Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure A real-world French observational cohort study

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Finding Support : Translation assistance was supported by a grant from Shire Pharmaceuticals Inc.

Abbreviations : Short bowel syndrome = SBS, intestinal failure = IF, intravenous = IV, SBS with IF = SBS-IF, parenteral support = PS, glucagon-like peptide-2 = GLP-2, teduglutide = TED.

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Disclosures :

FJ, CC, SMS have served as advisory board member and consultant for Shire, and as a study investigator, consultant, and advisory board member for NPS Pharmaceuticals, Inc. DQ, DS, FP, PB, VB, RT have served as advisory board members for Shire. AN, JL have none to declare.

Transcript profiling : None

Writing assistance : Sophie Pegorier

Author contributions : FJ generated and supervised the study. AN generated and supervised statistical analysis. All authors contributed interpretation of data, 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.

KEY WORDS : short-gut syndrome ; GLP2- receptor agonist ; parenteral nutrition; Inflammatory bowel disease

Acknowledgments
Charlotte Bergoin, Madeleine Lauverjat and Lore Billiauws

ABSTRACT

- **Background & Aims:** Teduglutide, a GLP-2-analog, has proven effective in two placebo-controlled studies in reducing parenteral support (PS) in patients with short bowel syndrome-associated intestinal failure (SBS-IF) after 24 weeks. The aim of this study was to describe in a real-life situation the effects of teduglutide treatment and their predictive factors.
- **Methods:** We included 54 consecutive SBS-IF patients treated with teduglutide in France for at least 6 months from 10 expert centers. Small bowel length was 62±6 cm and 65% had colon in continuity. PS was 4.4±.2 infusions per week, started 9.8±1.2 years before. Response (PS reduction ≥ 20%) and PS discontinuation rates were assessed at week 24. Adjusted *p* values of factors associated with response and weaning were calculated using a multivariate logistic regression model.
- **Results:** At week 24, 85% of patients were responders and 24% had been weaned off PS, with a 51% reduction of PS needs and 1.5±0.2 days off PS per week. Response to teduglutide was influenced by a higher baseline oral intake (p=.02). Weaning off PS was influenced by the presence of colon (p=.04), a lower PS volume (p=.03) and a higher oral intake (p=.01). There were no differences based on age, bowel length or SBS-IF causes.
- **Conclusions:** Our study confirms the effectiveness of teduglutide in reducing PS needs in SBS-IF patients. We associated reduced parenteral support volume with baseline parenteral volume support, bowel anatomy, and oral intake. These findings underline the role of nutritional optimization when starting the treatment.
- **Keywords:** short-gut syndrome ; GLP2- receptor agonist ; parenteral nutrition; Inflammatory bowel disease ; intestinal failure

INTRODUCTION

Patients with intestinal failure associated with short bowel syndrome (SBS–IF) do not absorb enough nutrients and/or fluids through oral or enteral intake alone to maintain life and growth. This clinically significant reduction in intestinal absorptive capacity is a consequence of substantial intestinal resection or functional impairment commonly due to a disease, a trauma, surgical complications or congenital abnormalities and requires routine, regular, complete or partial parenteral support (PS; parenteral nutrition (PN) and/or intravenous fluids (IVF))[1, 2]. In patients with SBS-IF who require PN and/or IVF, the therapeutic management aims to reduce the long-term dependence on PS and, when possible, to get patients weaned from it. In the last two decades, a hormonal treatment paradigm focusing on intestinal rehabilitation through the promotion of intestinal hyperadaptation has been proposed. To date, only two trophic factors have been approved in SBS patients: growth hormone (GH; somatotropin) (only in the USA) and the glucagon-like peptide-2 (GLP-2) analog, teduglutide (TED) (in the USA, Canada and Europe) [3-6]. In France, TED is marketed since October 2015. Both GLP-2 and its degradation-resistant analog TED increase intestinal wet weight absorption [7, 8] and decrease the need for PS in SBS-IF patients [9-11]. Phase III clinical studies have shown that treatment with TED was associated with a reduction by at least 20% in PS at 6 months in adult SBS-IF patients [9, 11]. Due to the heterogeneity in patient response to TED in randomized studies and to the high cost of the drug, the ESPEN guidelines have mentioned the need to identify candidates for trophic factors among SBS-IF patients [2]. The aim of this study was to investigate predictive factors of early response and of weaning off PS and to determine the rate of responders in a "real-life" nationwide SBS-IF cohort treated with TED,

