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ORIGINAL ARTICLE

Gastroenterology

Long-term teduglutide associated with improved response in pediatric short bowel syndrome-associated intestinal failure

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Abstract

Objectives: Patients with short bowel syndrome-associated intestinal failure (SBS-IF) require long-term parenteral nutrition and/or intravenous fluids (PN/IV) to maintain fluid or nutritional balance. We report the long-term safety, efficacy, and predictors of response in pediatric patients with SBS-IF receiving teduglutide over 96 weeks.

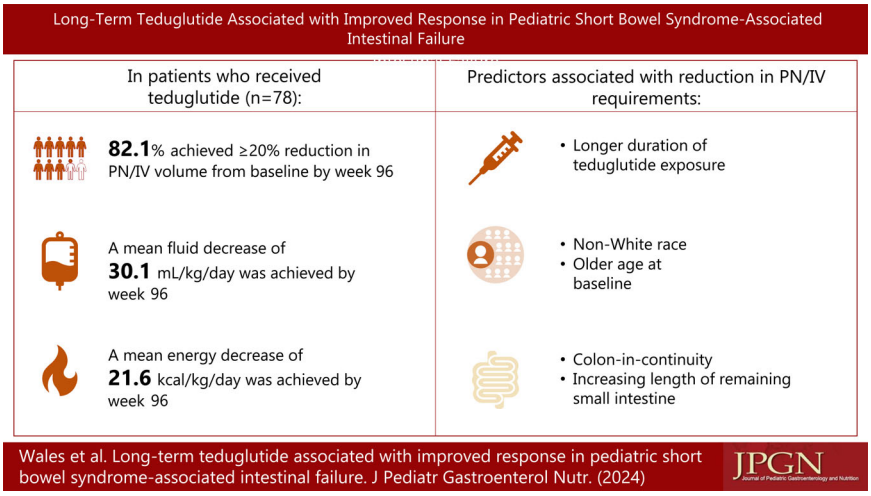
Methods: This was a pooled, post hoc analysis of two open-label, long-term extension (LTE) studies (NCT02949362 and NCT02954458) in children with SBS-IF. Endpoints included treatment-emergent adverse events (TEAEs) and clinical response (≥20% reduction in PN/IV volume from baseline). A multivariable linear regression identified predictors of teduglutide response; the dependent variable was mean change in PN/IV volume at each visit over 96 weeks.

Results: Overall, 85 patients were analyzed; 78 patients received teduglutide in the parent and/or LTE studies (any teduglutide [TED] group), while seven patients did not receive teduglutide in either the parent or LTE studies. Most TEAEs were moderate or severe in intensity in both groups. By week 96, 82.1% of patients from the any TED group achieved a clinical response, with a mean fluid decrease of 30.1 mL/kg/day and an energy decrease of 21.6 kcal/kg/day. Colon-in-continuity, non-White race, older age at baseline, longer duration of teduglutide exposure, and increasing length of remaining small intestine were significantly associated with a reduction in mean PN/IV volume requirements.

Conclusions: In pediatric patients with SBS-IF, teduglutide treatment resulted in long-term reductions in PN/IV requirements. The degree of PN/IV volume reduction depended on the duration of teduglutide exposure, underlying bowel anatomy, and demographics.

Bram P. Raphael: Affiliation at the time of study.

Website and Trial Identification Numbers: https://www.clinicaltrials.gov/ NCT02949362, NCT02954458.



KEYWORDS

Gattex, glucagon-like peptide-2, parenteral nutrition, pediatrics, Revestive

1 | INTRODUCTION

Short bowel syndrome-associated intestinal failure (SBS-IF) results from the inability of the remnant bowel to absorb sufficient nutrients and fluids following considerable intestinal resection.[1] Management of SBS-IF in children includes parenteral nutrition and/or intravenous fluids (PN/IV) to support growth, development, and participation in everyday activities such as attending school. However, long-term dependence on PN/IV can lead to potentially life-threatening complications, such as intestinal failure-associated liver disease, central line-associated bloodstream infections, and loss of venous access.[1]

Glucagon-like peptide-2 (GLP-2) is an intestinotrophic growth factor that binds to GLP-2 receptors in the gastrointestinal tract, enhancing nutrient absorption and promoting intestinal adaptation. Teduglutide is a recombinant human GLP-2 analog with a single amino acid substitution that renders the molecule resistant to degradation by the enzyme dipeptidyl-peptidase IV, extending the half-life and increasing the potency in comparison with native GLP-2.[2–4] Teduglutide is approved in several countries and continents, including North America, Europe, and Japan, for the treatment of pediatric patients with SBS who are dependent on parenteral support (e.g., with SBS-IF). Published phase 3 studies have demonstrated the safety and efficacy of 0.05 mg/kg/day teduglutide in children and adults with SBS-IF at 12 weeks and 24 weeks.[5–7] In a pediatric study, 69% of patients receiving 0.05 mg/kg/day teduglutide achieved the endpoint of a 20% or greater reduction in PN/IV at 24 weeks. This translated into a reduction of approximately 40% in PN/IV fluids and calories, and 10% of patients achieved enteral autonomy.[6]

What is Known

- The safety and efficacy of teduglutide have been demonstrated in pediatric patients with short bowel syndrome-associated intestinal failure (SBS-IF).
- There are limited data on the long-term safety, efficacy, and predictors of response to teduglutide in pediatric patients with SBS-IF.

