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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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1 **TITLE: Six-month Outcomes of Teduglutide Treatment in Adult Patients With Short Bowel**
2 **Syndrome with Chronic Intestinal Failure: a real-world French observational cohort study**

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40 **Abbreviations** : Short bowel syndrome = SBS, intestinal failure = IF, intravenous = IV, SBS

41 with IF = SBS-IF, parenteral support = PS, glucagon-like peptide-2 = GLP-2, teduglutide = TED.

42

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57

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64 manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work

65 and read and approved the final manuscript.

66

67

68 **KEY WORDS** : short-gut syndrome ; GLP2- receptor agonist ; parenteral nutrition;

69 Inflammatory bowel disease

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78

79 **ABSTRACT**

80 • **Background & Aims:** Teduglutide, a GLP-2-analog, has proven effective in two
81 placebo-controlled studies in reducing parenteral support (PS) in patients with short
82 bowel syndrome-associated intestinal failure (SBS-IF) after 24 weeks. The aim of this
83 study was to describe in a real-life situation the effects of teduglutide treatment and
84 their predictive factors.

85 • **Methods:** We included 54 consecutive SBS-IF patients treated with teduglutide in
86 France for at least 6 months from 10 expert centers. Small bowel length was 62 ± 6 cm
87 and 65% had colon in continuity. PS was 4.4 ± 2 infusions per week, started 9.8 ± 1.2
88 years before. Response (PS reduction $\geq 20\%$) and PS discontinuation rates were
89 assessed at week 24. Adjusted *p* values of factors associated with response and
90 weaning were calculated using a multivariate logistic regression model.

91 • **Results:** At week 24, 85% of patients were responders and 24% had been weaned off
92 PS, with a 51% reduction of PS needs and 1.5 ± 0.2 days off PS per week. Response to
93 teduglutide was influenced by a higher baseline oral intake ($p=.02$). Weaning off PS
94 was influenced by the presence of colon ($p=.04$), a lower PS volume ($p=.03$) and a
95 higher oral intake ($p=.01$). There were no differences based on age, bowel length or
96 SBS-IF causes.

97 • **Conclusions:** Our study confirms the effectiveness of teduglutide in reducing PS
98 needs in SBS-IF patients. We associated reduced parenteral support volume with
99 baseline parenteral volume support, bowel anatomy, and oral intake. These findings
100 underline the role of nutritional optimization when starting the treatment.

101 • **Keywords:** short-gut syndrome ; GLP2- receptor agonist ; parenteral nutrition;
102 Inflammatory bowel disease ; intestinal failure

103 **INTRODUCTION**

104 Patients with intestinal failure associated with short bowel syndrome (SBS–IF) do not absorb enough
105 nutrients and/or fluids through oral or enteral intake alone to maintain life and growth. This clinically
106 significant reduction in intestinal absorptive capacity is a consequence of substantial intestinal
107 resection or functional impairment commonly due to a disease, a trauma, surgical complications or
108 congenital abnormalities and requires routine, regular, complete or partial parenteral support (PS;
109 parenteral nutrition (PN) and/or intravenous fluids (IVF))^{1, 2}. In patients with SBS-IF who require PN
110 and/or IVF, the therapeutic management aims to reduce the long-term dependence on PS and, when
111 possible, to get patients weaned from it. In the last two decades, a hormonal treatment paradigm
112 focusing on intestinal rehabilitation through the promotion of intestinal hyperadaptation has been
113 proposed. To date, only two trophic factors have been approved in SBS patients: growth hormone
114 (GH; somatotropin) (only in the USA) and the glucagon-like peptide-2 (GLP-2) analog, teduglutide
115 (TED) (in the USA, Canada and Europe)³⁻⁶. In France, TED is marketed since October 2015. Both GLP-2
116 and its degradation-resistant analog TED increase intestinal wet weight absorption^{7, 8} and decrease
117 the need for PS in SBS-IF patients⁹⁻¹¹. Phase III clinical studies have shown that treatment with TED
118 was associated with a reduction by at least 20% in PS at 6 months in adult SBS-IF patients^{9, 11}. Due to
119 the heterogeneity in patient response to TED in randomized studies and to the high cost of the drug,
120 the ESPEN guidelines have mentioned the need to identify candidates for trophic factors among SBS-
121 IF patients². The aim of this study was to investigate predictive factors of early response and of
122 weaning off PS and to determine the rate of responders in a "real-life" nationwide SBS-IF cohort
123 treated with TED,

124

125 **METHODS**

126

127 **Patient selection and management**

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

146

147 **Data collection**

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

154 of colon in continuity, group 2; <50% of colon in continuity, group 3) according to Jeppesen et al¹². IF
155 was classified according to energy needs (PN or only fluids and electrolytes) and the volume of IVF
156 supplementation (class 1-4), according to ESPEN recommendations¹³. The response to treatment
157 was assessed at weeks 12 and 24.