METHODS

Patient selection and management

This study was a multicenter, open-label, retrospective, observational cohort study assessing all SBS-IF patients who received TED for at least six months in France since its marketing authorization. The database was locked on September 1, 2017, meaning that the treatment had to be initiated between October 2015 and March 2017. According to the French good medical practice consensus, TED initiation was allowed in the 15 authorized expert adult IF centers. SBS-IF patients selected to receive treatment were stable SBS-IF patients who remained PS dependent despite the use of all other intestinal rehabilitation modalities. Treatment was initiated after a stabilization period to ensure adequate nutrition and hydration status as well as patient compliance with therapy. Patients received a dose of 0.05mg/kg/day subcutaneously. They were trained to perform themselves the injection on the abdomen or thighs, aiming to alternate the sites of injection. An adaptation of dosage was performed in case of chronic renal disease. TED was not prescribed in patients who had undergone digestive surgery or PS initiation in the 6 months preceding the study, in patients with history of cancer within the last five years, with severe heart failure, with specific allergy or in case of patient refusal. As no prescription guidelines are available for TED, the previously published screening and pre-TED assessment, including colonoscopy, follow-up, adaptation of PS volume and frequency procedures were followed [11] and left to the discretion of the expert physician in charge of the patient. This study was conducted in accordance with the ethical standards of the Committee on Human Experimentation of our institution. [14]

Data collection

Epidemiological and clinical variables were collected in each center, including age, gender, body weight, body mass index (BMI), SBS causes (mesenteric ischemia, Crohn's disease, volvulus, radiation enteritis), SBS anatomical features (remnant bowel length and colon in continuity, type of stoma, reverse intestinal interposition surgery), IF features (PS duration, number of weekly infusions and daily infused volume, and energy needs, oral intake, daily fecal volume and steatorrhea in a 72-hour stool collection). SBS anatomy was classified into 3 groups (jejunostomy or ileostomy, group 1; ≥50%

of colon in continuity, group 2; <50% of colon in continuity, group 3) according to Jeppesen et al [12]. IF was classified according to energy needs (PN or only fluids and electrolytes) and the volume of IVF supplementation (class 1-4), according to ESPEN recommendations[13] . The response to treatment was assessed at weeks 12 and 24.

Primary and secondary outcomes

The primary outcome was the predictive factors of response and of weaning off PS 24 weeks after TED initiation. The response was defined as the achievement of a 20-100% reduction in daily PS volume from baseline. For the study "non – response" was defined as the increase in daily PS volume or a PS volume reduction inferior by 20% from baseline, 24 weeks after TED initiation. Secondary outcomes were the percentage of patients who discontinued PS (weaned) and the percentage and absolute change in PS volume 24 weeks after TED initiation.

Statistical analysis

Quantitative data are presented as means ± standard deviation. Normally distributed quantitative data were analyzed using the Student t test. The Mann-Whitney U test was used otherwise. Qualitative data are presented as the number of patients (percentage of patients) and were compared using either the Pearson $\chi 2$ test or the Fisher exact test, depending on the sample size. Missing data were not analyzed or estimated. Adjusted *p* values of factors associated with response and with weaning off PS were calculated using a multivariate logistic regression model including all variables with $p < 0.10$ in univariate analysis and controlling for the following factors: age, bowel length, SBS causes (Crohn's disease vs. others) and small bowel anatomy (Group 1 vs. others). Multicollinearity among selected variables was assessed using variance inflation factors, considered suspicious for collinearity when >4. Results of the multivariate analysis are presented as odds ratios (OR) [95% confidence interval]. Percentage and absolute change in PS volume between SBS causes and small bowel anatomical groups were compared using the Student t test. Adjustment was

performed using a covariance analysis (ANCOVA) model with the change in PS volume as the dependent variable, SBS causes and small bowel anatomical classification as independent variables and the following covariates: baseline oral intake, PS volume and remaining small bowel length. Correlation analysis was performed using a simple linear regression model with unadjusted r^2 values reported. All tests were two sided. A *p* value <0.05 was considered significant. All analyzes were performed using the Statistical Package for the Social Sciences (SPSS) for Mac OSX software (version 22.0, Chicago, Illinois, USA). All authors had access to the study data and reviewed and approved the final manuscript. There was no missing data at any time point for the variables studied.

RESULTS

Patient characteristics

From October 2015 to September 2017, a total of 54 consecutive patients [(19 (35%) women; mean age 52.3 ± 2.1 years)] were included, i.e. all patients treated for at least six months with TED among the 74 patients who initiated TED treatment in France. Patient baseline characteristics are presented in **tables 1 & 2**. The most common underlying causes of SBS were acute mesenteric ischemia (SBS-Vasc, n=21, 39%) and Crohn's disease (SBS-IBD, n=16, 30%). Other causes included volvulus (n=7, 13%), radiation enteritis (n=3, 5.5%), congenital disorders (n=3, 2%), postoperative complications (n=3, 18%) and abdominal traumatic injury (n=1, 6%). The mean length of remaining bowel was 61.8 ± 5.9 cm. Thirty-five patients (65%) had a remaining colon in continuity (mean percentage of length: 49%). Three patients (6%) had undergone reverse intestinal interposition surgery that failed to achieve PS weaning. TED was initiated 9.8 ± 1.2 years after definitive diagnosis of IF requiring PS. At baseline, patients received a mean number of 4.4 ± 0.2 infusions per week, corresponding to a mean volume of 1595 ± 163 mL/day on a seven-day basis.

