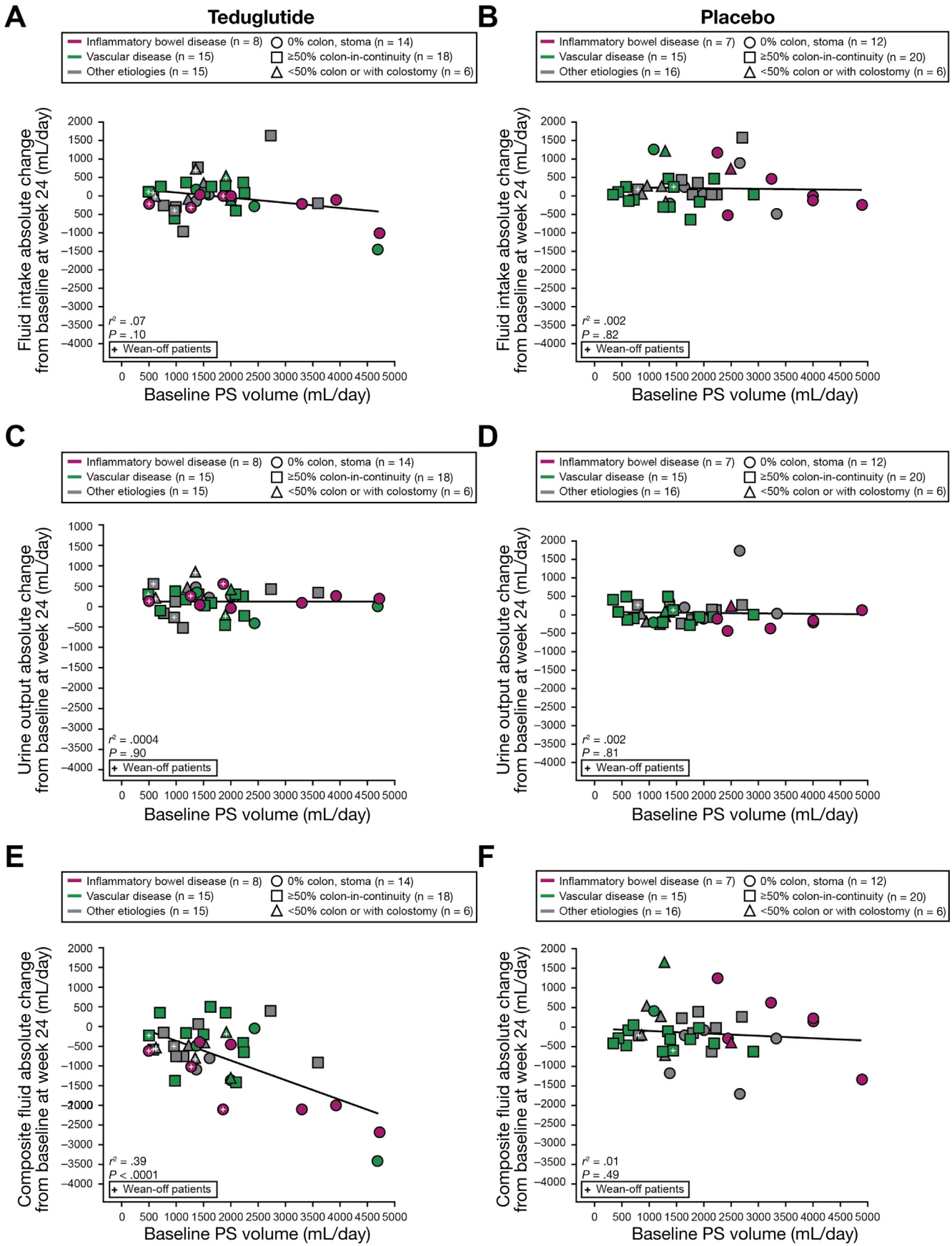

Figure 2. Absolute change in oral fluid intake (*A*, *B*), urine volume (*C*, *D*), and fluid composite effect (*E*, *F*) at week 24 vs baseline PS volume in patients treated with teduglutide (*A*, *C*, *E*) or placebo (*B*, *D*, *F*). + symbol represents patients who became PS independent by the end of the 2-year, open-label extension of this phase III study (NCT00930644; EudraCT 2009-011679-65).