158

159 **Primary and secondary outcomes**

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

166

167 **Statistical analysis**

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

180 performed using a covariance analysis (ANCOVA) model with the change in PS volume as the
181 dependent variable, SBS causes and small bowel anatomical classification as independent variables
182 and the following covariates: baseline oral intake, PS volume and remaining small bowel length.
183 Correlation analysis was performed using a simple linear regression model with unadjusted r^2 values
184 reported. All tests were two sided. A p value <0.05 was considered significant. All analyzes were
185 performed using the Statistical Package for the Social Sciences (SPSS) for Mac OSX software (version
186 22.0, Chicago, Illinois, USA). All authors had access to the study data and reviewed and approved the
187 final manuscript. There was no missing data at any time point for the variables studied.

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189

190 **RESULTS**

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192 **Patient characteristics**

193 From October 2015 to September 2017, a total of 54 consecutive patients [(19 (35%) women; mean
194 age 52.3 ± 2.1 years)] were included, i.e. all patients treated for at least six months with TED among
195 the 74 patients who initiated TED treatment in France. Patient baseline characteristics are presented
196 in **tables 1 & 2**. The most common underlying causes of SBS were acute mesenteric ischemia (SBS-
197 Vasc, $n=21$, 39%) and Crohn's disease (SBS-IBD, $n=16$, 30%). Other causes included volvulus ($n=7$,
198 13%), radiation enteritis ($n=3$, 5.5%), congenital disorders ($n=3$, 2%), postoperative complications
199 ($n=3$, 18%) and abdominal traumatic injury ($n=1$, 6%). The mean length of remaining bowel was 61.8
200 ± 5.9 cm. Thirty-five patients (65%) had a remaining colon in continuity (mean percentage of length:
201 49%). Three patients (6%) had undergone reverse intestinal interposition surgery that failed to
202 achieve PS weaning. TED was initiated 9.8 ± 1.2 years after definitive diagnosis of IF requiring PS. At
203 baseline, patients received a mean number of 4.4 ± 0.2 infusions per week, corresponding to a mean
204 volume of 1595 ± 163 mL/day on a seven-day basis.

205

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

207 Twenty-four weeks after TED treatment initiation, 46 patients (85%) were responders and 13 (24%)
208 were weaned from PS, resulting in a 51% decrease in basal PS needs (mean: 698 ± 83 mL/day) and
209 1.5 ± 0.2 days off PS per week (**table 3**).

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

222

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

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

232 $p=0.26$ and $-54 \pm 35\%$ vs. $-50 \pm 35\%$ in the SBS-Vasc group and in the SBS-Others group, $p=0.33$,
233 respectively). After controlling for underlying disease and bowel anatomy covariates in the ANCOVA
234 model, the only factors associated with a higher absolute reduction in PS volume at week 24 were a
235 higher baseline oral intake ($p=0.045$) and a higher basal PS volume ($p < 0.001$). Overall, there was a
236 reduction in both PS volume and energy needs in the cohort (**Figure 2**).