Response and predictive factors of response and of weaning off PS at week 24

Twenty-four weeks after TED treatment initiation, 46 patients (85%) were responders and 13 (24%) were weaned from PS, resulting in a 51% decrease in basal PS needs (mean: 698 ± 83 mL/day) and 1.5 ± 0.2 days off PS per week (**table 3**).

Results of the univariate and multivariate analyzes of predictive factors of response and of weaning off PS are reported in **tables 4 & 5**. An increased basal oral intake was the only factor significantly associated with a response at week 24. This association remained significant after adjustment for age, bowel length, SBS causes and anatomical classification **(Table 4).** No significant association with the response to TED was found in regards to epidemiological variables, the underlying disease and the bowel anatomy. Compared to patients who still required PS at week 24, patients weaned from PS had significantly less basal PS volume needs (738 vs. 1,867 mL/day, *p*=0.03), increased basal oral intake (2,845 vs. 2,294 kcal/day, *p*=0.01) (**Table 5**). Moreover, an increased number of patients with remaining colon in continuity were significantly weaned from PS compared to patients of Group 1 after adjustment for the main covariates (*p*=0.04). As a result, 85% of weaned patients were classified into Group 2 or 3 (vs. 15% of patients into Group 1). No epidemiological variable or underlying disease was significantly predictive of weaning off PS at week 24.

Absolute change in PS volume and reduction in PS volume percentage at week 24

The reduction in weekly PS volume correlated with the baseline PS volume **(Figure 1).** The absolute change in PS volume and reduction in PS volume percentage at week 24 according to bowel anatomy are presented in table 3. The absolute reduction in PS volume at week 24 was significantly higher in patients of Group 1 (-954 ± 721 mL/day vs. -560 ± 493 mL/day in Groups 2 and 3, *p*=0.02) but the difference was no longer statistically significant when considering the reduction in PS volume percentage (-45 ± 27% vs. -54 ± 38% in Groups 2 and 3, *p*=0.33). Similarly, the absolute reduction in PS volume and the reduction in PS volume percentage in the SBS-IBD subgroup of patients did not significantly differ from those found in the other groups (-843 ± 781 mL/day vs. -638 ± 518 mL/day,

p=0.26 and -54 ± 35% vs. -50 ± 35% in the SBS-Vasc group and in the SBS-Others group, *p*=0.33, respectively). After controlling for underlying disease and bowel anatomy covariates in the ANCOVA model, the only factors associated with a higher absolute reduction in PS volume at week 24 were a higher baseline oral intake (p=0.045) and a higher basal PS volume (p <0.001). Overall, there was a reduction in both PS volume and energy needs in the cohort **(Figure 2).**

Side effects and treatment cessation

The side effects were not specifically collected and investigated as part of this study. However, the main side effects reported were abdominal pain requiring medication such as paracetamol or antispasmodic drug. Opioids were never required. In one case, a reduction in drug administration frequency (every other day) improved the tolerance. Another patient experienced acute cholecystitis requiring cholecystectomy after 40 days of drug exposure. This patient discontinued TED for 2 weeks and resumed TED at the same dose without experiencing new complications.

At the end of the study, among the 20 patients who received at least one dose of TED but treated for less than 6 months, TED was discontinued in only 1 patient after 15 days of drug exposure. This patient experienced acute radial arterial thrombosis without obvious relationship with TED. But this patient decided to definitively discontinue TED.

DISCUSSION

This study is the first to report the results of a comprehensive national cohort of SBS patients treated with TED for 6 months. In line with previously published randomized clinical trials (RCTs) assessing the response at 24 weeks [9, 11], this observational study confirmed the efficacy of TED to reduce PS dependence in adult SBS-IF patients. In our study, 85% (n=46) of patients were responders and 24%