Table 1. Baseline Patient Characteristics Stratified by Bowel Anatomy Classification

Parameter	Group 1: 0% colon remaining Stoma No colon-in-continuity		Group 2: ≥50% colon remaining No stoma Colon-in-continuity		Group 3: <50% colon or with colostomy	
	TED (n = 17)	PBO (n = 16)	TED (n = 18)	PBO (n = 20)	TED (n = 7)	PBO (n = 7)
Age, *y*, mean (SD)	52.1 (10.27)	50.7 (12.86)	51.3 (14.94)	50.3 (18.68)	49.6 (11.72)	46.0 (13.17)
Sex, n (%)						
Male	8 (47.1)	7 (43.8)	9 (50.0)	10 (50.0)	3 (42.9)	2 (28.6)
Female	9 (52.9)	9 (56.3)	9 (50.0)	10 (50.0)	4 (57.1)	5 (71.4)
Body weight, *kg*, mean (SD)	66.3 (13.03)	62.3 (14.96)	61.0 (10.48)	62.2 (11.04)	58.6 (7.87)	59.1 (12.57)
BMI, kg/m^2, mean (SD)	23.6 (3.63)	22.4 (3.24)	22.1 (2.86)	22.3 (3.02)	20.8 (2.05)	22.0 (3.62)
SBS history						
Causes of SBS–IF, n (%)						
Crohn's disease	9 (52.9)	7 (43.8)	0	0	1 (14.3)	1 (14.3)
Vascular complications	3 (17.6)	2 (12.5)	10 (55.6)	13 (65.0)	2 (28.6)	2 (28.6)
Injury	1 (5.9)	3 (18.8)	3 (16.7)	1 (5.0)	0	0
Volvulus	0	0	2 (11.1)	4 (20.0)	1 (14.3)	2 (28.6)
Cancer	1 (5.9)	0	0	1 (5.0)	0	1 (14.3)
Other	3 (17.6)[a]	4 (25.0)[b]	3 (16.7)[c]	1 (5.0)[d]	3 (42.9)[e]	1 (14.3)[f]
Stoma present, n (%)	17 (100)	16 (100)	0	0	4 (57.1)	1 (14.3)
Jejunostomy	11 (64.7)	5 (31.3)	0	0	0	0
Ileostomy	6 (35.3)	9 (56.3)	0	0	0	0
Colostomy	0	0	0	0	4 (57.1)	1 (14.3)
Other	0	2 (12.5)[g]	0	0	0	0
Colon-in-continuity, n (%)	0	0	18 (100)	20 (100)	7 (100)	7 (100)
Estimated remaining small bowel length, *cm*, mean (SD)	137.7 (70.93)[h]	113.7 (79.76)[h]	52.2 (27.39)	39.2 (30.41)[i]	59.3 (44.39)[j]	49.3 (29.96)[j]
PS duration, *y*, mean (SD)	7.1 (6.73)	5.1 (3.07)	6.2 (6.45)	6.1 (6.44)	6.4 (5.64)	7.2 (8.24)
Number of PS days per week (actual based), mean (SD)	5.8 (1.54)	6.4 (1.14)	5.2 (1.60)	5.9 (1.49)	5.9 (1.59)	5.2 (1.68)
PS volume (actual based), *mL/d*, mean (SD)	2068.9 (1364.94)	2686.5 (1122.35)	1509.4 (827.31)	1502.9 (750.85)	1768.9 (1007.11)	1301.1 (552.18)
Oral volume intake, *mL/d*, mean (SD)	2186.5 (916.45)	1641.8 (591.78)	1567.0 (709.57)	1656.6 (649.07)	1990.2 (1043.00)	1572.4 (571.73)
Urine output, *mL/d*, mean (SD)	1237.8 (194.66)	1359.4 (268.90)	1478.9 (196.77)	1432.5 (285.47)	1290.4 (131.58)	1227.1 (172.79)

