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Impact of Teduglutide on Quality of Life Among Patients With Short Bowel Syndrome and Intestinal Failure

Kristina Chen, PharmD, MS[1]; Fan Mu, PhD[2]; Jipan Xie, MD, PhD[3]; Sneha S. Kelkar, PhD[4]; Clément Olivier, MD[5]; James Signorovitch, PhD[2]; and Palle B. Jeppesen, MD, PhD[6]

Abstract

Background: Teduglutide reduces or eliminates parenteral support (PS) dependency in patients with short bowel syndrome (SBS). Recent post hoc analyses demonstrated that effects are correlated with baseline PS volume. We assessed the SBS-related quality-of-life (QoL) impact of teduglutide, particularly whether improvements are greater among subgroups achieving more PS volume reduction. *Methods:* Using phase 3 trial data of teduglutide in patients with SBS (NCT00798967), change in Short Bowel Syndrome–Quality of Life (SBS-QoL) scores from baseline were compared between teduglutide vs placebo in the overall population and subgroups classified by baseline PS volume requirement, disease etiology, and bowel anatomy. Generalized estimating equation models were fitted to assess impact of teduglutide on SBS-related QoL using data from all visits, adjusted for baseline characteristics. *Results:* Of 86 patients, 43 each were randomized to teduglutide or placebo (mean age: 51 vs 50 years, respectively). In adjusted analyses, teduglutide had a nonsignificant reduction (improvement) of −8.6 points (95% CI: 2.6 to −19.8) in SBS-QoL sum score from baseline to Week-24 vs placebo. The impact of teduglutide varied by subgroup. Patients treated with teduglutide experienced significantly greater reductions in SBS-QoL sum score at Week-24 vs placebo in 2 subgroups, ie, the third (highest) tertile baseline PS volume (−27.3, 95% CI: −50.8 to −3.7) and inflammatory bowel disease (IBD; −29.6, 95% CI: −46.3 to −12.9). Results were similar for SBS-QoL subscale and item scores. *Conclusions:* The impact of teduglutide treatment on SBS-related QoL vs placebo varied among subgroups and was significant and most pronounced among patients with highest baseline PS volume requirement or IBD. (*JPEN J Parenter Enteral Nutr.* 2020;44:119–128)

Keywords

intestinal failure; parenteral nutrition; quality of life; short bowel syndrome; teduglutide

Clinical Relevancy Statement

Parenteral support (PS) dependency in patients with short bowel syndrome and intestinal failure (SBS-IF) has a significant impact on quality of life (QoL). Teduglutide reduces the PS volume requirement and, in some patients, assists PS independence. However, treatment response and teduglutide's impact on QoL may vary depending on the

From [1]Shire Human Genetic Therapies, Inc. (a member of the Takeda group of companies), Cambridge, Massachusetts, USA; [2]Analysis Group, Inc., Boston, Massachusetts, USA; [3]Analysis Group, Inc., Los Angeles, California, USA; [4]Analysis Group, Inc., New York, New York, USA; [5]Shire International GmbH (a member of the Takeda group of companies), Zug, Switzerland; and the [6]Department of Medical Gastroenterology, Rigshospitalet, Copenhagen, Denmark.

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Conflicts of interest: Shire is a member of the Takeda group of companies. K. Chen and C. Olivier are employees of Shire and own stock/options. F. Mu, J. Xie, S. S. Kelkar, and J. Signorovitch are employees of Analysis Group, Inc., which has received research funding from Shire. P. B. Jeppesen has served as a speaker bureau member and consultant for Shire, and a study investigator, consultant, and advisory board member for NPS Pharmaceuticals, Inc.

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Corresponding Author:
Kristina Chen, PharmD, MS, 650 E. Kendall Street, Cambridge, MA 02142.
Email: kristina.chen@takeda.com

etiology, bowel anatomy, and PS volume requirement. This analysis explored teduglutide's impact on QoL in subgroups of patients with SBS-IF defined by these characteristics and found that QoL improvements were most pronounced among patients with the highest PS volume requirements or inflammatory bowel disease.

Introduction

Short bowel syndrome (SBS) is a rare malabsorption disorder of the gastrointestinal (GI) tract related to conditions such as inflammatory bowel disease (IBD), mesenteric ischemia, or cancer.[1] Many patients with SBS rely on parenteral support (PS) for nutrient and fluid supplementation and consequently suffer from intestinal failure (IF).[2,3] The prevalence of IF is estimated to be 3–4 per million people in the United States[4] and about 5–20 per million people in Europe.[1,3,5] As a result of inadequate absorption of nutrients, fluid, and electrolytes, patients with IF associated with SBS (SBS-IF) may experience complications that incur additional healthcare burden and negatively impact patients' quality of life (QoL).[6-9] Although PS may be lifesaving, it is also associated with lifestyle disruptions and potentially severe complications that negatively impact QoL and may increase mortality risk.[10-18] Thus, alleviation of malabsorption and PS reduction and weaning is a major clinical goal in the treatment of SBS-IF patients with PS dependency.