What is New

- Pediatric patients with SBS-IF treated with teduglutide experienced continued and sustained reductions in parenteral nutrition and/or intravenous fluids (PN/IV) volume over 96 weeks.
- The degree of PN/IV volume reduction depended on the duration of teduglutide exposure, underlying bowel anatomy, and demographics.

The open-label extension study findings support the safety, tolerability, and clinical utility of teduglutide in the treatment of adults with SBS-IF for up to 36 months, where patients who received long-term teduglutide treatment experienced further decreases in PN/IV dependence.[8] Integrated data from four clinical studies suggest that the safety profile of teduglutide following long-term treatment is consistent with findings from the parent pediatric studies, which were 12 and 24 weeks long.[7] Furthermore, in a real-world, single-center case series, the majority of patients (12/17) with SBS-IF who

received long-term teduglutide treatment achieved enteral autonomy by 12 months, although no predictors of response were identified.[9]

Given that further data on safety, efficacy, and predictors of response with long-term teduglutide treatment in children with SBS-IF are needed,[9] we sought to evaluate these outcomes as our primary objectives in this post hoc analysis of the pediatric long-term extension (LTE) studies.

2 | METHODS

2.1 | Study design

The pooled data from two phase 3 LTE clinical trials (NCT02949362, NCT02954458) were analyzed up to 96 weeks. The study period was December 2016 to July 2020 for NCT02949362, and January 2017 to November 2020 for NCT02954458. Patients with a diagnosis of SBS-IF who were PN/IV-dependent were eligible for enrollment in the LTE studies if they had participated in one of the initial three parent phase 3 clinical trials of teduglutide. The parent studies were phase 3, randomized, open-label clinical trials of teduglutide that enrolled patients aged 4–12 months corrected gestational age for 24 weeks (NCT03571516), patients aged ≥1–17 years of age for 12 weeks (NCT01952080),[10] and patients aged ≥1–17 years of age for 24 weeks (NCT02682381).[6]

During the LTE studies, patients receiving teduglutide underwent 24-week treatment cycles at a dose of 0.05 mg/kg/day followed by a 4-week follow-up period without treatment (Figure 1). Guidelines for nutritional support management and details of the algorithms for weaning off PN/IV were provided to the investigators for their consideration. At the discretion of the investigator, the 4-week follow-up period could be interrupted or omitted, and patients could proceed directly to the pretreatment visit if one or more of the escape criteria were met (Digital Content S1). Teduglutide-naïve patients aged 12 and older were screened via colonoscopy or sigmoidoscopy at the pretreatment visit, if screening had not been performed within 1 year. Teduglutide-exposed patients who had received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) underwent colonoscopy or sigmoidoscopy or if they were newly positive for fecal occult blood test results (Digital Content S2).

Patients were eligible for teduglutide treatment if they met one or more of the teduglutide treatment inclusion criteria and none of the teduglutide exclusion criteria (Digital Content S3, S4). Patients not receiving teduglutide treatment were seen approximately every 12 weeks for safety and PN/IV data collection; at any point during this period, patients who met one or more of the teduglutide treatment inclusion criteria could proceed directly to the pretreatment visit to begin teduglutide therapy. To evaluate safety and efficacy from the time patients completed the parent study to the time they entered the NCT02949362 LTE study, retrospective data collection was planned in addition to prospective data collection.

All study protocols were conducted in compliance with the International Council for Harmonisation Good Clinical Practice guidelines and the World Medical Association Declaration of Helsinki and its amendments. Local institutional review boards or medical ethics committees approved all protocols; central institutional review boards were the Western Institutional Review Board, Washington, U.S.A. and South West REC Center, Bristol, UK. Written consent was provided by patients, guardians, or parents before study participation.

2.2 | Assessments and outcomes

Baseline characteristics were described for patients assigned to all treatment arms. Safety endpoints included treatment-emergent adverse events (TEAEs), the number of patients with antidrug antibodies, and growth parameters (e.g., height, weight, and head circumference) through 96 weeks. Height z-score, weight z-score, and body mass index (BMI) z-score were calculated using the retrospective height and weight data; head circumference z-score was calculated for patients younger than 36 months. Baseline PN/IV volume and energy intake were defined as the start of the parent phase 3 clinical trials. Clinical endpoints assessed included a 20% or greater reduction in PN/IV volume (mL/kg/day), change from baseline (defined as the beginning of a parent study) in PN/IV volume (mL/kg/day), change from baseline in PN/IV energy intake (kcal/kg/day), and achievement of enteral autonomy. Change from baseline in PN/IV volume and energy intake were based on prescribed data. Predictors of response to teduglutide treatment in patients who received teduglutide in both the parent and LTE studies were investigated.