237

238

239 **Side effects and treatment cessation**

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

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

250

251

252 **DISCUSSION**

253

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

258 (n=13) were weaned from PS, resulting in a 51% decrease in basal PS needs (mean: 698 ± 83 mL/day)
259 and 1.5 ± 0.2 days off PS per week. In the latest RCT¹¹, the response rate at 24 weeks was higher in
260 patients treated with TED than in those treated with placebo, reaching 63%, a value that is much
261 lower than in our study. Furthermore, no patients were weaned during the first 24 weeks of this RCT.
262 While in our SBS-IF patients the bowel anatomy was similar to that reported in previous studies, the
263 difference could be explained by the following points¹¹. First, the RCTs have used a strict algorithm
264 for assessing PS reductions based on the increase in urine volume (reflecting an enhanced intestinal
265 wet weight absorption and reduced fecal wet weight losses) whereas in our “real-life” study, PS
266 adjustments were left to the discretion of each expert physician in charge of the patient. In our “real-
267 life” experience of the weaning process, fluid intake and urine output monitoring could be less strict
268 than in the published trials, allowing more freedom in PS reduction. However, physicians were very
269 attentive to the hydroelectrolytic balance (diuresis greater than 1 liter) and to the nutritional status
270 (weight, intake, albumin). Second, to be included in the RCTs, the patients had to require at least 3
271 weekly infusions. In a “real-life” setting, we did not need a minimum amount of PS to offer TED to
272 patients, and 7 patients (13%) received PS only one or two nights per week at the time of TED
273 prescription. After 24 weeks of TED exposition, 13 patients were weaned off PS. They required oral
274 micronutrients supplementation and regular intramuscular vitamin B12 administration. TED dosage
275 and administration was not changed. The routine follow up included a nutritional assessment during
276 an outpatient visit every 3 months. The long term follow up will be essential to confirm the long term
277 efficacy in this population. Therefore, it would be very interesting to follow our cohort over time and
278 assess our patients one year after TED initiation to confirm that the enteral autonomy was
279 maintained along with the absence of nutrition status degradation. This one-year assessment would
280 also allow investigating the efficacy in terms of response, absolute reduction in PS volume, decrease
281 in the number of days of PS infusion in the whole population as well as determining whether an
282 additional gain in intestinal absorption capacity is possible after 6 months of TED exposure.

283 In a recent post-hoc analysis of the STEPS clinical trial data, Jeppesen et al. have studied predictive
284 factors of response to TED in 85 patients with SBS-IF, who received TED or placebo between
285 November 25, 2008 and January 4, 2011 in 27 sites from 10 countries¹². Changes in PS volume were
286 evaluated according to the baseline PS volume, the bowel anatomy, and the underlying cause of SBS
287 (inflammatory bowel disease, mesenteric vascular diseases, or other conditions). The aim of this
288 post-hoc analysis was to identify the characteristics of patients in whom TED was the most effective
289 on the PS volume response. Jeppesen et al. have shown that the PS volume reduction with TED
290 treatment correlated with the baseline PS volume ($y = -0.3870x + 90.0279$, $r^2=0.61$; $P < 0.0001$). In
291 our study, the effect of TED on the absolute reduction in PS volume was significantly greater in
292 patients of Group 1 than in patients of Group 2 (-919 ± 644 mL/day vs. -355 ± 306 mL/day; $P=0.0066$).
293 Our results are consistent with those of Jeppesen et al. as we confirmed that the absolute reduction
294 in PS volume correlated with the baseline PS volume with a very similar mean decrease in PS volume
295 (-954 ± 165 mL/day in Group 1 vs. -527 ± 82 mL/day in Group 2). Therefore, we confirmed that end-
296 jejunostomy patients (who have the highest fluid and energy needs) had the greatest benefits in
297 terms of absolute reduction in PS volume. Interestingly, the difference was no longer significant
298 when considering the reduction in PS volume percentage ($p=0.33$). Similarly, we did not find any
299 significant difference according to the underlying disease (SBS-IBD vs. SBS-Vasc and SBS-Others),
300 suggesting that all patients could benefit from TED regardless of their disease and small bowel
301 anatomy.

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

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

315

316 Our results also highlighted that more patients could be weaned from PS in patients with colon in
317 continuity. This is quite understandable as their baseline PS volume needs are generally lower
318 compared to those of patients with end-jejunostomy (Group 1) and consistent with the substantial
319 evidence that preserving the colon as an energy salvage organ is essential for reducing the need for
320 PS in SBS patients¹⁵⁻¹⁷.

321

322 Finally, eight patients showed no or insufficient response after 6 months of drug exposure, of whom
323 seven were patients with colon in continuity. While this could seem paradoxical, it could be related
324 to an impaired compliance or to impaired hormonal response mechanisms. Indeed, increased plasma
325 levels of endogenous GLP1 and GLP2 have been reported after extensive bowel resection and even
326 further after a meal¹⁸⁻²⁰. This is believed to be a natural compensatory mechanism. However, the
327 patients with colon in continuity had the highest endogenous plasma levels^{19, 20}, suggesting that they
328 could be less responsive to TED therapy than end-jejunostomy patients due to their preserved
329 endogenous GLP2 release. However, we did not observe any significant difference in response rates
330 under TED therapy between groups, and this mechanism could explain why 7 out of the 8 non-
331 responders in our study had colon in continuity. Furthermore, the post-hoc analysis performed in
332 early and late responders from the STEPS & STEPS-2 trials has shown responder rates of 63% at 6
333 months and 93% at 24 months in STEPS-2 (88% at year 1). The long-term analysis of our real-life
334 cohort will thus be essential.