Teduglutide, a glucagon-like peptide-2 analogue,[19] has been approved in the United States and Europe to reduce PS dependency for patients with SBS-IF.[20,21] Association between PS volume reduction and SBS-related QoL improvement was first evaluated using the phase 3 Study of Teduglutide Effectiveness in PS-Dependent SBS Subjects (STEPS) trial.[17] Although that study reported statistically significant improvement in the Short Bowel Syndrome–Quality of Life (SBS-QoL)[22] scores at Week-24 compared with baseline in patients treated with teduglutide, there were no statistically significant differences compared with placebo.[17] Jeppesen et al hypothesized that the heterogeneity in bowel anatomy (patients with or without colon-in-continuity and presence of stoma) may lead to variation in the SBS-related QoL improvement in patient subgroups, thus emphasizing the importance of considering SBS-related QoL response to treatment in specified patient subgroups.[17,19]

In 2015, the European Society for Clinical Nutrition and Metabolism (ESPEN) endorsed the classification of patients with SBS based on functional, pathophysiological, and clinical disease features.[23] Accordingly, a recent study by Jeppesen et al[24] in 2018 used the STEPS trial data to assess the predictors of response to teduglutide in subgroups based on the ESPEN recommendations. Jeppesen et al found the effect of teduglutide varied among different subgroups and was largely correlated with their baseline PS volume requirement.[24] Subgroups with high baseline PS volume requirements, such as patients with IBD or with jejunostomy/ileostomy without colon-in-continuity, experienced significantly larger PS volume reductions from using teduglutide vs placebo.

The effect of teduglutide on SBS-related QoL has not been thoroughly examined in the ESPEN-endorsed subgroups in the existing literature. Jeppesen et al used STEPS trial data to assess the change in SBS-QoL scale scores among patients taking teduglutide compared with placebo; however, the study adjusted for PS volume reduction, which may have acted as a mediator for teduglutide's impact on SBS-related QoL and masked significant associations between teduglutide and SBS-related QoL.[17] Therefore, it is necessary to understand the impact of teduglutide on SBS-related QoL without adjusting for PS volume reduction and to assess this impact in specific patient subgroups. Thus, the objective of the current analysis was to assess the impact of teduglutide on the changes in SBS-QoL scores from baseline among patients with SBS-IF with PS dependency in the overall STEPS population and among patient subgroups defined by PS volume requirement at baseline, disease etiology, and bowel anatomy as per the ESPEN-endorsed subgroup classifications and Jeppesen et al.[24]

Materials and Methods

Data Source

This post hoc analysis included de-identified individual patient-level data from the STEPS (NCT00798967) trial.[25] STEPS was a randomized, double-blind, placebo-controlled, multinational phase 3 study of teduglutide to demonstrate efficacy compared with placebo after 24 weeks of treatment in patients with SBS with PS dependency. The trial included 86 participants (43 each in the teduglutide and placebo groups) in the intent-to-treat (ITT) population, which comprised all patients who were randomized to receive the allocated treatment. However, 1 randomized subject discontinued before the first dose and subsequently did not contribute to any study period assessments.

The detailed methods and data from this trial have been previously published[25]; thus, approval from an institutional review board was not required for the present study.

Study Variables

Baseline characteristics, as reported in STEPS,[25] included demographics, PS characteristics, and SBS-related characteristics. Before the postrandomization evaluations, all patients in STEPS maintained an electronic diary initiated at the time of screening to record PS volume infused in the last 24 hours. The baseline PS volume per week was determined based on patients' diary entries.

The main outcome in this analysis was change in SBS-QoL score from baseline to each follow-up visit, scheduled at weeks 4, 8, 12, 16, 20, and 24 during the STEPS trial. SBS-related QoL was assessed with the disease-specific SBS-QoL scale,[22] which is a multidomain, SBS-specific, patient-reported QoL questionnaire with a recall period of 7 days. It was developed to measure the effect of SBS and its treatment on physical, psychologic, and social aspects of patients' lives.[22] The 17 items are grouped into subscale-1 and subscale-2, yielding 2 subscale scores (subscale-1: 0–110; subscale-2: 0–60) and a sum score (0–170). Higher scores indicate worse SBS-related QoL; thus, a reduction in SBS-QoL score represents an improvement in QoL.

Statistical Analysis

Baseline characteristics. Baseline characteristics were compared between patients receiving teduglutide vs placebo using Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables (when cell counts were >5) or Fisher's exact test (when cell counts were ≤ 5).

SBS-QoL scores. The mean change in SBS-QoL sum score from baseline to Week-24 was calculated for patients in the teduglutide and placebo arms. The difference in score change from baseline to Week-24 between the teduglutide and placebo arms was estimated, and the significance of the difference was assessed using Wilcoxon rank-sum test.

For the adjusted analyses, a generalized estimating equation (GEE) model was fitted using the changes in SBS-QoL sum scores from baseline to each follow-up visit as the dependent variable. The independent variables (covariates) included in the model were treatment (teduglutide vs placebo), each follow-up visit, interaction terms between treatment and each follow-up visit, cause of major intestinal resection, baseline demographics and SBS characteristics, SBS-QoL score at stabilization visit 1, baseline SBS-QoL sum score, and baseline PS volume per week. Last observation carried forward was used to impute missing SBS-QoL scores at each follow-up visit.

Similar GEE models were fitted for each subscale and item scores to estimate the impact of teduglutide on SBS-QoL subscale/item scores.

Patient subgroup analyses. Patients were stratified into the following subgroups based on 3 classification systems. In the first system, patients were stratified into tertiles based on their baseline PS volume requirements: baseline PS requirements of <9 L/wk (first), 9 to <14 L/wk (second), and ≥ 14 L/wk (third). In the second system, patients were stratified based on the etiology of major intestinal resection (ie, IBD, vascular disease [VD], or "other" reasons). In the third system, patients were stratified based on their bowel anatomy (ie, patients with 0% colon remaining, a stoma, and no colon-in-continuity; patients with at least 50% colon remaining, no stoma, and colon-in-continuity; and "others," which included the rest of the patients). The analyses of SBS-QoL sum score were repeated in each subgroup. The analyses of SBS-QoL subscale and item scores were repeated in the subgroups of patients with the highest baseline PS requirement in each of the 3 classification systems (ie, in patients in the third [highest] tertile of baseline PS volume, in patients with IBD, and in patients with 0% colon remaining, a stoma, and no colon-in-continuity).