2.3 | Statistical analysis

Continuous variables were summarized using descriptive statistics. For categorical variables, frequency and percentages were used. Descriptive statistics were used for the following three groups: no teduglutide treatment (NTT)/NTT (patients who were never treated with teduglutide in the parent or LTE studies), teduglutide (TED)/TED (patients who were treated with teduglutide in both the parent and LTE studies), and the any TED group (any patient who received teduglutide in either the parent or the LTE studies).

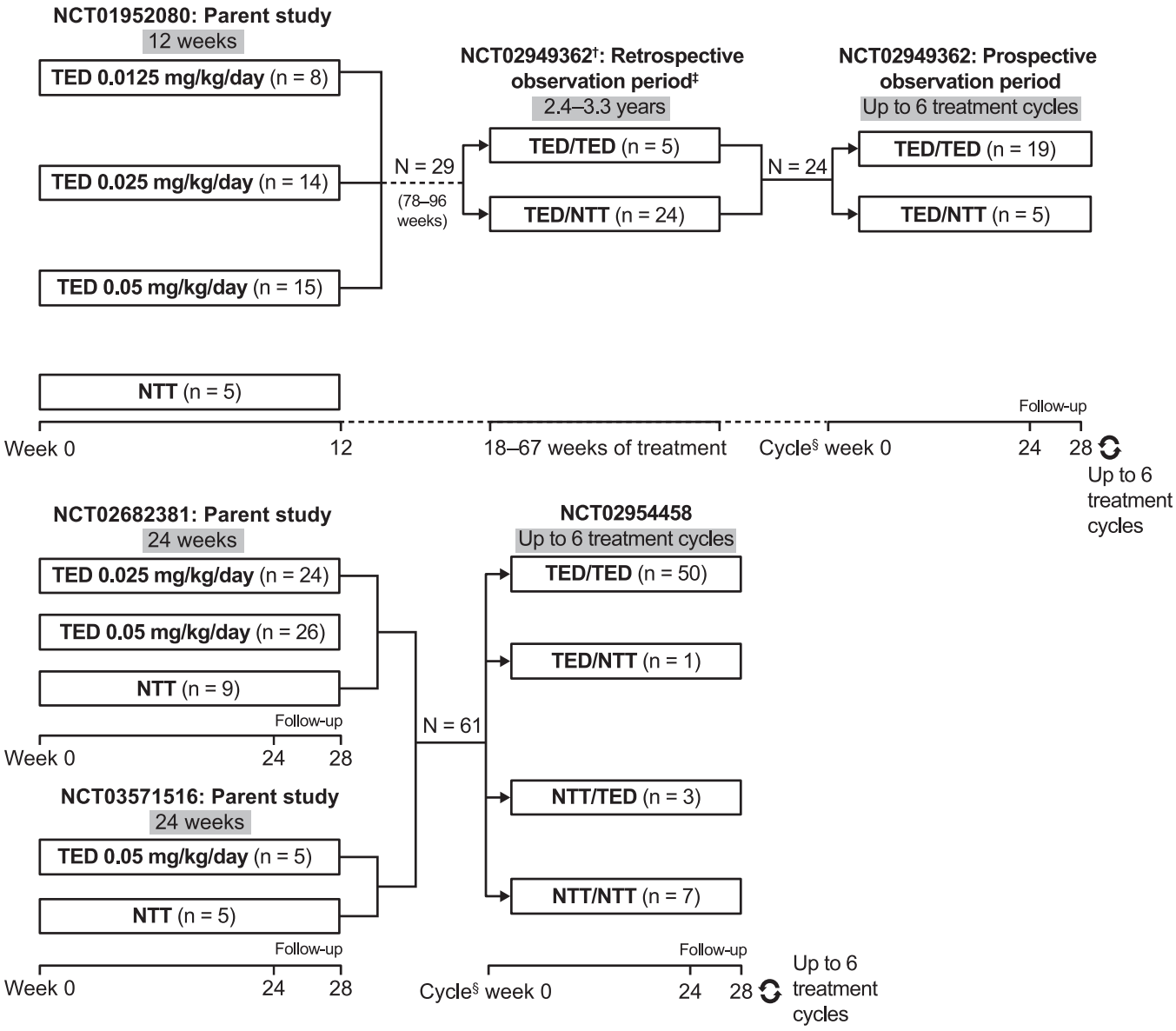


FIGURE 1 Study design. †All patients enrolled in NCT02949362 were treated with TED during NCT01952080. ‡Retrospective TED/TED patients resumed TED treatment 78–96 weeks after NCT01952080; patients received TED treatment for 18–67 weeks. §Each cycle comprised 24 weeks of TED 0.05 mg/kg subcutaneous once daily and 4 weeks of follow-up. Patients who deteriorated during 4 weeks of off-treatment follow-up could reinitiate TED; all other patients entered a "no TED" treatment period of observation. Patients could receive up to 6 treatment cycles. LTE, long-term extension; NTT, no teduglutide treatment; TED, teduglutide.

