Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome

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Objective To determine safety and pharmacodynamics/efficacy of teduglutide in children with intestinal failure associated with short bowel syndrome (SBS-IF).

Study design This 12-week, open-label study enrolled patients aged 1-17 years with SBS-IF who required parenteral nutrition (PN) and showed minimal or no advance in enteral nutrition (EN) feeds. Patients enrolled sequentially into 3 teduglutide cohorts (0.0125 mg/kg/d [n = 8], 0.025 mg/kg/d [n = 14], 0.05 mg/kg/d [n = 15]) or received standard of care (SOC, n = 5). Descriptive summary statistics were used.

Results All patients experienced ≥1 treatment-emergent adverse event; most were mild or moderate. No serious teduglutide-related treatment-emergent adverse events occurred. Between baseline and week 12, prescribed PN volume and calories (kcal/kg/d) changed by a median of –41% and –45%, respectively, with 0.025 mg/kg/d teduglutide and by –25% and –52% with 0.05 mg/kg/d teduglutide. In contrast, PN volume and calories changed by 0% and –6%, respectively, with 0.0125 mg/kg/d teduglutide and by 0% and –1% with SOC. Per patient diary data, EN volume increased by a median of 22%, 32%, and 40% in the 0.0125, 0.025, and 0.05 mg/kg/d cohorts, respectively, and by 11% with SOC. Four patients achieved independence from PN, 3 in the 0.05 mg/kg/d cohort and 1 in the 0.025 mg/kg/d cohort. Study limitations included its short-term, open-label design, and small sample size.

Conclusions Teduglutide was well tolerated in pediatric patients with SBS-IF. Teduglutide 0.025 or 0.05 mg/kg/d was associated with trends toward reductions in PN requirements and advancements in EN feeding in children with SBS-IF. *(J Pediatr 2017;181:102-11).*

Trial registration ClinicalTrials.gov: NCT01952080; EudraCT: 2013-004588-30.

AE	Adverse event
EN	Enteral nutrition
GI	Gastrointestinal
GLP	Glucagon-like peptide
IF	Intestinal failure
ITT	Intent-to-treat
PD	Pharmacodynamics
PN	Parenteral nutrition
SBS	Short bowel syndrome
SBS-IF	Intestinal failure associated with short bowel syndrome
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

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Funded by NPS Pharmaceuticals, Inc., Lexington, MA, a wholly owned indirect subsidiary of Shire. Potential conflicts of interest are available at www.jpeds.com (**Appendix**).

Portions of the study were presented as poster or oral presentations at: European Society for Clinical Nutrition and Metabolism, September 5-8, 2015, Lisbon, Portugal; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, October 7-11, 2015, Washington, DC; American Society for Parenteral and Enteral Nutrition Clinical Nutrition Week, January 16-19, 2016, Austin, TX; British Society of Paediatric Gastroenterology, Hepatology and Nutrition, January 27-29, 2016, Bristol, United Kingdom; Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica, May 12-14, 2016, Gijón, Spain; and European Society for Paediatric Gastroenterology, Hepatology and Nutrition, May 25-28, 2016, Athens, Greece.

http://dx.doi.org10.1016/j.jpeds.2016.10.027

Pediatric short bowel syndrome (SBS) is a malabsorptive condition usually caused by surgical intestinal resection due to congenital abnormalities, vascular insufficiency, or severe inflammatory intestinal disease.[1] The incidence in childhood varies between 0.02% and 1.2% of live births.[1-3] Although parenteral nutrition (PN) can be a life-saving therapy, long-term dependence on PN is associated with severe, possibly life-threatening complications, including catheter-related bloodstream infections, loss of central venous access, liver disease, and metabolic bone disease,[4-6] resulting in impaired quality of life.[7] With advances in the management of intestinal failure (IF) in pediatric patients and the institution of interdisciplinary teams, up to 85% of infants with IF achieve PN independence within 1-3 years with aggressive attempts at enteral feeding[8-11]; however, older pediatric patients with intestinal failure associated with short bowel syndrome (SBS-IF) who do not experience sufficient intestinal adaptation to achieve enteral autonomy under the current standard of care (SOC) are less likely to experience further intestinal adaptation sufficient to permit advancements in oral/enteral feeds or reductions in PN.[11,12] Additional strategies and therapies that promote intestinal adaptation in these patients are needed for both the subset of infants that fails to adapt within the first year and the older pediatric patients who remain dependent on PN.