All analyses were conducted in the ITT population enrolled in the STEPS trial using SAS v.9.4 (SAS Institute, Cary, NC, USA). Significance was assessed at 0.05 level.

Results

Baseline Characteristics

Of the 86 total patients from the ITT population, 43 were randomized to teduglutide and 43 were randomized to placebo (Table 1). The mean age was comparable between the 2 treatment groups (mean [SD]: 50.9 [12.6] vs 49.7 [15.6] years, respectively; $P = 0.819$). Both arms had numerically more women than men (teduglutide: 51.2%, placebo: 55.8%; $P = 0.666$), were predominately white ($\geq$95%), and had a mean body mass index of approximately 22 (mean [SD] for teduglutide: 22.5 [3.2], placebo: 22.2 [3.1]; $P = 0.778$).

Patients in the teduglutide arm had a significantly lower percentage of colon remaining (mean [SD] 55.8 [20.4] vs 70.3 [27.1], respectively; $P = 0.021$), and fewer patients had the ileocecal valve (7.0% vs 23.3%, respectively; $P = 0.035$), compared with the placebo arm (Table 1). Over half of patients in both arms had colon-in-continuity (teduglutide: 60.5%, placebo: 53.5%; $P = 0.514$). The most common cause of intestinal resection in both arms was VD (34.9% vs 39.5%, respectively; $P = 0.656$), followed by IBD (25.6% vs 18.6%; $P = 0.436$). Patients treated with teduglutide had numerically longer remaining small intestine compared with the placebo arm (mean [SD]: 84.4 [64.6] cm vs 68.7 [63.9] cm, respectively; $P = 0.157$). A numerically higher proportion of patients treated with teduglutide did not have a stoma compared with the placebo arm (48.8% vs 39.5%, respectively; $P = 0.385$). Among patients who had a stoma, patients who had teduglutide treatment had a numerically higher rate of jejunostomy (52.4% vs 29.4%; $P = 0.096$) but a numerically lower rate of ileostomy (28.6% vs 52.9%; $P = 0.394$) compared with placebo. Patients treated with teduglutide had slightly lower baseline PS volume requirements than the placebo arm, but the difference was not significant (mean [SD] 12.5 [7.8] L/wk vs 13.4 [7.4] L/wk, respectively; $P = 0.429$).

The baseline characteristics of the subgroups are presented in Supplementary Tables 1–3. Overall, the patient

Table 1. Baseline Characteristics of the ITT Population.

Characteristics	Teduglutide (N = 43)	Placebo (N = 43)	*P*-Value
Demographics			
Age (years), mean (SD)	50.9 (12.6)	49.7 (15.6)	0.819
Men, n (%)	21 (48.8)	19 (44.2)	0.666
Race, n (%)			
White	42 (97.7)	41 (95.3)	1.000
Black	0 (0.0)	1 (2.3)	1.000
Asian	1 (2.3)	1 (2.3)	1.000
BMI (kg/m^2), mean (SD)[a]	22.5 (3.2)	22.2 (3.1)	0.778
Baseline short bowel syndrome characteristics			
Cause of major intestinal resection, n (%)			
Inflammatory bowel disease	11 (25.6)	8 (18.6)	0.436
Vascular disease	15 (34.9)	17 (39.5)	0.656
Injury	4 (9.3)	4 (9.3)	1.000
Volvulus	3 (7.0)	6 (14.0)	0.483
Cancer	1 (2.3)	2 (4.7)	1.000
Other	9 (20.9)	6 (14.0)	0.394
Presence of stoma, n (%)			0.385
Yes	21 (48.8)	17 (39.5)	
No	22 (51.2)	26 (60.5)	
Types of stoma, n (%)			
Jejunostomy	11 (25.6)	5 (11.6)	0.096
Ileostomy	6 (14.0)	9 (20.9)	0.394
Colostomy	4 (9.3)	1 (2.3)	0.360
Other	0 (0.0)	2 (4.7)	0.494
Colon-in-continuity, n (%)			0.514
Yes	26 (60.5)	23 (53.5)	
No	17 (39.5)	20 (46.5)	
Percent of colon remaining, mean (SD)	32.4 (31.8)	40.9 (40.6)	0.294
Estimated remaining small intestine length (cm), mean (SD)[b]	84.4 (64.6)	68.7 (63.9)	0.157
Estimated remaining small intestine length (cm), n (%)			
<60 cm	16 (37.2)	24 (55.8)	0.084
≥60 cm	24 (55.8)	16 (37.2)	0.084
Presence of distal/terminal ileum, n (%)			0.336
Yes	10 (23.3)	14 (32.6)	
No	33 (76.7)	29 (67.4)	
Presence of ileocecal valve, n (%)			0.035[c]
Yes	3 (7.0)	10 (23.3)	
No	40 (93.0)	33 (76.7)	
Time since last small bowel resection (years), mean (SD)	6.9 (6.7)	7.6 (7.8)	0.656
Baseline PS characteristics			
Composite fluid balance (fluid composite effect), mean (SD)	16.2 (11.6)	15.2 (8.9)	0.775
Baseline PS volume per week (L), mean (SD)	12.5 (7.8)	13.4 (7.4)	0.429
Time since start of PS dependency (years), mean (SD)	6.8 (6.3)	5.9 (5.7)	0.763
Actual weekly number of days of PS, mean (SD)	5.6 (1.6)	6 (1.4)	0.273

BMI, body mass index; ITT, intent-to-treat; PS, parenteral support (includes fluids and electrolytes, and may include energy and micronutrients).
[a]The sample size for the teduglutide arm was 42. The measure was missing in 1 patient.
[b]The sample size for both arms was 40. The measure was missing in 6 patients.
[c]Statistically significant at $P < 0.05$.