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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 weeks²². 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.

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

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- 432
- 433

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

| | Group 1 | Group 2 | Group 3 | Overall SBS population n=54 |
|--|--------------------------|-----------------------------|--|-----------------------------|
| | Jejunostomy or ileostomy | ≥50% of colon in continuity | <50% of colon in continuity or colostomy | |
| | n=19 | n=33 | n=2 | |
| 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/m ² , 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) |

436

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

439

440 **Table 2. Baseline characteristics of short bowel syndrome patients according to**
 441 **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/m ² , 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) |

442
 443
 444 ¹ Other causes were 7 volvulus (13%), 3 radiation enteritis (5.5%), 3 congenital (5.5%), 3 postoperative complications
 445 (5.5%), 1 traumatic (2%)
 446 Abbreviations: BMI: Body Mass Index; PS: parenteral support; SBS: short bowel syndrome; SD: standard deviation

447

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

| | Group 1 | Group 2 | Group 3 | Overall SBS population |
|---|--------------------------|-----------------------------|--|------------------------|
| | Jejunostomy or ileostomy | ≥50% of colon in continuity | <50% of colon in continuity or colostomy | |
| | n=19 | n=33 | n=2 | 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) |

451
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 453 Abbreviations: SBS: short bowel syndrome; SD: standard deviation; PS: parenteral support
 454

455 **Table 4 Univariate and multivariate analysis of risk factors associated with response 24**
 456 **weeks after teduglutide treatment**

457

458

| | Responders n=46 | Non- responders n=8 | Unadjusted <i>p value</i> | Multivariate adjusted analysis ¹ <i>p value</i> |
|--|--------------------|---------------------------|------------------------------|--|
| Age, years, mean (SD) | 53 (14) | 48 (21) | 0.37 | 0.05 |
| BMI, kg/m ² , 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

465 **Table 5. Univariate and multivariate analysis of risk factors associated with weaning off**

466 **PS 24 weeks after teduglutide treatment**

| | Weaned n=13 | Non- weaned n=41 | Unadjusted <i>p value</i> | Multivariate adjusted analysis ¹ <i>p value</i> |
|--|--------------------|------------------------|------------------------------|--|
| Age, years, mean (SD) | 55 (13) | 51 (16) | 0.41 | 0.06 |
| BMI, kg/m ² , 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 | |

467

468 ¹ Model adjusted for the following factors: age, bowel length, SBS causes and bowel anatomy.