BMI, body mass index; IF, intestinal failure; PBO, placebo; TED, teduglutide.
[a]Other cause of SBS–IF = radiation enteritis, ulcerative colitis, and ileus.
[b]Other cause of SBS–IF = adhesions (n = 2), mechanical ileus (n = 1), and jejunal fistula (n = 1).
[c]Other cause of SBS–IF = strangulated small intestine (n = 2) and unspecified intestinal obstruction and peritoneal adhesions of intestine (n = 1).
[d]Other cause of SBS–IF = congenital intestinal atresia.
[e]Other cause of SBS–IF = radiation enteritis, recurrent small bowel obstruction due to adhesions, and complications of hysterectomy.
[f]Other cause of SBS–IF = familial adenomatous polyposis.
[g]Other stoma types = duodenostomy (n = 1) and jejunostomy and ileostomy (n = 1).
[h]n = 15.
[i]n = 19.
[j]n = 6.

Table 2. Change From Baseline at Week 24 in PS Volume, Days Off PS, Body Weight, FCE Components, and FCE Stratified by Bowel Anatomy Classification

	Group 1: 0% colon remaining Stoma No colon-in-continuity		Group 2: ≥50% colon remaining No stoma Colon-in-continuity		Group 3: <50% colon or with colostomy	
Parameter	TED (n = 17)[a]	PBO (n = 16)	TED (n = 18)	PBO (n = 20)	TED (n = 7)	PBO (n = 7)[b]
PS volume (actual based), change from baseline, % change, mean (SD)	–40.3 (18.26)	–18.8 (29.10)[c]	–23.3 (15.84)	–23.8 (22.23)	–40.3 (18.75)	–18.7 (30.88)
Additional days off PS per week, n (%)						
≥1-day reduction at week 24	6 (42.9)	2 (15.4)[c]	10 (55.6)	6 (30.0)	5 (71.4)	1 (16.7)
≥2-day reduction at week 24	4 (28.6)	1 (7.7)[c]	2 (11.1)	2 (10.0)	2 (28.6)	0
≥3-day reduction at week 24	1 (7.1)	1 (7.7)[c]	1 (5.6)	1 (5.0)	2 (28.6)	0
Body weight change from baseline, *kg*, mean (SD)	1.0 (4.15)	0.3 (2.61)[c]	0.2 (2.68)	–1.1 (3.02)	3.0 (4.97)	–0.7 (2.20)
Components of FCE change from baseline, *mL/d*, mean (SD)						
PS volume	–919.3 (643.55)[d]	–339.9 (435.67)[c]	–354.8 (306.21)	–327.2 (348.71)	–728.4 (532.31)	–297.4 (498.46)
Oral volume intake	–248.7 (440.41)	239.8 (614.19)[e]	61.6 (571.65)	151.6 (440.58)	239.7 (364.39)[b]	448.1 (503.65)
Urine output	172.0 (236.19)	66.9 (570.06)[e]	76.6 (313.13)	47.1 (230.06)	307.9 (343.84)[b]	−34.6 (167.48)
FCE change from baseline, *mL/d*, mean (SD)	–1340.0 (992.79)[f]	−204.9 (850.77)[e]	–369.8 (577.13)	–222.7 (306.21)	–632.9 (397.38)[b]	185.3 (849.15)

PBO, placebo; TED, teduglutide.
[a]n = 14 with data available.
[b]n = 6 with data available.
[c]n = 13 with data available.
[d]$P = .0112$ for comparison with patients treated with PBO in group 1, and $P = .0066$ for comparison with patients treated with TED in group 2.
[e]n = 12 with data available.
[f]$P = .0044$ for comparison with patients treated with PBO in group 1.