(n=13) were weaned from PS, resulting in a 51% decrease in basal PS needs (mean: 698 ± 83 mL/day) and 1.5 ± 0.2 days off PS per week. In the latest RCT [11], the response rate at 24 weeks was higher in patients treated with TED than in those treated with placebo, reaching 63%, a value that is much lower than in our study. Furthermore, no patients were weaned during the first 24 weeks of this RCT. While in our SBS-IF patients the bowel anatomy was similar to that reported in previous studies, the difference could be explained by the following points[11]. First, the RCTs have used a strict algorithm for assessing PS reductions based on the increase in urine volume (reflecting an enhanced intestinal wet weight absorption and reduced fecal wet weight losses) whereas in our "real-life" study, PS adjustments were left to the discretion of each expert physician in charge of the patient. In our "real-life" experience of the weaning process, fluid intake and urine output monitoring could be less strict than in the published trials, allowing more freedom in PS reduction. However, physicians were very attentive to the hydroelectrolytic balance (diuresis greater than 1 liter) and to the nutritional status (weight, intake, albumin). Second, to be included in the RCTs, the patients had to require at least 3 weekly infusions. In a "real-life" setting, we did not need a minimum amount of PS to offer TED to patients, and 7 patients (13%) received PS only one or two nights per week at the time of TED prescription. After 24 weeks of TED exposition, 13 patients were weaned off PS. They required oral micronutrients supplementation and regular intramuscular vitamin B12 administration. TED dosage and administration was not changed. The routine follow up included a nutritional assessment during an outpatient visit every 3 months. The long term follow up will be essential to confirm the long term efficacy in this population. Therefore, it would be very interesting to follow our cohort over time and assess our patients one year after TED initiation to confirm that the enteral autonomy was maintained along with the absence of nutrition status degradation. This one-year assessment would also allow investigating the efficacy in terms of response, absolute reduction in PS volume, decrease in the number of days of PS infusion in the whole population as well as determining whether an additional gain in intestinal absorption capacity is possible after 6 months of TED exposure.

In a recent post-hoc analysis of the STEPS clinical trial data, Jeppesen et al. have studied predictive factors of response to TED in 85 patients with SBS-IF, who received TED or placebo between November 25, 2008 and January 4, 2011 in 27 sites from 10 countries [12]. Changes in PS volume were evaluated according to the baseline PS volume, the bowel anatomy, and the underlying cause of SBS (inflammatory bowel disease, mesenteric vascular diseases, or other conditions). The aim of this post-hoc analysis was to identify the characteristics of patients in whom TED was the most effective on the PS volume response. Jeppesen et al. have shown that the PS volume reduction with TED treatment correlated with the baseline PS volume ($y = –0.3870x + 90.0279$, $r2=0.61$; $P < 0.0001$). In our study, the effect of TED on the absolute reduction in PS volume was significantly greater in patients of Group 1 than in patients of Group 2 (-919 ± 644 mL/day vs. -355 ± 306 mL/day; $P=0.0066$). Our results are consistent with those of Jeppesen et al. as we confirmed that the absolute reduction in PS volume correlated with the baseline PS volume with a very similar mean decrease in PS volume (-954 ± 165 mL/day in Group 1 vs. -527 ± 82 mL/day in Group 2). Therefore, we confirmed that end-jejunostomy patients (who have the highest fluid and energy needs) had the greatest benefits in terms of absolute reduction in PS volume. Interestingly, the difference was no longer significant when considering the reduction in PS volume percentage ($p=0.33$). Similarly, we did not find any significant difference according to the underlying disease (SBS-IBD vs. SBS-Vasc and SBS-Others), suggesting that all patients could benefit from TED regardless of their disease and small bowel anatomy.

After controlling for underlying disease- and bowel anatomy-related covariates in the ANCOVA model, the only factors associated with a higher absolute reduction in PS volume at week 24 were a higher baseline oral intake ($p=0.045$) and a higher basal PS volume ($p < 0.001$). These factors were also associated with the weaning off PS. Hyperphagia appeared for the first time as an independent predictive factor not only of absolute reduction in PS volume but also of weaning off PS. This variable has not been evaluated, or at least is not described, in RCTs. In the French experience, dietetic optimization is considered a very important part of the overall management of SBS-IF patients.

Specific dietetic advices are repeatedly provided in order to promote a high oral calorie intake. Also, great attention is paid to any factor that may limit oral intake and absorption such as active Crohn's disease or persistent chronic intestinal ischemia, the presence of which prompts clinicians to treat the underlying cause of the altered intake and to postpone TED initiation. Moreover, since nausea is a commonly observed side effect of TED appearing during the first weeks of treatment, a closer monitoring of the oral intake could be required.

Our results also highlighted that more patients could be weaned from PS in patients with colon in continuity. This is quite understandable as their baseline PS volume needs are generally lower compared to those of patients with end-jejunostomy (Group 1) and consistent with the substantial evidence that preserving the colon as an energy salvage organ is essential for reducing the need for PS in SBS patients [15-17].