demographics were similar across the subgroups. In the subgroups of patients categorized by baseline PS volume tertiles, patients in first tertile had similar baseline PS volume requirements between the 2 treatment groups (mean [SD] teduglutide: 5.6 [2.3] L/wk vs placebo: 6.0 [2.2] L/wk). Patients who received teduglutide had numerically higher baseline PS volume than placebo in the second tertile (11.7 [1.9] L/wk vs 11.2 [1.8] L/wk, respectively) and the third tertile (22.8 [6.8] L/wk vs 20.7 [5.8] L/wk, respectively). In the third tertile, >54% of patients in both arms had stoma, and 54.5% in teduglutide compared with 35.3% in placebo had colon-in-continuity (Supplementary Table 1). In the

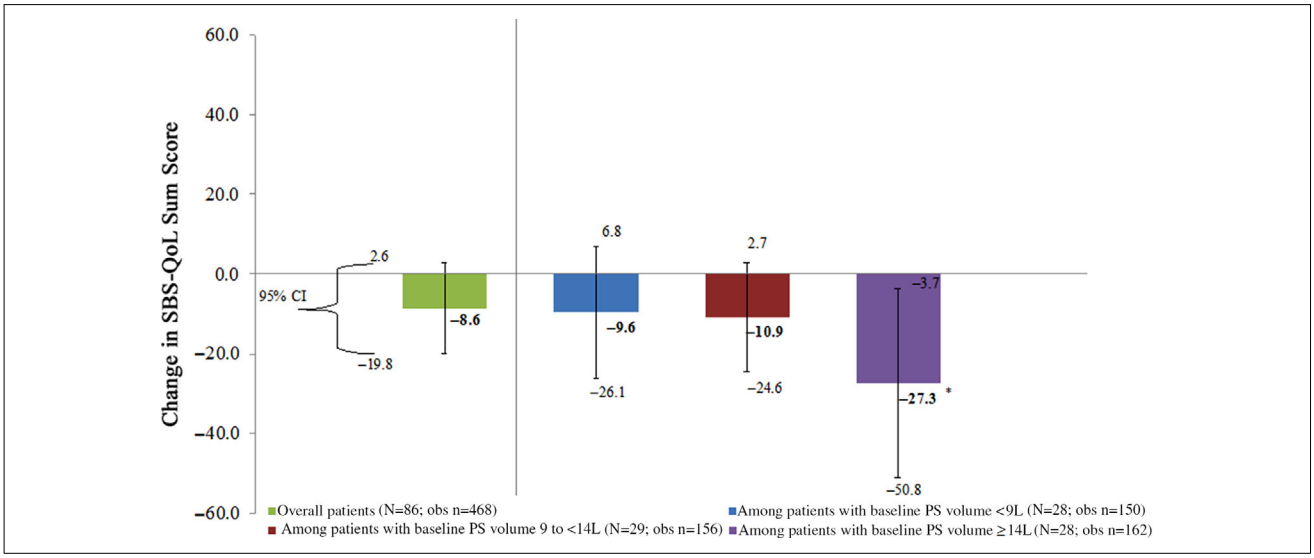

Figure 1. Impact of teduglutide on SBS-QoL sum score among patients stratified by baseline PS volume tertile in the ITT population. Adjusted changes in SBS-QoL sum score from baseline were estimated using generalized estimating equation models, adjusting for baseline characteristics. Observations from all follow-up visits were included in the analysis. *Statistically significant at $P < 0.05$. ITT, intent-to-treat; N, number of patients; obs n, number of observations; PS, parenteral support; SBS-QoL, Short Bowel Syndrome–Quality of Life scale.

subgroups based on disease etiology, the IBD subgroup had the highest PS volume requirements at baseline (teduglutide: 15.9 [10.4] L/wk; placebo: 21.6 [8.1] L/wk). In addition, >87% of patients with IBD had stoma and did not have colon-in-continuity (Supplementary Table 2). The baseline PS volume requirement was highest in the subgroup with 0% remaining colon (teduglutide: 14.5 [9.6] L/wk; placebo: 18.8 [7.9] L/wk) compared with the other groups (Supplementary Table 3).

Impact of Teduglutide on SBS-QoL Sum Score

In the descriptive analyses, generally, patients treated with teduglutide experienced greater numerical reductions in the change in SBS-QoL sum score from baseline to Week-24 compared with those in the placebo arm, although the difference was not significant (mean difference −5.4; $P = 0.407$) (Supplementary Table 4). In the subgroups defined by baseline PS volume, the mean differences in change in SBS-QoL sum score from baseline to Week-24 between the teduglutide and placebo groups ranged from −10.2 to −3.2, but the differences were not significant. The mean differences ranged from −11.4 to 2.5 in the subgroups defined by etiology of intestinal resection and from −21.9 to 32.2 in the subgroups defined by bowel anatomy. Almost all subgroups exhibited a trend of greater improvement in SBS-related QoL in the teduglutide group, except for patients with VD (mean difference 2.5; $P = 0.940$) and those with "other" colon anatomy (mean difference 32.2; $P = 0.024$). In these subgroups, patients treated with teduglutide had a reduction in SBS-QoL sum score from baseline; however, placebo patients had a greater reduction. There was a significantly greater reduction in the SBS-QoL sum score from baseline to Week-24 in the teduglutide vs placebo arms in the subgroup with ≥50% colon remaining (mean difference −21.9; $P = 0.037$).