effect of teduglutide on PS volume reduction was not significantly different from that in patients receiving placebo (−327 ± 349 mL/d, $P = .7964$). Although group 1 patients experienced the greatest benefits in terms of PS volume reductions with teduglutide, all bowel anatomy groups included a substantial proportion of patients who obtained additional days per week off PS. As a result of the combined positive effects of teduglutide (ie, the sum of the reduction in PS volume, the reduction in oral volume intake, and the increase in urine volume), a greater FCE reduction of −1340 ± 993 mL/d was seen in teduglutide-treated jejunostomy or ileostomy patients with SBS–IF (group 1) compared with −205 ± 851 mL/d in patients treated with placebo ($P = .0044$). Again, no significant difference was detected between teduglutide- and placebo-treated patients with SBS–IF with ≥50% colon-in-continuity and no ostomy (group 2; −370 ± 577 vs −223 ± 306 mL/d, respectively; $P = .336$). In patients with SBS–IF with <50% colon-in-continuity or the presence of a colostomy (group 3), the FCE effect of teduglutide was intermediate (−633 ± 397 mL/d), whereas the average placebo effect (185 ± 849 mL/d) resembled the placebo effect seen in SBS–IF group 2. Group 1 patients were then further divided into patients with jejunostomy (n = 16) and patients with ileostomy (n = 15). Patients with jejunostomy tended to have higher PS volume requirements at baseline (teduglutide arm [n = 11], 2455 ± 1463 mL/d; placebo arm [n = 5], 2557 ± 901 mL/d), compared with patients with ileostomy (teduglutide arm [n = 6], 1360 ± 866 mL/d; placebo arm [n = 9], 2691 ± 1006 mL/d). With 24 weeks of teduglutide treatment, patients with jejunostomy showed numerically greater reductions in PS volume (−1058 ± 695 mL/d [n = 10]) than did patients with ileostomy (−572 ± 344 mL/d [n = 4]). In contrast, patients treated with placebo showed little change in PS volume at week 24 in either the jejunostomy subgroup (−252 ± 407 mL/d [n = 5]) or the ileostomy subgroup (−180 ± 296 mL/d [n = 6]).

Baseline patient characteristics stratified by diagnosis are provided in Table 3. Only a few of the patients with SBS–IBD included in this study had a preserved colon-in-continuity, whereas the presence of a colon was more common in patients who had SBS–Vasc and SBS–IF due to other conditions (Other; see bolded row in Table 3; Figure 1*A* and *B*). Consequently, Table 4 illustrates that PS volume reductions were greater in patients with SBS–IBD treated with teduglutide (−1102 ± 654 mL/d) not only compared with placebo-treated patients with SBS–IBD (−357 ± 453 mL/d, $P = .0174$) but also compared with patients with SBS–Vasc (−513 ± 539 mL/d, $P = .0418$) and patients in the "Other" category (−450 ± 280 mL/d, $P = .0168$) receiving teduglutide. All etiology groups included patients who obtained additional days per week off PS, but teduglutide-induced FCE reduction was greater in patients with SBS–IBD (−1437 ± 900 mL/d) not only compared with patients with SBS–IBD treated with placebo (27 ± 818 mL/d, $P < .0168$) but also compared with patients with SBS–Vasc (−588 ± 995 mL/d, $P < .0029$); significance was not quite reached when these data were compared with those of patients with other diagnoses (−593 ± 444 mL/d, $P = .053$).

An ANCOVA was conducted to evaluate the effect of teduglutide on change from baseline in PS at week 24, while controlling for baseline PS volume, remaining small bowel length, and diagnosis classification. The effect of teduglutide remained significant in the model ($P = .0026$). In addition, baseline PS volume had an independent effect on change from baseline in PS volume ($P < .0001$). In contrast, small bowel length and diagnosis classification did not independently influence change from baseline in PS at week 24 ($P = .9387$ and $P = .7077$, respectively).

Discussion

SBS is characterized by widespread patient heterogeneity.[20] In addition, a large heterogeneity of response has been described in relation to teduglutide treatment.[21] Whereas previous studies have primarily reported teduglutide results based on group averages compared with placebo, this hypothesis-generating, post hoc study aimed to identify characteristics of individual patients with SBS or patient groups in which teduglutide could provide an especially favorable effect.

Previously, the classification of patients with SBS has mainly been based on the diagnosis leading to bowel resection and the remnant bowel anatomy. However, it has recently been suggested that the severity of IF be evaluated based on the magnitude of the need for PS volume.[18–20]

When exploring the effect of teduglutide in post hoc analyses based on these classifications, a significant correlation was found between absolute baseline PS volume requirements and absolute PS volume reduction. Additionally, in an ANCOVA model, baseline PS volume independently predicted change in PS volume at week 24 in patients treated with teduglutide. Thus, the patients with SBS–IF with the poorest remnant bowel function, illustrated by their need for a high volume of PS at baseline, experienced the largest absolute effect of teduglutide on PS volume reduction.