Finally, eight patients showed no or insufficient response after 6 months of drug exposure, of whom seven were patients with colon in continuity. While this could seem paradoxical, it could be related to an impaired compliance or to impaired hormonal response mechanisms. Indeed, increased plasma levels of endogenous GLP1 and GLP2 have been reported after extensive bowel resection and even further after a meal [18-20]. This is believed to be a natural compensatory mechanism. However, the patients with colon in continuity had the highest endogenous plasma levels[19, 20], suggesting that they could be less responsive to TED therapy than end-jejunostomy patients due to their preserved endogenous GLP2 release. However, we did not observe any significant difference in response rates under TED therapy between groups, and this mechanism could explain why 7 out of the 8 non-responders in our study had colon in continuity. Furthermore, the post-hoc analysis performed in early and late responders from the STEPS & STEPS-2 trials has shown responder rates of 63% at 6 months and 93% at 24 months in STEPS-2 (88% at year 1). The long-term analysis of our real-life cohort will thus be essential.

In a recent observational study of 18 patients treated with TED for >6 months in a "real-life" setting, 11 patients (61%) were weaned from PS after a median follow-up of 10 months (range: 3–36 months) [21]. Among them, 10 patients (91%) had a colon in continuity. About 50% of patients required TED therapy for >12 months to achieve enteral autonomy, suggesting a cumulative effect of TED therapy with longer treatment duration resulting in better odds for additional PS withdrawal. These results support those observed in extension studies of RCTs, where 16 out of 134 weaned patients achieved delayed oral/enteral autonomy after a median TED treatment duration of 89 weeks [22]. The extended follow-up of our national cohort to 12 months should allow determining whether the 6-month response/weaning off PS under TED treatment is safely sustained and whether some late responses are possible among non-responders at 6 months. A better understanding of the determinants of TED response would help to guide patient monitoring and to determine whether or not TED use is indicated knowing its cost.

It was not possible to precisely assess patient compliance with treatment, but the tolerance was satisfactory in the context of a close and individualized monitoring as provided in our expert centres. In addition, a close contact with the multidisciplinary nutrition team could have improved treatment monitoring and compliance. When needed, indications and follow-up modalities were discussed between clinicians of the expert centres.

CONCLUSION

Based on a comprehensive national experience and used in combination with other intestinal rehabilitation modalities, TED appears to effectively reduce PS volume and to promote weaning off in adult SBS-IF patients. While predictive factors of TED response are still being investigated, our study identified that the net reduction in PS volume is higher in patients with high baseline PS needs and that all types/causes of SBS could benefit from TED with a similar relative reduction in PS needs.

Furthermore, patients with colon in continuity, low baseline PS volume needs and high oral intake are more likely to be fully weaned from PS. These results highlight the importance of implementing expert multimodal and multidisciplinary individualized care together with TED prescription to maximize its effects, with the involvement of a specialized dietitian and intestinal rehabilitation team. Such a strategy would allow a careful selection of patients to ensure that TED is adequately administered only to patients considered as definitively PS-dependent after rehabilitation surgery, dietetic optimization, PS stabilization, patient information and training. Finally, the duration of action, long-term efficacy and safety of TED should be carefully and comprehensively monitored in all treated patients whether or not they are weaned from PS.

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Table 1. Baseline characteristics of short bowel syndrome patients according to small bowel anatomy classification

	Group 1 Jejunostomy or ileostomy n=19	Group 2 ≥50% of colon in continuity n=33	Group 3 <50% of colon in continuity or colostomy n=2	Overall SBS population n=54
Age, years, mean (SD)	51.6 (3.4)	50.8 (2.7)	72 (0)	52.3 (2.1)
Female, n (%)	5 (26)	15 (46)	2 (100)	19 (35)
Body weight, kg, mean (SD)	69.3 (4.1)	56.9 (1.7)	54 (6)	61.2 (1.9)
BMI, kg/m2, mean (SD)	23.7 (1.4)	20.1 (0.6)	21.9 (0.1)	21.4 (0.6)
Short bowel syndrome causes, n (%)				
Mesenteric ischemia	2 (10)	19 (58)	0 (0)	21 (39)
Crohn's disease	12 (63)	4 (12)	0 (0)	16 (30)
Radiation enteritis	0 (0)	2 (6)	1 (50)	3 (6)
Volvulus	1 (5)	5 (15)	1 (50)	7 (13)
Other	4 (21)	3 (9)	0 (0)	7 (13)
Bowel anatomy features				
Remnant bowel length, cm, mean (SD)	93.7 (11.5)	91.9 (10.5)	75 (5)	61.8 (5.9)
Remnant colon length, %, mean (SD)	0	79.1 (3.2)	30 (20)	48.7 (5.5)
Colon in continuity, n (%)	0 (0)	33 (100)	2 (100)	35 (65)
Jejunostomy, n (%)	19 (100)	0 (0)	(0)	19 (35)
Colostomy, n (%)	0 (0)	0 (0)	2 (100)	2 (4)
Reverse loop, n (%)	0 (0)	2 (6)	1 (50)	3 (6)
Intestinal failure features, mean (SD)				
PS duration, years	9.2 (2.2)	10 (1.6)	11 (3)	9.8 (1.2)
Number of days of infusion/week	5.3 (0.4)	3.8 (0.3)	4.5 (1.5)	4.4 (0.2)
PS volume, mL/day	2,295 (344)	1,197 (137)	1,693 (1,050)	1,595 (163)
PS calories, kcal/day	967 (175)	876 (92)	397 (128)	890 (82)
Oral intake, kcal/day	2,583 (176)	2,395 (138)	2,155 (310)	2,544 (105)
Feces volume, g/day	2,517 (304)	1,108 (145)	829 (209)	1,640 (177)
Steatorrhea, g/day	42.5 (9)	33.1 (4.3)	31.7 (0)	36.3 (4)