In the adjusted analysis, patients who received teduglutide experienced a greater but not statistically significant reduction of −8.6 (95% CI: 2.6 to −19.8) points compared with placebo patients in the SBS-QoL sum score from baseline to Week-24 (Figure 1). Among 3 subgroups stratified by baseline PS volume, patients treated with teduglutide experienced consistently greater reductions in SBS-QoL score at Week-24 compared with placebo, but the difference varied across subgroups. Specifically, patients who received teduglutide in the first tertile had a numerically −9.6 point greater reduction (95% CI: −26.1 to 6.8) in SBS-QoL score, the second tertile had a numerically −10.9 point greater reduction (95% CI: −24.6 to 2.7), and the third tertile (with the highest baseline PS volume) had the largest difference between the 2 arms, a statistically significantly greater reduction of −27.3 points (95% CI: −50.8 to −3.7).

In the adjusted analyses of the subgroups stratified by disease etiology, the impact of teduglutide was most pronounced in the IBD subgroup (Figure 2). This subgroup experienced a statistically significant −29.6 point greater reduction in SBS-QoL score vs placebo (95% CI: −46.3 to −12.9). In the VD subgroup and the "other" etiology subgroup, teduglutide had numerically greater reductions in SBS-QoL scores compared with placebo, but the differences

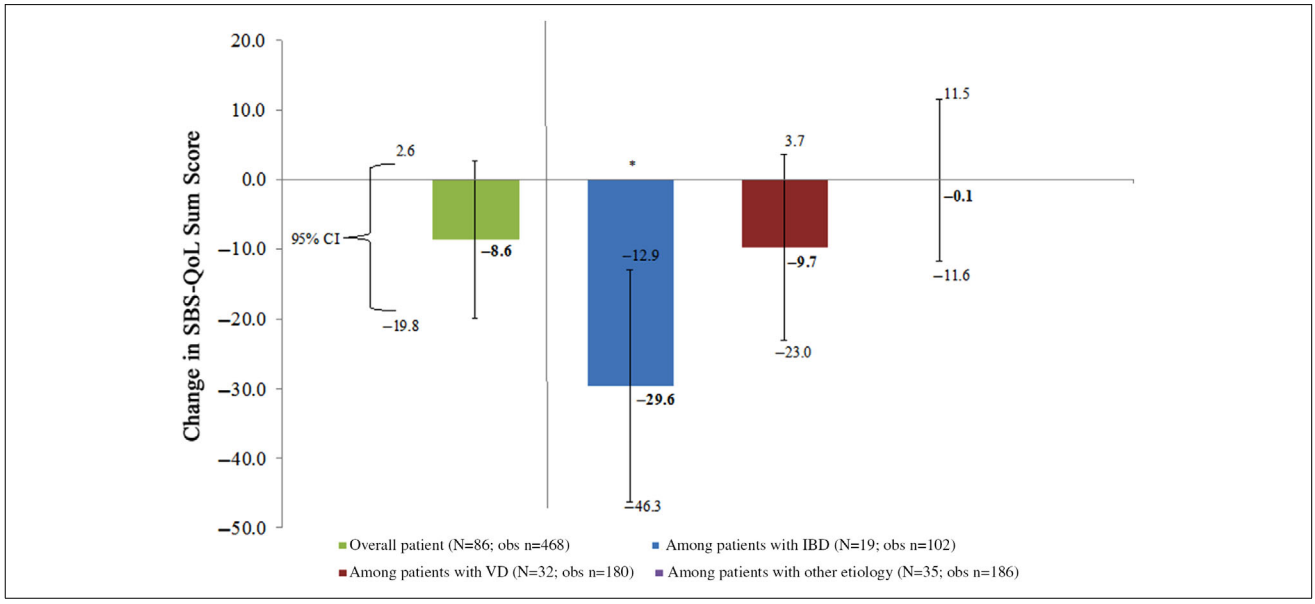

Figure 2. Impact of teduglutide on SBS-QoL sum score among patients stratified by etiology classification in the ITT population. Adjusted changes in SBS-QoL sum score from baseline were estimated using generalized estimating equation models, adjusting for baseline characteristics. Observations from all follow-up visits were included in the analysis. *Statistically significant at $P < 0.05$. IBD, inflammatory bowel disease; ITT, intent-to-treat; N, number of patients; obs n, number of observations; SBS-QoL, Short Bowel Syndrome–Quality of Life scale; VD, vascular disease.

were not statistically significant (−9.7 [95% CI: −23.0 to 3.7] and −0.1 [95% CI: −11.6 to 11.5], respectively).

In the adjusted analyses of the subgroups stratified by bowel anatomy, patients treated with teduglutide with 0% colon remaining, stoma, and no colon-in-continuity had a numerically greater reduction from baseline SBS-QoL score of −10.7 (95% CI: −29.0 to 7.6) points vs placebo; patients with ≥50% colon remaining had a numerically greater reduction of −12.7 (95% CI: −27.3 to 1.8) points vs placebo (Figure 3). However, among patients with other colon anatomies, patients who received teduglutide experienced statistically significantly less reduction in SBS-QoL score from baseline to Week-24 compared with placebo (39.5, 95% CI: 24.6 to 54.4). As mentioned above, patients treated with teduglutide had a reduction in SBS-QoL sum score from baseline, but the reduction was smaller compared with placebo.

Impact of Teduglutide on SBS-QoL Subscale and Item Scores

In the overall population, patients who received teduglutide had a numerically greater reduction in both subscales and in 16 out of 17 item scores from baseline to Week-24 compared with placebo (Table 2). Patients treated with teduglutide had a −6.1 point greater reduction (improvement) (95% CI: −13.9 to 1.7) in SBS-QoL subscale-1 and a −2.7 point reduction (improvement) (95% CI: −6.7 to 1.4) in SBS-QoL subscale-2 vs placebo, but the results were not significant. Significantly greater reductions (improvements) in the teduglutide group were observed in the item scores for leisure activities (−1.3, 95% CI: −2.2 to −0.3) and skeletal/muscle symptoms (−1.0, 95% CI: −1.8 to −0.2).