As illustrated in Figure 1*A*, anatomically, 5 of 6 patients who experienced the largest PS volume reductions (≥1500 mL/d) in relation to teduglutide treatment had a jejunostomy or ileostomy (group 1). In 5 of these 6 patients, IBD was the cause of intestinal resection and SBS–IF. Five of 6 patients required PS volume >3000 mL/d. In general, only 2 of 19 patients with IBD included in this study had a remnant part of their colon-in-continuity.

Both regression analysis and ANCOVA showed that remaining small bowel length cannot be used to predict the effects of teduglutide. In contrast, remnant bowel anatomy appears to affect clinical response with teduglutide treatment. Phenotypically, patients with jejunostomy or ileostomy (group 1) are frequently characterized by accelerated gastric emptying, gastric hypersecretion, and poor adaptation following resection.[19,22] As a consequence of the resection of the terminal ileum and the colon, where the L-cells are predominantly located, endogenous postprandial GLP-2 secretion is likely to be compromised in patients with

Table 3. Baseline Patient Characteristics Stratified by Diagnosis Classification

Parameter	SBS–IBD		SBS–Vasc		Other	
	TED (n = 11)	PBO (n = 8)	TED (n = 15)	PBO (n = 17)	TED (n = 16)	PBO (n = 18)
Age, *y*, mean (SD)	48.2 (7.31)	48.0 (6.91)	52.3 (13.52)	56.7 (13.78)	52.6 (14.37)	43.9 (17.91)
Sex, n (%)						
Male	6 (54.5)	3 (37.5)	9 (60.0)	8 (47.1)	5 (31.3)	8 (44.4)
Female	5 (45.5)	5 (62.5)	6 (40.0)	9 (52.9)	11 (68.8)	10 (55.6)
Body weight, *kg*, mean (SD)	66.6 (11.93)	62.5 (10.53)	63.9 (11.19)	66.6 (12.93)	59.0 (10.83)	56.7 (11.78)
BMI, kg/m^2, mean (SD)	23.3 (4.08)	22.6 (3.56)	22.6 (3.43)	23.3 (3.36)	21.7 (2.14)	21.1 (2.34)
SBS history						
Causes of SBS–IF, n (%)						
Crohn's disease	10 (90.9)	8 (100)	0	0	0	0
Vascular complications	0	0	15 (100)	17 (100)	0	0
Intestinal ischemia			5 (33.3)	4 (23.5)		
Mesenteric vessel thrombi or emboli			9 (60.0)	13 (76.5)		
Unknown vascular cause			1 (6.7)	0		
Injury	0	0	0	0	4 (25.0)	4 (22.3)
Volvulus	0	0	0	0	3 (18.8)	6 (33.3)
Cancer	0	0	0	0	1 (6.3)	2 (11.1)
Other	1 (9.1)[a]	0	0	0	8 (50.0)[b]	6 (33.3)[c]
Stoma present, n (%)	11 (100)	7 (87.5)	4 (26.7)	2 (11.8)	6 (37.5)	8 (44.4)
Jejunostomy	8 (72.7)	1 (12.5)	2 (13.3)	1 (5.9)	1 (6.3)	3 (16.7)
Ileostomy	2 (18.2)	5 (62.5)	1 (6.7)	0	3 (18.8)	4 (22.2)
Colostomy	1 (9.1)	0	1 (6.7)	0	2 (12.5)	1 (5.6)
Other	0	1 (12.5)[d]	0	1 (5.9)[e]	0	0
Colon-in-continuity, n (%)	1 (9.1)	1 (12.5)	12 (80.0)	15 (88.2)	12 (75.0)	11 (61.1)
Estimated remaining small bowel length, *cm*, mean (SD)	128.9 (77.01)	127.8 (98.34)	70.9 (57.77)	40.2 (29.90)	75.9 (55.01)	67.6 (49.95)
PS duration, *y*, mean (SD)	8.1 (7.95)	7.2 (7.40)	5.5 (4.71)	6.1 (6.19)	6.6 (6.55)	5.1 (4.47)
Number of PS days per week (actual based), mean (SD)	5.7 (1.60)	6.6 (1.24)	5.6 (1.47)	5.4 (1.68)	5.4 (1.72)	6.2 (1.13)
PS volume (actual based), *mL/d*, mean (SD)	2267.5 (1480.49)	3087.7 (1156.25)	1826.7 (982.12)	1338.0 (730.66)	1398.8 (811.29)	1927.9 (855.07)
Oral volume intake, *mL/d*, mean (SD)	2456.4 (1175.90)	1521.4 (531.76)	1779.7 (761.25)	1633.9 (536.42)	1599.5 (575.34)	1692.2 (707.56)
Urine output, *mL/d*, mean (SD)	1160.0 (160.42)	1301.6 (242.99)	1384.5 (251.50)	1389.3 (326.49)	1447.9 (113.99)	1386.7 (225.86)