The investigators proposed 21 specific patient characteristics a priori, such as cause of SBS, bowel anatomy, and demographics, as potential predictor variables. Each characteristic was modeled separately in a univariate analysis and those reaching significance of $p < 0.2$ were included in the final multivariable regression model. In both LTE studies, a backwards, stepwise, multivariable linear regression was used to determine individual predictors of mean change in PN/IV volume (mL/kg/day) at each visit through 96 weeks. Data between 96 and 144 weeks were censored from analysis, because data were sparse owing to loss at follow-up and would not provide enough power to accurately assess study outcomes. An α value of <0.05 was deemed significant, and 95% confidence intervals were calculated for the parameter estimates. All analyses were conducted with SAS version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Baseline demographics and characteristics

A total of 85 patients who were enrolled during the study period of the LTE studies (December 2016–November 2020) were included in this pooled analysis: seven patients in the NTT/NTT group, 69

patients in the TED/TED group, and 78 patients in the any TED group (Figure 2). Baseline demographics and characteristics are summarized in Table 1. The median (range) extent of teduglutide exposure was 110.3 (28.3, 165.3) weeks and 102.1 (11.9, 165.3) weeks in the TED/TED and any TED groups, respectively. The median (standard deviation [SD]) treatment break between the parent and LTE studies was 38 (80) days. Mean (SD) length of follow-up was 92.8 (10.9) weeks for all patients.

3.2 | Safety

Overall, TEAEs were reported in 97.4% of patients in the any TED group and in 85.7% of patients in the NTT/NTT group (Table 2). Most TEAEs were moderate or severe in intensity in the NTT/NTT and in the any TED groups.

Three study discontinuations were reported in patients from the any TED group; no study discontinuations or deaths were reported in the NTT/NTT group (Digital Content S5). One patient, in the TED/TED group, had a severe serious adverse event of pulmonary mycosis which required hospitalization for fever. Curvularia (a dematiaceous mold) was identified and treated. The event was considered to be consistent with an opportunistic infection, and not related to the study drug.

Two deaths that were not related to the study drug were reported in the any TED group; one patient who had additional comorbid conditions died owing to worsening of SBS following withdrawal of enteral and PN/IV support, while one died owing to central nervous system vasculitis and ischemic stroke (Digital Content S6).

There were no reported incidences of colorectal polyps in either group; one incidence of a benign neoplasm (skin papilloma of mild severity) was reported in the any TED group. The most common TEAEs in the NTT/NTT group and in the any TED group were vomiting, pyrexia, upper respiratory tract infection, and cough (Digital Content S7). Weight, height, BMI, and head circumference z-scores remained stable from baseline through 96 weeks of teduglutide treatment (Digital Content S8).

3.3 | Efficacy

At baseline, the mean (SD) PN/IV volume was 65.2 (30.9) and 66.9 (24.3) mL/kg/day in the any TED and NTT/NTT groups; prescribed PN/IV energy intake was 46.8 (19.2) and 51.8 (21.9) kcal/kg/day, respectively. At weeks 48 and 96, the mean (SD) change from baseline in the prescribed PN/IV volume was −24.0 (26.3) and −30.1 (26.6) mL/kg/day in the any TED group and −14.8 (13.1) and −13.0 (13.3) mL/kg/day in the NTT/