In the third PS volume tertile (≥14 L/wk), patients who received teduglutide experienced a significantly greater reduction (improvement) from baseline in SBS-QoL subscale-2 score (−8.1, 95% CI: −14.1 to −2.0) compared with placebo (Table 2). In addition, patients receiving teduglutide experienced significantly greater reductions (improvements) in 6 of the 17 item scores: general well-being, leisure activities, physical health, GI symptoms, skeletal/muscle symptoms, and other symptoms/discomfort (all $P < 0.05$).

Among the IBD subgroup, patients treated with teduglutide experienced a significantly greater reduction (improvement) from baseline in SBS-QoL subscale-1 score (−31.1, 95% CI: −43.5 to −18.6) and in 14 of 17 item scores (general well-being; everyday activities; work life/ability to work; leisure activities; social life; energy life; pain; diet, eating and drinking habits; emotional life; sleep; fatigue/wakefulness; diarrhea/stomal output; skeletal/muscle symptoms; other symptoms/discomfort; all $P < 0.05$); for 3 items (physical health, mobility/self-care, and GI symptoms) scores were improved but did not achieve significance vs placebo (Table 2). In addition, patients who received teduglutide in the subgroup categorized by bowel anatomy of 0% colon remaining, a stoma, and no colon-in-continuity experienced significantly greater reductions (improvements) from baseline in the SBS-QoL subscale-1 score (−18.7, 95% CI: −32.3

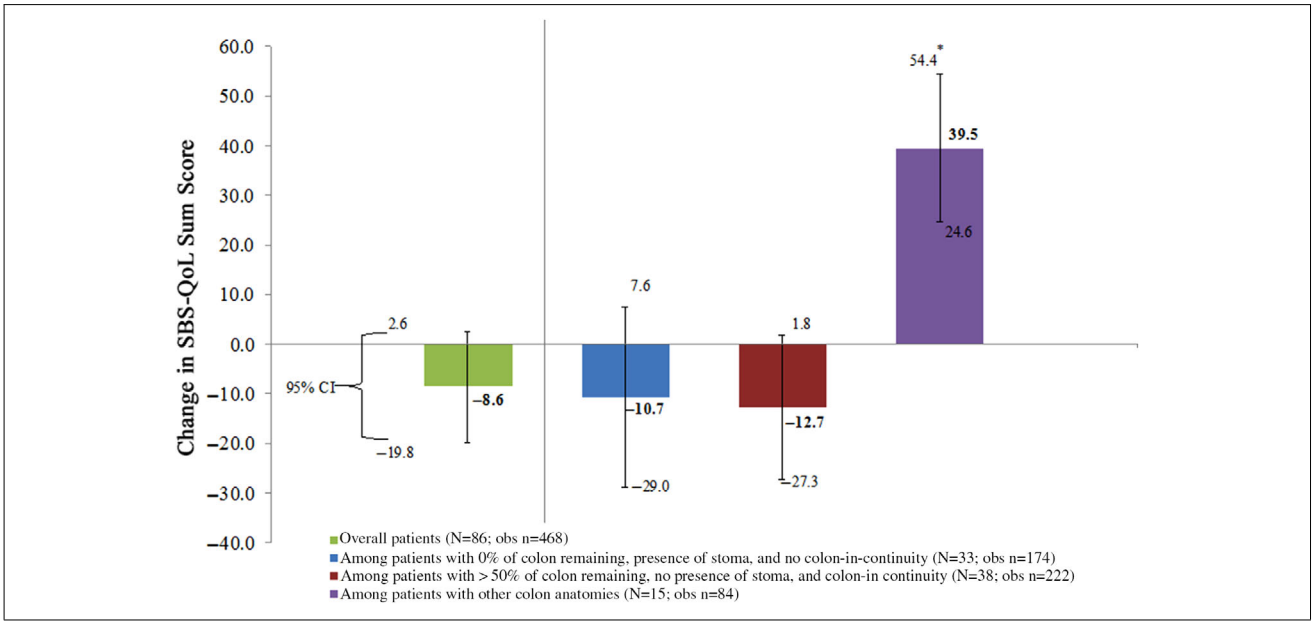

Figure 3. Impact of teduglutide on SBS-QoL sum score among patients stratified by anatomical classification in the ITT population. Adjusted changes in SBS-QoL sum score from baseline were estimated using generalized estimating equation models, adjusting for baseline characteristics. Observations from all follow-up visits were included in the analysis. *Statistically significant at $P < 0.05$. ITT, intent-to-treat; N, number of patients; obs n, number of observations; SBS-QoL, Short Bowel Syndrome–Quality of Life scale.

to −5.2) and in 2 of 17 item scores (everyday activities and leisure activities; all $P < 0.05$) compared with placebo (Table 2).

Discussion

SBS-IF is a complex condition to manage, especially considering the underlying causes, patients' bowel anatomy, and the extent of the PS dependency. Prior research has shown that the patient population with SBS-IF and PS dependency is highly heterogeneous,[26] although teduglutide has demonstrated efficacy in reducing the volume of PS requirement in this patient population.[27] However, a previous study examining SBS-related QoL showed that teduglutide demonstrated a directional but statistically nonsignificant benefit in improving the outcome in the overall population.[27] Given the current understanding in the expectations of response to teduglutide in heterogeneous subpopulations, there was a need to further examine the impact of teduglutide on improvement of SBS-related QoL within these subpopulations.