BMI, body mass index; PBO, placebo; TED, teduglutide.
[a]Other cause of SBS–IF = ulcerative colitis.
[b]Other cause of SBS–IF = radiation enteritis (n = 2), strangulated small intestine (n = 2), ileus (n = 1), recurrent small bowel obstruction due to adhesions (n = 1), complications of hysterectomy (n = 1), and unspecified intestinal obstruction and peritoneal adhesions of intestine (n = 1).
[c]Other cause of SBS–IF = adhesions (n = 2), mechanical ileus (n = 1), congenital intestinal atresia (n = 1), familial adenomatous polyposis (n = 1), and jejunal fistula (n = 1).
[d]Other stoma type = duodenostomy.
[e]Other stoma type = jejunostomy and ileostomy.

Table 4. Change From Baseline at Week 24 in PS Volume, Days Off PS, Body Weight, FCE Components, and FCE Stratified by Diagnosis Classification

	SBS–IBD		SBS–Vasc		Other	
Parameter	TED (n = 11)	PBO (n = 8)[a]	TED (n = 15)	PBO (n = 17)	TED (n = 16)[b]	PBO (n = 18)[c]
PS volume (actual based), change from baseline, % change, mean (SD)	–45.2 (18.29)[d]	–11.4 (14.57)	–24.9 (18.42)	–25.2 (34.48)[c]	32.2 (16.42)	–21.8 (17.36)
Additional days off PS per week, n (%)						
≥1-day reduction at week 24	3 (33.3)[d]	0	8 (53.3)	5 (31.3)[c]	10 (66.7)	4 (25.0)
≥2-day reduction at week 24	2 (22.2)[d]	0	3 (20.0)	3 (18.8)[c]	3 (20.0)	0
≥3-day reduction at week 24	1 (11.1)[d]	0	2 (13.3)	2 (12.5)[c]	1 (6.7)	0
Body weight change from baseline, *kg*, mean (SD)	2.2 (5.41)[d]	1.5 (2.66)	0.4 (3.15)	1.5 (3.41)[c]	0.9 (3.20)	–0.5 (1.48)
Components of FCE change from baseline, *mL/d*, mean (SD)						
PS volume	–1101.7 (653.66)[d,e]	–357.1 (453.15)	–512.6 (539.17)	–277.4 (428.26)[c]	–450.1 (280.06)	–363.0 (345.27)
Oral volume intake	–220.3 (337.92)[f]	246.1 (608.02)	–23.9 (500.12)	187.5 (530.73)[b]	79.0 (611.10)	253.9 (470.17)
Urine output	190.6 (179.81)[f]	–138.2 (238.53)	51.8 (285.63)	30.9 (242.63)[b]	222.1 (341.47)	127.5 (465.62)
FCE change from baseline, *mL/d*, mean (SD)	–1436.5 (900.14)[f,g]	27.2 (818.38)	–588.3 (995.07)	–146.9 (574.79)[b]	–593.2 (443.71)	–236.6 (587.73)

PBO, placebo; TED, teduglutide.
[a]n = 7 with data available.
[b]n = 15 with data available.
[c]n = 16 with data available.
[d]n = 9 with data available.
[e]$P = .0174$ for comparison with patients treated with PBO in the SBS–IBD group, $P = .0418$ for comparison with patients treated with TED in the SBS–Vasc group, and $P = .0168$ for comparison with patients treated with TED in the "Other" group.
[f]n = 8 with data available.
[g]$P < .0168$ for comparison with patients treated with PBO in the SBS–IBD group, $P < .0029$ for comparison with patients treated with TED in the SBS–Vasc group, and $P = .053$ for comparison with patients treated with TED in the "Other" group.