Abbreviations: BMI: Body Mass Index; PS: parenteral support; SBS: short bowel syndrome; SD: standard deviation

Table 2. Baseline characteristics of short bowel syndrome patients according to underlying disease leading to SBS

	SBS-IBD n=16	SBS-Vasc n=21	SBS-Other[1] n=17	Overall SBS population n=54
Age, years, mean (SD)	51.4 (3.2)	56.7 (2.6)	47.6 (4.8)	52.3 (2.1)
Female, n (%)	5 (31)	8 (38)	9 (53)	19 (35)
Body weight, kg, mean (SD)	66.1 (5.2)	60.9 (2.4)	57 (1.9)	61.2 (1.9)
BMI, kg/m2, mean (SD)	23.1 (1.8)	20.7 (0.7)	20.8 (0.7)	21.4 (0.6)
Bowel anatomy features				
Remnant bowel length, cm, mean (SD)	101 (12)	39.7 (6.1)	52.2 (6.2)	61.8 (5.9)
Remnant colon length, %, mean (SD)	15.6 (7.1)	67.6 (6.3)	56.6 (2.7)	48.7 (5.5)
Colon in continuity, n (%)	4 (25)	19 (90)	12 (71)	35 (61)
Jejunostomy, n (%)	12 (75)	2 (9.5)	5 (29)	19 (35)
Colostomy, n (%)	0 (0)	0 (0)	2 (18)	2 (4)
Reverse loop, n (%)	0 (0)	2 (9.5)	1 (6)	3 (6)
Intestinal failure features, mean (SD)				
PS duration, years	9.7 (2.2)	7.5 (1.6)	12.7 (2.5)	9.8 (1.2)
Number of days of infusion/week	4.5 (0.4)	4.2 (0.3)	4.4 (0.5)	4.4 (0.2)
PS volume, mL/day	1,628 (305)	1,463 (269)	1,725 (290)	1,595 (163)
PS calories, kcal/day	784 (161)	925 (134)	946 (141)	890 (82)
Oral intake, kcal/day	2,590 (205)	2,327 (185)	2,472 (151)	2,544 (105)
Feces volume, g/day	1,997 (329)	1,615 (313)	1,285 (259)	1,640 (177)
Steatorrhea, g/day	45.4 (10)	35.9 (6.3)	28.9 (3.8)	36.3 (4)

[1] Other causes were 7 volvulus (13%), 3 radiation enteritis (5.5%), 3 congenital (5.5%), 3 postoperative complications (5.5%), 1 traumatic (2%)

Abbreviations: BMI: Body Mass Index; PS: parenteral support; SBS: short bowel syndrome; SD: standard deviation

Table 3. Change between baseline and Week 24 in PS volume, calories, days off PS, rate of response and weaned patients after teduglutide treatment, according to bowel anatomy

	Group 1 Jejunostomy or ileostomy n=19	Group 2 ≥50% of colon in continuity n=33	Group 3 <50% of colon in continuity or colostomy n=2	Overall SBS population n=54
Intestinal failure, change from baseline, mean (SD)				
PS volume, mL/day	-954 (165)	-527 (82)	-1221 (579)	-698 (83)
% of change	-45 (6)	-53 (7)	-83 (17)	-51 (5)
Calories, kcal/day	-520 (89)	-410 (63)	-283 (243)	-436 (49)
% of change	-48 (9)	-47 (7)	-57 (43)	-47 (5)
Days off PS / week	-1.4 (0.3)	-1.6 (3)	-3 (0)	-1.5 (0.2)
Responders, n (%)	18 (95)	26 (79)	2 (100)	46 (85)
Weaned, n (%)	2 (11)	10 (31)	1 (50)	13 (24)

Abbreviations: SBS: short bowel syndrome; SD: standard deviation; PS: parenteral support

455 **Table 4 Univariate and multivariate analysis of risk factors associated with response 24**