The current study built upon the previous literature, mainly studies by Jeppesen et al,[17,19,24] to further assess the impact of teduglutide on SBS-related QoL in the overall patient population with SBS-IF and PS dependency and among subgroups of patients defined by baseline PS volume, etiology of major intestinal resection, and remnant, functional bowel anatomy. This study improves upon previous studies in the following ways. First, data were analyzed from all visits in the ITT population, which could help address the issue of small sample size and limited power. Second, when evaluating the impact of teduglutide on SBS-related QoL, there was no adjustment for PS volume, which can be a mediator between teduglutide and SBS-related QoL and obscure the true impact of the treatment. Third, patient subgroups were defined based on the recommendation of ESPEN. This last approach is crucial given that the impact of teduglutide on PS volume reduction has varied considerably across these subgroups,[24] with greater impact among patients with higher baseline PS volume requirements, and that PS volume reduction is associated with SBS-related QoL improvement.

The current results showed that, in the overall population, teduglutide was generally associated with a greater SBS-related QoL improvement compared with placebo, but the differences were not significant for most scores. Similarly, there was a trend of greater SBS-related QoL improvement in the teduglutide vs placebo arm in almost all subgroups. However, there was substantial heterogeneity regarding the impact of teduglutide on SBS-related QoL, which was demonstrated in the magnitude and statistical significance of the SBS-QoL score changes. Significant and substantial SBS-related QoL improvements were observed in patients in the third tertile for baseline PS volume and in patients with IBD, who also had a high baseline PS volume requirement. The differences in SBS-related QoL

Table 2. Summary of the Impact of Teduglutide on SBS-QoL Subscale Scores and Item Scores at Week-24 in the ITT Population.

	Overall Patients		Baseline PS volume ≥14 L/wk		IBD Patients		0% Colon Remaining, Stoma, No Colon-in-Continuity	
SBS-QoL Models	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Subscale 1	−6.1	(−13.9, 1.7)	−15.8	(−32.2, 0.5)	−31.1	(−43.5, −18.6)[a]	−18.7	(−32.3, −5.2)[a]
Subscale 2	−2.7	(−6.7, 1.4)	−8.1	(−14.1, −2.0)[a]	−16.2	(−42.3, 9.8)	−2.9	(−10.3, 4.5)
Individual Items								
1. General well-being	−0.4	(−1.2, 0.5)	−1.9	(−3.3, −0.4)[a]	5.8	(4.4, 7.1)[a]	−0.2	(−1.6, 1.2)
2. Everyday activities	−0.6	(−1.4, 0.2)	−0.7	(−2.2, 0.8)	−3.6	(−5.1, −2.1)[a]	−1.6	(−2.8, −0.4)[a]
3. Work life/ability to work	0.0	(−1.0, 1.1)	−1.3	(−2.7, 0.1)	−4.3	(−7.2, −1.3)[a]	−0.9	(−2.3, 0.6)
4. Leisure activities	−1.3	(−2.2, −0.3)[a]	−2.3	(−4.0, −0.7)[a]	−4.1	(−5.7, −2.5)[a]	−2.2	(−3.6, −0.8)[a]
5. Social life	−0.6	(−1.6, 0.4)	−1.2	(−2.4, 0.0)	−3.8	(−6.1, −1.6)[a]	−0.8	(−2.4, 0.8)
6. Energy life	−0.5	(−1.4, 0.4)	−1.4	(−2.8, 0.1)	−2.1	(−4.1, −0.1)[a]	−0.5	(−1.4, 0.5)
7. Physical health	−0.7	(−1.6, 0.2)	−2.6	(−4.3, −0.9)[a]	−1.7	(−4.9, 1.5)	−0.7	(−2.2, 0.8)
8. Mobility and self-care activities	−0.4	(−1.2, 0.5)	−0.9	(−2.7, 0.8)	−2.4	(−4.8, 0.0)	−0.8	(−2.0, 0.4)
9. Pain	−0.1	(−1.1, 0.8)	−0.4	(−2.0, 1.2)	3.7	(0.4, 7.0)[a]	0.0	(−1.5, 1.5)
10. Diet, eating, and drinking habits	−0.5	(−1.6, 0.6)	−1.2	(−2.6, 0.1)	−5.9	(−9.7, −2.1)[a]	0.7	(−1.2, 2.6)
11. Emotional life	−0.5	(−1.4, 0.4)	−1.2	(−2.6, 0.3)	−3.1	(−5.9, −0.4)[a]	−1.4	(−3.0, 0.1)
12. Sleep	−0.7	(−1.6, 0.2)	−1.6	(−3.6, 0.4)	−6.0	(−7.2, −4.8)[a]	−1.5	(−3.3, 0.2)
13. Gastrointestinal symptoms	−0.7	(−1.6, 0.2)	−2.5	(−3.9, −1.1)[a]	−0.9	(−5.0, 3.2)	0.3	(−1.9, 2.4)
14. Fatigue/weakness	−0.7	(−1.6, 0.2)	−0.8	(−2.0, 0.4)	−1.9	(−3.5, −0.3)[a]	−0.2	(−1.1, 0.8)
15. Diarrhea/stomal output	−0.5	(−1.5, 0.5)	0.8	(−1.0, 2.5)	−5.1	(−6.6, −3.6)[a]	−0.5	(−2.5, 1.5)
16. Skeletal/muscle symptoms	−1.0	(−1.8, −0.2)[a]	−2.5	(−3.9, −1.2)[a]	−4.6	(−5.9, −3.2)[a]	−0.5	(−1.8, 0.9)
17. Other symptoms/ discomfort	−0.3	(−1.2, 0.6)	−2.2	(−3.9, −0.4)[a]	−3.9	(−6.3, −1.5)[a]	−1.3	(−3.2, 0.5)