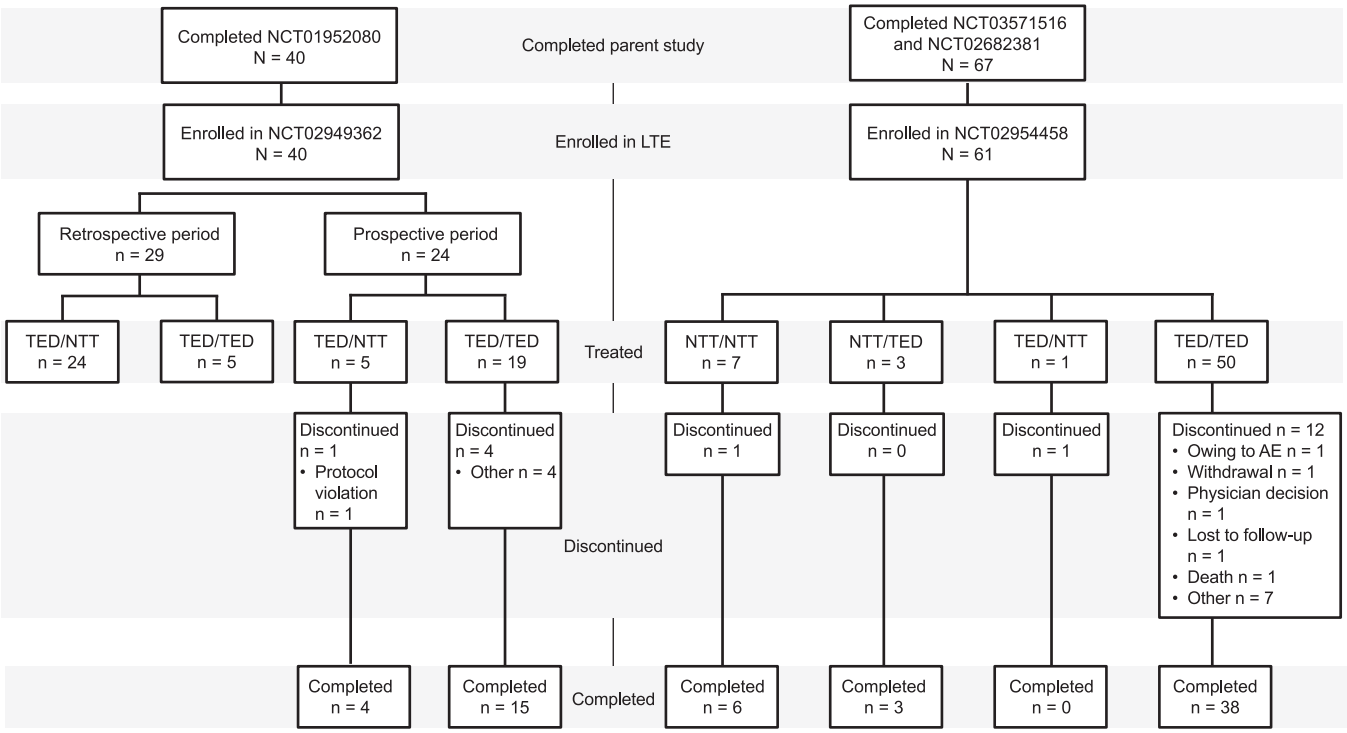


FIGURE 2 CONSORT diagram. AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials; LTE, long-term extension; NTT, no teduglutide treatment; TED, teduglutide.

TABLE 1 Patient characteristics and demographics at baseline.

Characteristic	NTT/NTT (*n* = 7)	TED/TED (*n* = 69)	Any TED (*n* = 78)
Age, years, median (range)	4 (0.7, 17.0)	5 (0.5, 15.0)	4 (0.5, 15.0)
Male, *n* (%)	4 (57.1)	46 (66.7)	54 (69.2)
Race, *n* (%)			
White	3 (42.9)	53 (76.8)	59 (75.6)
Black or African American	1 (14.3)	9 (13.0)	9 (11.5)
Asian	1 (14.3)	2 (2.9)	3 (3.8)
Other[a]	1 (14.3)	1 (1.4)	2 (2.6)
Not allowed based on local regulations	1 (14.3)	4 (5.8)	5 (6.4)
Ethnicity, *n* (%)			
Hispanic or Latino	3 (42.9)	18 (26.1)	20 (25.6)
Not Hispanic or Latino	3 (42.9)	46 (66.7)	52 (66.7)
Height-for-age z-score, mean (SD)	1.1 (2.4)	0.0 (2.0)	0.1 (2.1)
Weight-for-age z-score, mean (SD)	1.5 (2.7)	0.2 (2.2)	0.2 (2.2)
BMI-for-age z-score, mean (SD)	0.2 (0.5)	−0.1 (1.0)	−0.1 (1.0)
Head circumference (<3 years old) z-score, mean (SD)	−1.1 (0.0)	−0.4 (1.3)	−0.6 (1.3)
Residual small intestine length (cm), median (range)	35.0 (5.0, 95.0)	30.0 (0.0, 147.0)	30.0 (0.0, 147.0)
Presence of stoma, *n* (%)	0 (0.0)	10 (14.5)	13 (16.7)
Colon-in-continuity, *n* (%)	7 (100.0)	63 (91.3)	69 (88.5)
Presence of any remaining colon, *n* (%)	7 (100.0)	66 (95.7)	73 (93.6)
Presence of distal/terminal ileum, *n* (%)	3 (42.9)	19 (27.5)	22 (28.2)
Presence of ileocecal valve, *n* (%)	3 (42.9)	14 (20.3)	17 (21.8)
Reason for major intestinal resection, *n* (%)			
Gastroschisis	2 (28.6)	22 (31.9)	24 (30.8)
With distal jejunal/ileal atresia	0 (0.0)	0 (0.0)	1 (1.3)
With intestinal atresia, midgut volvulus	0 (0.0)	1 (1.4)	1 (1.3)
Midgut volvulus	3 (42.9)	20 (29.0)	23 (29.5)
With proximal jejunal atresia	0 (0.0)	1 (1.4)	1 (1.3)
Necrotizing enterocolitis	1 (14.3)	11 (15.9)	12 (15.4)
Intestinal atresia	0 (0.0)	5 (7.2)	5 (6.4)
Hirschsprung's disease	0 (0.0)	1 (1.4)	1 (1.3)
Volvulus and ischemic bowel	0 (0.0)	1 (1.4)	1 (1.3)

Abbreviations: BMI, body mass index; NTT, no teduglutide treatment; SD, standard deviation; TED, teduglutide.

[a]Includes "multiracial" or "refused to respond."

NTT group, respectively (Figure 3). At weeks 48 and 96, the mean (SD) change from baseline in the prescribed PN/IV energy intake was −18.4 (20.2) and −21.6 (20.6) kcal/kg/day in the any TED group and −9.2 (13.4) and −12.3 (9.5) kcal/kg/day in the NTT/NTT group, respectively (Digital Content S9).