jejunostomy or ileostomy.[16] It is possible that jejunostomy or ileostomy patients with the shortest remnant bowels, particularly those with the largest ileal resections, would have the smallest endogenous, fasting, and postprandial GLP-2 feedback signal. Therefore, jejunostomy patients would experience the most accelerated gastric emptying and gastric hypersecretion as well as the poorest mucosal stimulation for adaptive growth. Accordingly, these patients would experience the most pronounced benefits from supplementation of the exogenous GLP-2 analog teduglutide. In fact, among the jejunostomy or ileostomy patients with SBS–IF (group 1) in this study, a significant correlation was demonstrated between remnant small bowel length and the need for PS volume at baseline; those with the shortest remnant bowels had the highest PS volume needs ($y = -7.8571x + 3459.7501$ [where y is PS volume in mL/d at baseline and x is small bowel length in cm], $r^2 = 0.21$, $P = .01$). Furthermore, when we divided group 1 into jejunostomy and ileostomy subgroups, the jejunostomy subgroup showed greater reductions in PS volume with teduglutide than both the ileostomy subgroup and group 1 as a whole, consistent with the premise that this subgroup includes patients with the least endogenous GLP-2 signaling and therefore benefits most from teduglutide treatment. Endogenous postprandial GLP-2 secretion was not measured in patients included in this study to support this hypothesis.

As anticipated, the well-known benefits from the fluid-, electrolyte-, and energy-salvaging effects of the colon could be demonstrated in the patients with SBS–IF in this study who had a substantial colon-in-continuity (≥50%) and no ostomy (group 2).[23–25] Thus, in spite of having significantly shorter average small bowel lengths (Table 1) compared with the jejunostomy or ileostomy patients with SBS–IF (group 1), these group 2 patients had significantly lower baseline PS volume needs (group 1: 2368 ± 1273 mL/d vs group 2: 1506 ± 777 mL/d, $P = .001$). None of these group 2 patients suffered from IBD, and most (22 of 38) suffered from mesenteric vascular complications leading to SBS–IF. Consequently, only 1 of the 38 patients in group 2 had a need for PS volume exceeding 3000 mL/d. It is likely that the provision of PS volume in many of these patients was mainly to provide parenteral energy rather than fluid and electrolytes. However, the composition of PS volume content (parenteral energy vs fluid and electrolytes) was not investigated in this study.

The absolute effect of teduglutide on PS volume reduction in group 2 patients was significantly less pronounced when compared with group 1. Thus, a PS volume reduction >500 mL/d was observed in only 4 of 18 patients in group 2 treated with teduglutide. The maximal effect of teduglutide on PS volume reduction was 964 mL/d (1 patient in group 2). Equivalently, a PS volume reduction >500 mL/d was demonstrated in 6 of 20 patients in group 2 receiving placebo, suggesting that effects of teduglutide on PS volume reduction were in fact limited in most patients with SBS–IF with this anatomy. Thus, compared with placebo, no effect of teduglutide was seen in group 2 patients with regard to PS volume reduction or changes in the FCE at the time of this evaluation. The effects of teduglutide on intestinal energy absorption were not measured in this study.

Phenotypically, patients with SBS–IF who have a substantial part of the colon in the absence of a stoma are frequently characterized by a more typical pattern of gastric emptying and gastric acid secretion, and good structural and functional adaptation compared with patients with jejunostomy or ileostomy. Apart from the fluid-, electrolyte-, and energy-salvaging effects of the preserved colon, these patients may benefit from a preserved or even elevated endogenous hormone secretion and neuroendocrine feedback signaling from the distal to the proximal gastrointestinal tract,[17,26,27] although endogenous hormonal secretion was not measured in this study. Indeed, many of these group 2 patients with SBS–IF spontaneously adapt and are gradually weaned from PS in the years following their midbowel resection.[28] This is also illustrated by the fact that patients with SBS–IF with this particular anatomy are rare and frequently constitute <25% of the patients in adult IF cohorts in centers with aggressive PS weaning programs.[20] Although the effect of teduglutide seems limited with regard to PS volume reduction in the well-adapted group 2 patients with SBS–IF with >50% colon-in-continuity and no ostomy who may already have benefited from their preserved endogenous GLP-2 secretion, it is not clear whether teduglutide could accelerate early post resectional adaptation. In metabolic balance studies, it has been demonstrated that teduglutide improves intestinal energy absorption by approximately 1 MJ/d in these patients.[21] Because the algorithm for PS reductions was based on increases in urine volume reflecting reductions in fecal wet weight losses and increases in intestinal wet weight absorption, PS volume weaning was modest and late in these patients. However, in the open-label extension studies, in which weaning policies were more liberal, the benefit on energy absorption may have been clinically appreciated, leading to the provision of days off PS or even PS weaning in some of these patients.