IBD, inflammatory bowel disease; ITT, intent-to-treat; PS, parenteral support; SBS-QoL, Short Bowel Syndrome–Quality of Life scale.
[a]Statistically significant at $P < 0.05$.

improvement between teduglutide and placebo in these 2 subgroups exceeded a previously communicated minimal clinically important difference of 18.4 points as determined using twofold measurement error and clinical experts' opinions.[28] These results are consistent with the clinical findings by Jeppesen et al,[24] which showed that teduglutide had a greater impact on PS volume reduction among subgroups of patients who had higher PS volume requirements at baseline. These findings further support the hypothesis that PS volume reduction, as a consequence of improved intestinal function and indicative of associated reduction of fecal losses, may mediate the impact of teduglutide on SBS-related QoL. Although a statistically significant impact of teduglutide on SBS-related QoL in the overall population was not found, the associations between PS volume reduction and SBS-related QoL improvement are supported by previous studies[17,29] and the current findings. Together, these studies suggest that teduglutide potentially improves SBS-related QoL through its impact on PS volume reduction indicative of improved intestinal absorption.

Interestingly, in the 3 subgroups defined by bowel anatomy, SBS-related QoL measured by SBS-QoL sum score was not significantly improved in the teduglutide group compared with the placebo group. Our hypothesis was that patients with 0% colon remaining, a stoma, and no colon-in-continuity had higher baseline PS volume requirements and thus may exhibit greater SBS-related QoL improvement when treated with teduglutide vs placebo. However, we observed numerically greatest SBS-related QoL improvement in patients with ≥50% colon remaining, no stoma, and colon-in-continuity. Although such findings do not support our hypothesis, they are consistent with the previous study by Jeppesen et al,[17] which reported greater SBS-related QoL improvement in patients with colon-in-continuity and those without a stoma. It is also worth noting the findings for the subgroup with "other" bowel anatomy. Contrary to our expectations, in this subgroup, the SBS-related QoL improvement from baseline was larger in patients receiving placebo vs those receiving teduglutide, although both treatment arms experienced improvement.

As this subgroup only included a very small number of patients (7 in placebo and 8 in teduglutide), it is uncertain as to whether this reflects the true treatment effect or is just due to random chance.

When assessing the change from baseline in SBS-QoL item and subscale scores, the current results showed that teduglutide consistently improved scores related to "leisure activities" and "skeletal and muscle symptoms" in the overall population and the subgroups requiring a high baseline PS volume (except for "skeletal/muscle symptoms" in the subgroup with 0% colon remaining, a stoma, and no colon-in-continuity). Among all 3 subgroups examined, patients with IBD treated with teduglutide had the largest number of significantly improved item scores compared with placebo (15/17 item scores). In addition, the reductions in SBS-QoL subscale-1 scores for patients with IBD and 0% colon remaining, stoma, and no colon-in-continuity, and the subscale-2 for the third tertile of baseline PS volume, were significantly greater for teduglutide vs placebo. These results show that teduglutide had a heterogeneous effect on different subgroups as well as on different aspects of SBS-related QoL. It remains to be established if teduglutide's beneficial effects relate to less stoma production or diarrhea, the associated improved intestinal wet-weight absorption and less diurnal electrolyte fluxes, potential effects of muscle cramping, and reduced time spent at parenteral infusions. Understanding the aspects of SBS-related QoL for which teduglutide is most impactful could help with clinical decision-making.

Overall, teduglutide is an effective treatment for patients with SBS-IF and PS dependency; however, response varies substantially in terms of clinical and SBS-related QoL outcomes across patients. Patients were randomized to teduglutide and placebo in the overall trial population but not in each subgroup. Therefore, similar to observational studies, there may be unobserved baseline differences between treatment groups influencing the subgroup comparisons. This study is limited to the small sample size and exclusion/inclusion criteria of the STEPS trial, which may limit the generalizability of the results. Real-world studies assessing the impact of teduglutide on clinical and SBS-related QoL outcomes are indicated, as are future studies to understand the mechanism by which teduglutide impacts SBS-related QoL and to identify patient populations in which teduglutide may show the greatest benefit based on multiple outcomes.

The minimally clinically important difference (MCID) with regard to the SBS-QoL score may render some debate. The first published MCID (18.4) was determined by an approach combining the measured error and experts' opinions, and was not anchored on a clinical change that is meaningful to patients, which is the preferred methodology recommended by the U.S. Food and Drug Administration.[28,30] A recent cross-sectional study by Nordsten et al found PS volume (L/day) was significantly correlated with SBS-QoL score with an estimate of 7 QoL points per L/day (95% CI: 1 to 13; $P = 0.044$).[31] However, no clinical consensus has been reached on what the MCID is, and the benchmark is developing as more research is conducted on the QoL of patients with SBS.

In the STEPS trial, teduglutide resulted in a numerically greater improvement in SBS-related QoL compared with placebo in patients with SBS-IF and PS dependency. There was substantial heterogeneity in the impact of teduglutide on SBS-related QoL in the subgroups, which was more pronounced among patients with higher baseline PS volume requirements and those with IBD. Compared with placebo, teduglutide had a greater impact on improving the enjoyment of leisure activities and skeletal/muscle symptoms in the overall study patients; impact on improving additional aspects of SBS-related QoL were achieved by the subgroups. The results of this analysis may help identify patient populations that may experience a greater SBS-related QoL benefit from teduglutide treatment and provide additional evidence to assist with clinical decision-making in the treatment of patients with SBS-IF and PS dependency.

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Statement of Authorship

K. Chen, F. Mu, J. Xie, S. S. Kelkar, C. Olivier, J. Signorovitch, and P. B. Jeppesen equally contributed to the conception and design of the research; F. Mu, J. Xie, S. S. Kelkar, and J. Signorovitch contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

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

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