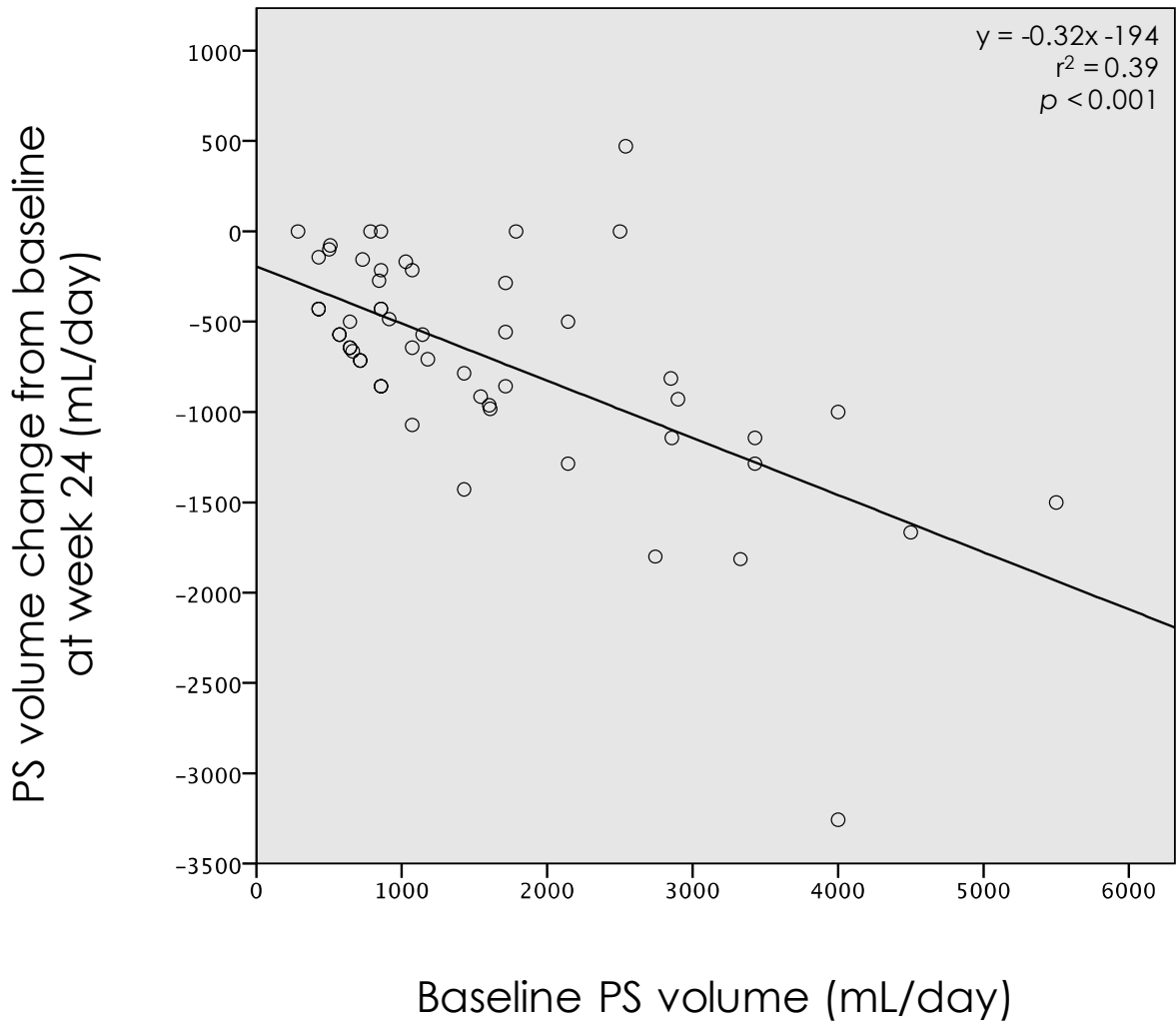
469 ² Mean (SD)

470 Abbreviations: BMI: Body Mass Index; PS: parenteral support; Group 1: jejunostomy or ileostomy; Group 2: >50% of

471 remaining colon without stoma

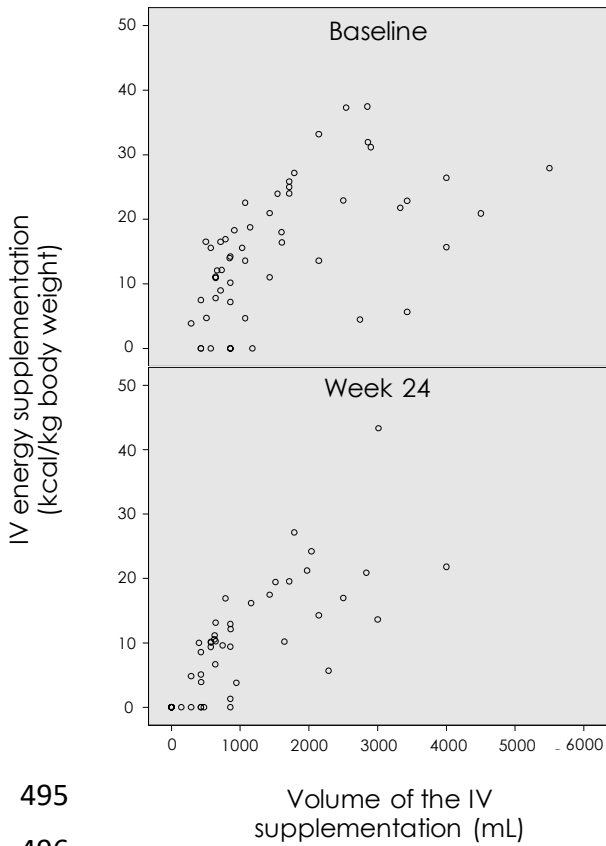
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473 **Figure 1. Reduction in absolute PS volume at week 24 versus baseline PS volume in SBS**
474 **patients treated with teduglutide.**
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479 **Figure 2. Distribution of the 54 patients at baseline and 24 weeks after teduglutide**
 480 **treatment according to ESPEN clinical classification of intestinal failure**
 481 **A. Scatter plot**



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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 |