456 **weeks after teduglutide treatment**

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458

	Responders n=46	Non-responders n=8	Unadjusted *p value*	Multivariate adjusted analysis[1] *p value*
Age, years, mean (SD)	53 (14)	48 (21)	0.37	0.05
BMI, kg/m2, mean (SD)	21 (4)	23 (9)	0.67	
Short bowel syndrome causes, n (%)				
Crohn's disease (vs. others)	14 (30)	2 (25)	0.75	0.74
Bowel anatomy				
Group 1 (vs. others), n (%)	18 (39)	1 (13)	0.15	0.26
Group 2 (vs. others), n (%)	26 (57)	7 (88)	0.13	
Remnant bowel length, cm, mean (SD)	63 (40)	55 (60)	0.62	0.32
Remnant colon length, %, mean (SD)	46 (41)	64 (33)	0.19	
Reverse bowel loop, n (%)	3 (7)	0 (0)	0.46	
Intestinal failure features, mean (SD)				
Basal PS volume, mL/day	1,650 (1,246)	1,277 (873)	0.42	
Basal oral intake, kcal/day	**2,540 (710)**	**1,875 (601)**	**0.02**	**0.02**
Feces volume, g/day	1,695 (1,192)	1,208 (1,025)	0.39	
Steatorrhea, g/day	37 (24)	34 (36)	0.85	

459

460 [1] Model adjusted for the following factors: age, bowel length, SBS causes and bowel anatomy.
461 [2] Mean (SD)
462 Abbreviations: BMI: Body Mass Index; PS: parenteral support; Group 1: jejunostomy or ileostomy; Group 2: >50% of
463 remaining colon without stoma
464

Table 5. Univariate and multivariate analysis of risk factors associated with weaning off PS 24 weeks after teduglutide treatment

	Weaned n=13	Non-weaned n=41	Unadjusted *p value*	Multivariate adjusted analysis[1] *p value*
Age, years, mean (SD)	55 (13)	51 (16)	0.41	0.06
BMI, kg/m2, mean (SD)	20 (3)	22 (5)	0.11	
Short bowel syndrome causes, n (%)				
Crohn's disease (vs others)	4 (31)	12 (29)	0.91	0.06
Bowel anatomy				
Group 1 (vs. others), n (%)	**2 (15)**	**17 (42)**	**0.11**	**0.04**
Group 2 (vs. others), n (%)	10 (77)	23 (56)	0.18	
Remnant bowel length, cm, mean (SD)	66 (32)	60 (46)	0.70	0.51
Remnant colon length, %, mean (SD)	59 (34)	46 (42)	0.25	
Reverse bowel loop, n (%)	1 (8)	2 (5)	0.70	
Intestinal failure features, mean (SD)				
Basal PS volume, mL/day	**738 (272)**	**1,867 (1,253)**	**<0.001**	**0.03**
Basal oral intake, kcal/day	**2,845 (787)**	**2,294 (657)**	**0.02**	**0.01**
Feces volume, g/day	1,207 (920)	1,822 (1,233)	0.11	
Steatorrhea, g/day	38 (32)	35 (21)	0.73	

[1] Model adjusted for the following factors: age, bowel length, SBS causes and bowel anatomy.
[2] Mean (SD)
Abbreviations: BMI: Body Mass Index; PS: parenteral support; Group 1: jejunostomy or ileostomy; Group 2: >50% of remaining colon without stoma

Figure 1. Reduction in absolute PS volume at week 24 versus baseline PS volume in SBS patients treated with teduglutide.