Patients with SBS–IF in group 3 either had <50% colon-in-continuity, a colostomy, or both. On average, the effect of teduglutide on PS volume reduction was somewhat intermediate (728.4 ± 532.3 mL/d) compared with groups 1 and 2. This may reflect the fact that the anatomy of these patients was less beneficial with regard to the fluid-, electrolyte-, and energy-salvaging effects of a relatively shorter colon and perhaps weaker adaptive neuroendocrine feedback signaling.

Although remnant bowel anatomy appears to affect the clinical response in terms of absolute reductions in PS volume, patients in all bowel anatomy groups obtained additional days off PS per week with teduglutide treatment. Even in the context of lower baseline and absolute PS volume reductions, most patients in bowel anatomy groups 2 and 3 were able to obtain ≥1 additional PS-free day per week with teduglutide treatment.

In conclusion, findings from these post hoc analyses suggest that the effect of teduglutide on improving fluid

balance, increasing urine production, and thereby reducing the need for PS volume is highly variable among patients with SBS–IF. In general, the greater absolute effects of teduglutide on PS volume reduction were seen in patients with SBS–IF with higher baseline PS volume requirements. These were mainly patients with SBS–IF with jejunostomies or ileostomies, and in this study, most of these patients suffered from IBD. The more rapid and pronounced effects of teduglutide on intestinal fluid absorption in these jejunostomy or ileostomy patients with high PS volume requirements should alert clinicians to more careful monitoring and rapid adjustment of PS volume prescriptions, preferably guided according to standard protocols resembling the original study procedures. By performing simple fluid balance studies, measuring changes in body weight, and surveying conventional biochemistry, it may be possible to minimize the inconveniences of fluid retention related to the introduction of teduglutide in some patients with SBS–IF. Thereby, these patients may be able to reduce jejunostomy or ileostomy output while simultaneously reducing the need for PS volume, thereby reducing or at best eliminating the inconveniences of PS infusions. The effect of teduglutide on PS volume reductions was lower in patients with SBS–IF with >50% colon-in-continuity and no colostomy and in patients with <50% remaining colon-in-continuity or a colostomy. These findings show that a significant knowledge regarding the SBS–IF patient heterogeneity and heterogeneity of response to teduglutide treatment is required to provide the best individualized care for these patients suffering from a rare organ failure disease.

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Received June 30, 2017. Accepted November 17, 2017.

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Acknowledgments
The authors thank Kristina Chen, MS, PharmD, of Shire Human Genetic Therapies, Inc (Lexington, MA) for contributions to the design and data analysis of initial studies leading up to the work presented here, and the investigators in the Teduglutide 020 Study Group (Gastroenterology 2012;143:1473–1481) who conducted the phase III study from which this post hoc analysis is derived. Editorial support was provided by Heather Heerssen, PhD, of Complete Healthcare Communications, LLC (West Chester, PA) and was funded by Shire International GmbH (Zug, Switzerland).

Conflicts of interest
Palle B. Jeppesen has served as a speaker bureau member and consultant for Shire, and as a study investigator, consultant, and advisory board member for NPS Pharmaceuticals, Inc. Simon M. Gabe and Douglas L. Seidner have served as advisory board members and consultants for Shire, and as advisory board members and study investigators for NPS Pharmaceuticals, Inc. Hak-Myung Lee and Clément Olivier are employees of Shire. NPS Pharmaceuticals, Inc, is a wholly owned indirect subsidiary of Shire.

Funding
This research was funded by Shire International GmbH, Zug, Switzerland.