The cumulative proportion of patients from the any TED group achieving a 20% or greater reduction in PN/

TABLE 2 TEAE through 96 weeks.

TEAE,[a] *n* (%)	NTT/NTT (*n* = 7)	TED/TED (*n* = 69)	Any TED (*n* = 78)
Any TEAE	6 (85.7)	68 (98.6)	76 (97.4)
Related to treatment	0 (0.0)	17 (24.6)	19 (24.4)
Leading to treatment discontinuation	0 (0.0)	3 (4.3)	3 (3.8)
Leading to study discontinuation	0 (0.0)	3 (4.3)	3 (3.8)
Leading to death	0 (0.0)	2 (2.9)	2 (2.6)
TEAE by severity			
Mild	0 (0.0)	12 (17.4)	15 (19.2)
Moderate	5 (71.4)	26 (37.7)	28 (35.9)
Severe	1 (14.3)	30 (43.5)	33 (42.3)
Any TESAE	4 (57.1)	54 (78.3)	60 (76.9)
Related to treatment	0 (0.0)	4 (5.8)	5 (6.4)

Abbreviations: NTT, no teduglutide treatment; TEAE, treatment-emergent adverse event; TED, teduglutide; TESAE, treatment-emergent serious adverse event.

[a]Adverse events that started or worsened on or after the date of first dose for TED/TED and any TED groups, and adverse events that started or worsened on or after the parent study baseline visit for NTT/NTT.

IV volume was 76.9% and 82.1% at 48 and 96 weeks, respectively; this was achieved by 42.9% of patients in the NTT/NTT group at weeks 48 and 96 (Digital Content S10). The cumulative proportion of patients in the any TED group achieving enteral autonomy was 19.2% and 21.8% at 48 and 96 weeks, respectively; this was achieved in 14.3% and 14.3% of patients at weeks 48 and 96 weeks in the NTT/NTT group, respectively (Digital Content S11).

3.3.1 | Antidrug antibodies

Among patients in the any TED group, antidrug antibodies were detected in 16 patients (20.5%) at the first LTE study visit and in 12 patients (15.4%) at the last study visit; out of 12 patients with positive antibodies, neutralizing activity was detected in four patients. No antidrug antibodies were detected in the NTT/NTT group at either visit.

3.3.2 | Predictors of response

A univariate analysis indicated that change in PN/IV volume may be affected by cause of SBS, bowel anatomy, and demographics (Digital Content S12).

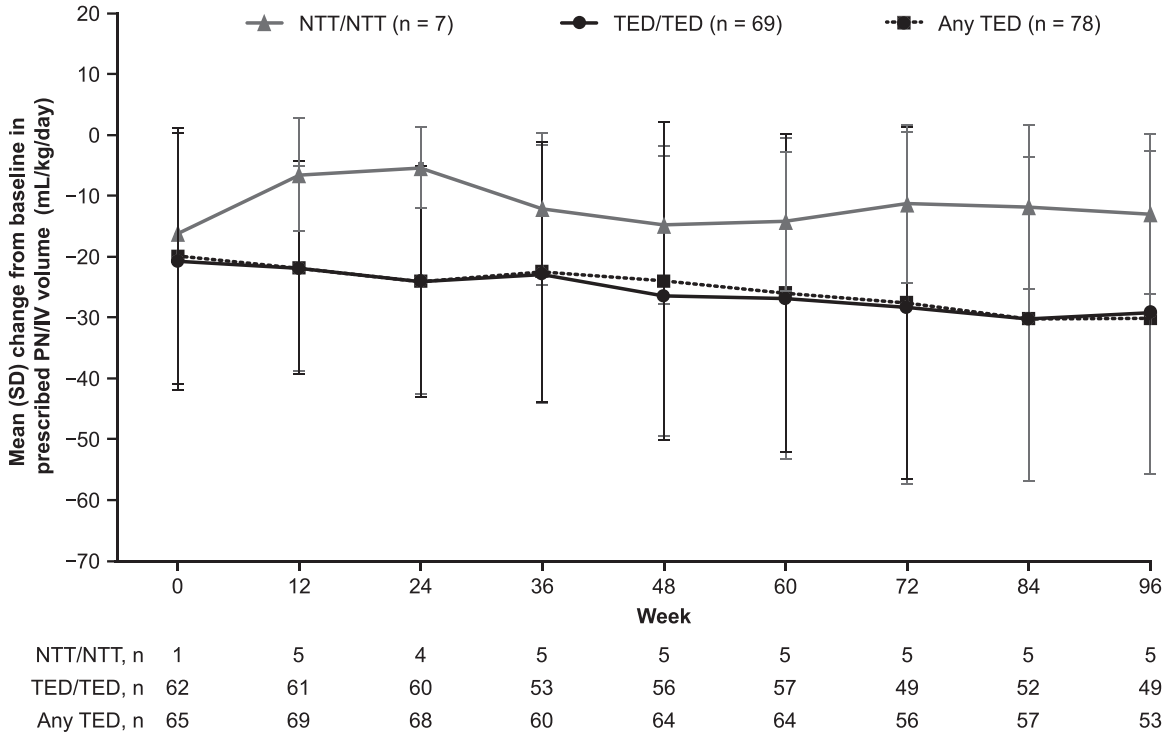


FIGURE 3 Mean change from baseline in mean prescribed PN/IV volume through 96 weeks. Baseline defined as the beginning of a parent study. NTT, no teduglutide treatment; PN/IV, parenteral nutrition and/or intravenous fluids; SD, standard deviation; TED, teduglutide.