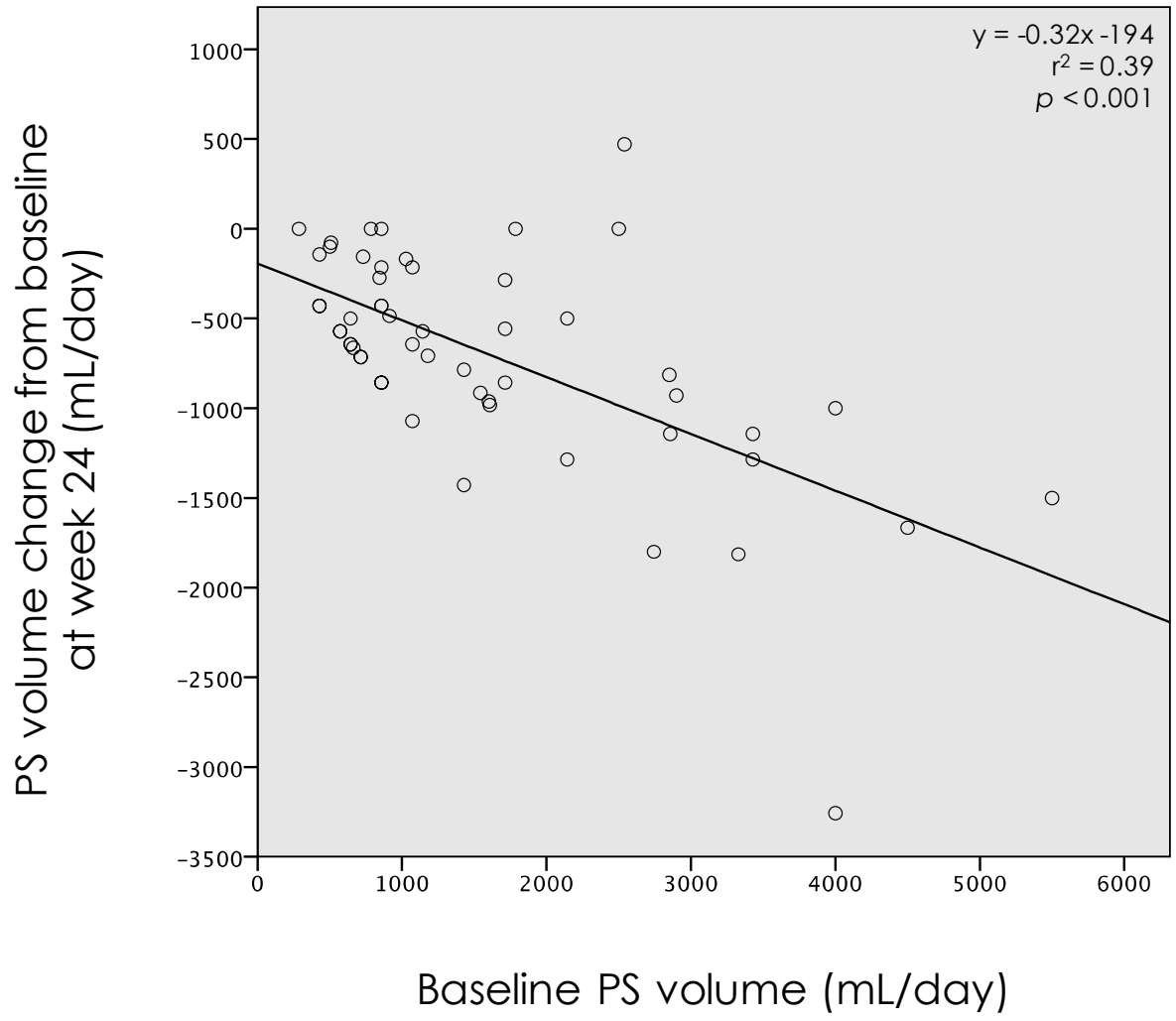
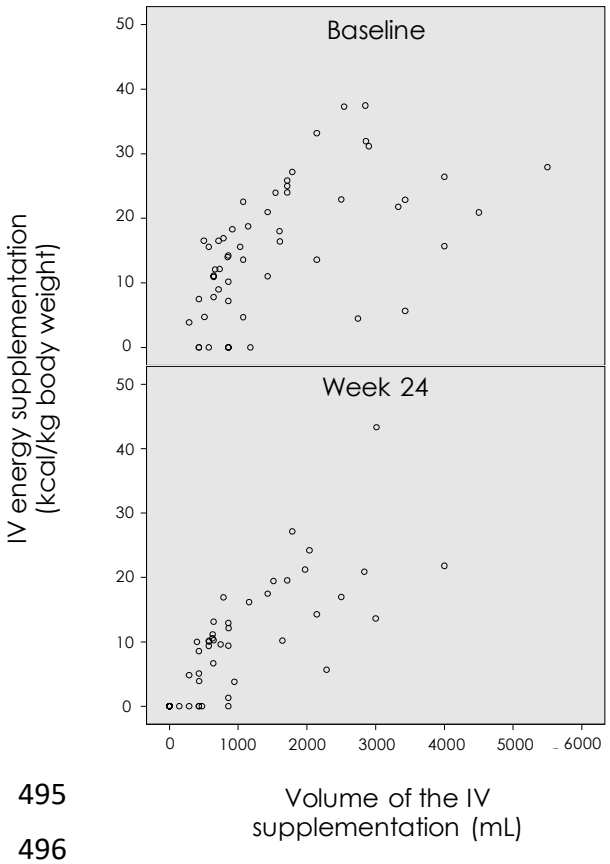


Figure 2. Distribution of the 54 patients at baseline and 24 weeks after teduglutide treatment according to ESPEN clinical classification of intestinal failure

A. Scatter plot



B. Chart table

IV energy supplementation	Volume of the IV supplementation (mL)			
	≤1,000 (1)	1,001 – 2,000 (2)	2,001 – 3,000 (3)	>3,000 (4)
Distribution of patients at baseline				
No parenteral support	0	-	-	-
Fluids and electrolytes	6	1	0	0
Parenteral nutrition	18	14	8	7
Distribution of patients at Week 24				
No parenteral support	13	-	-	-
Fluids and electrolytes	6	0	0	0
Parenteral nutrition	20	7	6	2