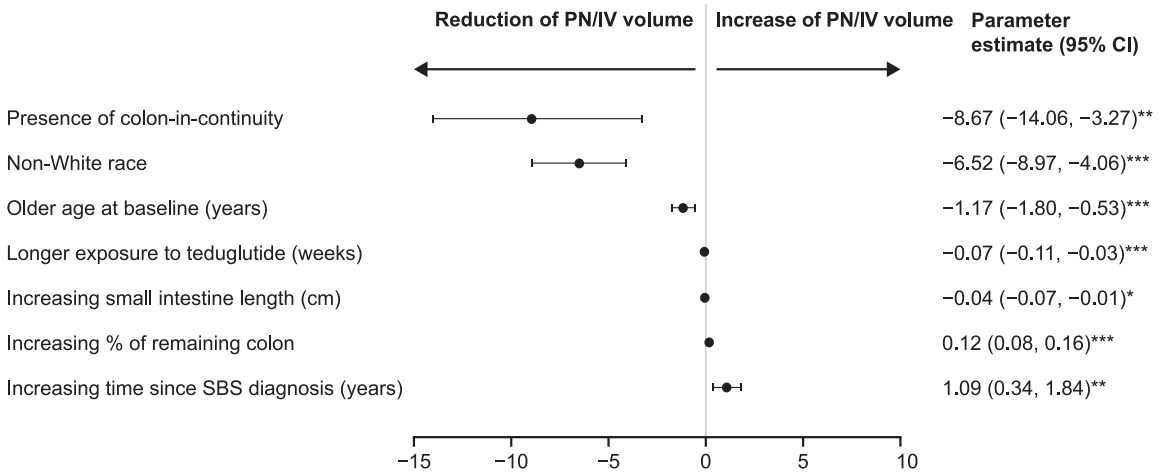


FIGURE 4 Multivariate analysis: predictors of change in PN/IV volume over 96 weeks. *$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$. The dependent variable is change in PN/IV volume at each visit through 96 weeks during the long-term extension studies (NCT02949362, NCT02954458). *p* values calculated from type III sum of square tests. CI, confidence interval; PN/IV, parenteral nutrition and/or intravenous fluids; SBS, short bowel syndrome.

Following multivariable regression, the following characteristics were associated with a significant reduction in PN/IV fluid requirements: presence of colon-in-continuity (−8.67; $p < 0.01$), non-White race (−6.52; $p < 0.001$), older age at baseline (years: −1.17; $p = 0.001$), longer exposure to teduglutide (weeks: −0.07; $p < 0.001$), and increasing mean length of small intestine (cm: −0.04; $p < 0.05$). The characteristics significantly associated with an increase in PN/IV fluid requirements were increasing percentage of remaining colon (0.12; $p < 0.001$) and increasing time since SBS diagnosis (years; 1.09; $p < 0.01$) (Figure 4).

4 | DISCUSSION

Teduglutide is the first and only GLP-2 analog licensed for the treatment of SBS-IF. The findings from this post hoc analysis using pooled data from two LTE clinical trials of up to 96 weeks support the safety and efficacy of teduglutide in pediatric patients with SBS-IF. These results were also consistent with previously reported data in pivotal multinational pediatric and adult studies.[5,6,10]

Pediatric patients with SBS-IF experienced continued and sustained reductions in PN/IV volume while maintaining stable anthropometric measurements over time despite increasing energy needs for typical growth and development. At 96 weeks, clinically meaningful reduction in PN/IV volume was achieved by 82% and 43% of patients in the any TED and NTT/NTT groups, respectively. Furthermore, 22% of patients in the any TED group achieved enteral autonomy at 96 weeks. In a prospective study of 17 pediatric patients with SBS-IF who were treated with teduglutide, 12 patients achieved enteral autonomy after 1 year of teduglutide.[9] The lower proportion of patients achieving enteral autonomy in the present study is likely due to the number of patients with a complex disease background, that is, patients with gastroschisis, or other conditions associated with abnormal intestinal motility predisposing to intestinal atresia, rendering a low likelihood of improved intestinal function.

This study suggests that extended exposure to teduglutide appears to be well tolerated in children with SBS-IF.[8,11,12] Similar to previously reported results, the most common adverse events were vomiting (47.4%), pyrexia (46.4%), upper respiratory tract infection (30.8%), and cough (25.6%). Owing to the intestinotrophic mechanism of action of teduglutide, previous studies have reported an increased incidence of dysplastic changes and neoplasms in rodent models exposed to exogenous GLP-2.[6,7,10,11,13] Colorectal polyps have also been reported in adult patients with SBS-IF treated with teduglutide, but not more frequently than would be expected in an age-matched population,[11,14] and in this study, there were no cases of colorectal polyps or neoplasia reported. The long-term risk of neoplasia will need to be monitored and the ongoing SBS-IF global registry study (NCT01990040) should be able to provide further insights. Over the entire study, antidrug antibodies were detected in 15.4% of patients in the any TED group, which is lower than previously reported in adult patients with SBS-IF who received teduglutide over 24 months (43%).[5,11]

We explored patient-level factors associated with teduglutide treatment response. Our analysis identified anatomical factors historically associated with successful intestinal adaptation in children, such as colon-in-continuity, residual small intestine length, and percentage of remaining colon.[15] Interestingly, colon-in-continuity was associated with a stronger effect in

weaning PN/IV than percentage of remaining colon; future studies might examine whether the distal small bowel and right colon are intact, as these are key areas where GLP-2 is synthesized.

The impact of teduglutide on intestinal adaptation is suggested by the association of increasing duration of exposure with PN/IV volume reduction. Racial disparities in outcomes have previously been reported in children with IF. In a multicenter chart review study of 272 infants with IF who were followed for 2 years, non-White children were significantly more likely to die and less likely to receive an intestinal transplant than white children.[16] Here, we report that non-White race was associated with positive outcomes. The finding that non-White race was associated with PN/IV volume reduction was not explored in a granular fashion, but deserves further study that should be addressed through a contemporary claims-based real-world evidence study.

Response to teduglutide treatment may depend on treatment duration, which can vary according to underlying anatomy and diagnosis. It has previously been reported in adults that inflammatory bowel disease, the presence of stoma, and the absence of an ileocecal valve were positively associated with an early sustained response to teduglutide, while vascular disease and colon-in-continuity were associated with late response.[17] In the 24-week parent study, three of the five patients who achieved enteral autonomy at week 24 did so as early as 12 weeks of teduglutide treatment.[6] In a real-world study over 12 months, up to seven of the 12 patients who achieved enteral autonomy did so by 6 months; however, five patients were weaned off PN/IV by 12 months.[9] A delayed response to treatment has implications for the clinical practice and management of patients with SBS-IF. Without a good understanding of the response time to treatment, it is possible that treatment may be prematurely discontinued in patients who may have otherwise achieved a late response; we therefore suggest that treatment should continue for a year before deciding on the effectiveness of the drug. Future studies should examine whether there are differences in the characteristics of pediatric patients with SBS-IF who respond before or after 24 weeks of teduglutide treatment. As young children have a greater capacity for adaptation than adults due to inherent growth potential, future studies should also examine whether treatment with teduglutide leads to faster improvements in children who may have been able to naturally wean off PN/IV as they grow, and whether lifelong treatment with teduglutide is needed in children as in adults. Indeed, an analysis of adult patients with SBS-IF who had received at least 24 weeks of teduglutide found that 3 out of 25 patients were weaned off PN/IV, stopped teduglutide, and remained independent of PN/IV 12 months later.[18] In addition, a study of adults with SBS-IF and Crohn's disease found that 2 of 13 patients stopped teduglutide after weaning from PN/IV after 14 and 23 months of therapy.[19] Future studies in pediatric patients with SBS-IF may also investigate differential adaptive responses to GLP-2 depending upon how early treatment was initiated.

This study had some limitations. It is notable that many patients had interruption of exposure to teduglutide when moving from parent study to extension studies. The impact of treatment interruption on response is unknown. Only a small number of patients were never treated with teduglutide in the parent or LTE studies (NTT/NTT, $n = 7$), and although this group represented a control arm of sorts, no formal control arm was available for comparison. The open-label treatment allocation may have led to investigators introducing selection and reporting bias, and the study was underpowered to detect differences between treatment groups. No adjustment for covariates was made, and as such, we cannot fully distinguish the impact of certain covariates on our findings; however, the multivariable linear regression did facilitate the determination of predictors of teduglutide response. Since the study was designed before the Sex and Gender Equity in Research (SAGER) guidelines were published,[20] sex and gender were not differentiated within the baseline characteristics, nor were specific criteria for transgender or nonbinary people included. It is worth noting, however, that the SAGER guidelines do not include specific guidance regarding pediatric patients. A major strength of the study was the multicenter collaboration and the wide variety of patient diagnoses that were included. Additionally, even after a break in treatment of 78–96 weeks, teduglutide remained effective when restarted. This is an important observation because patients may also have a break from treatment in real-life clinical practice.

5 | CONCLUSIONS

In conclusion, this post hoc analysis of pediatric patients with SBS-IF who were treated with teduglutide for up to 96 weeks demonstrated progressive reduction in PN/IV support over 96 weeks and the degree of that reduction depended on the duration of teduglutide exposure, underlying bowel anatomy, and demographics. Furthermore, approximately one-fifth of the teduglutide-treated patients achieved enteral autonomy. Future studies should evaluate how timing of teduglutide response and interruption of treatment might predict long-term clinical outcomes.

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CONFLICTS OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after being deidentified, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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SUPPORTING INFORMATION

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

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