Glucagon-like peptide (GLP)-2 is an intestinotrophic hormone that acts by increasing crypt epithelial proliferation, reducing epithelial apoptosis, enhancing visceral blood flow, amplifying nutrient absorption, and slowing intestinal motility.[13] Teduglutide, a GLP-2 analogue with resistance to in vivo degradation, expands the absorptive intestinal epithelium by significantly increasing villus height in adult patients with SBS.[14-16] This article reports the results of a 12-week, open-label, dose-finding study that assessed the short-term safety and pharmacodynamics (PD)/efficacy of teduglutide compared with SOC in pediatric patients (aged 1-17 years) with SBS who were dependent on PN for >1 year.

Methods

We performed a 12-week, open-label, multicenter, phase 3 study at 17 sites in the US and the United Kingdom (ClinicalTrials.gov: NCT01952080; EudraCT: 2013-004588-30). The centers featured intestinal rehabilitation programs with multidisciplinary clinical teams experienced in the care of pediatric patients with SBS-IF.

After approval from local institutional review boards and medical ethics committees, centers screened patients aged 1-17 years who had a ≥12-month history of SBS and dependence on PN (defined as PN and/or intravenous fluids) for at least 30% of caloric and/or fluid/electrolyte needs. PN needs were required to be stable at baseline, without any clinically meaningful or substantial reduction in PN or advancement in enteral nutrition (EN; oral and/or tube feeding) for ≥3 months. Key exclusion criteria included body weight below the fifth percentile for age or <10 kg; gastrointestinal (GI) obstruction within 6 months of screening; any major GI surgical intervention within 3 months of screening; history of cancer or clinically significant lymphoproliferative disease (excluding in situ nonaggressive and surgically resected cancer); active Crohn's disease treated with biologic therapy within 6 months of screening or active inflammatory bowel disease treated with immunosuppressant therapy; evidence of pseudo-obstruction or dysmotility syndrome; use of native GLP-2, GLP-1, or human growth hormone within 3 months before screening, or any previous use of teduglutide; and >3 SBS- or PN-related hospital admissions within 3 months or any unscheduled hospital admission within 1 month before screening.

Patients were enrolled in 3 temporally staggered escalating dose cohorts that received respective subcutaneous teduglutide doses of 0.0125 mg/kg/d, 0.025 mg/kg/d, and 0.05 mg/kg/d (**Figure 1**). The selection of doses was based on population pharmacokinetic modeling and simulation data that suggested that pediatric patients >1 year of age are likely to require the same dosage used in adults (ie, 0.05 mg/kg/d).[17] Patient compliance with teduglutide dosing was verified during the study by questioning patients or guardians regarding drug administration and by accounting for empty medication vials collected during scheduled study visits. In addition to the 3 dosing cohorts, a fourth observational cohort received SOC. A data safety monitoring board evaluated the safety and tolerability for each sequential dosing cohort at week 4. The data safety monitoring board review established that there were no unexpected safety signals in ≥6 patients before the next cohort proceeded. All patients were screened for ≥2 weeks before the start of treatment to establish baseline characteristics and safety, eligibility, and nutritional support variables.

After screening, study visits occurred weekly for the first 4 weeks and then every 2 weeks through the end of treatment (weeks 5-12; **Figure 1**). To further monitor safety, patients were contacted by telephone at the end of weeks 5, 7, 9, and 11. A final study visit occurred at week 16 (4 weeks after treatment finished). During the study period, patients or their guardians maintained daily diaries to record EN intake. Decisions regarding changes to nutritional and fluid intake were left to the discretion of the primary treating physician, but the study protocol provided guidelines for PN modifications (**Table I**; available at www.jpeds.com).

Data Endpoints and Statistical Analyses

Data collected at every study visit included serum electrolytes, liver and pancreatic enzymes, albumin, blood urea nitrogen, creatinine, and weight and height measurements. Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) were recorded. Samples for teduglutide-specific antibody analysis were drawn at baseline, final treatment visit (≥14 hours after the last dose), and 4 weeks after treatment was completed. Teduglutide-specific antibodies could be non-neutralizing antibodies (ie, those that bind to teduglutide without affecting biological activity) or neutralizing antibodies (ie, those that reduce drug activity). The following PD/efficacy endpoints were used: change in PN requirements, including the number of patients that achieved complete PN independence; change in EN tolerance;

and changes in plasma citrulline. PN volume, PN calorie, and EN calorie endpoints were calculated based on provider prescriptions. Changes in hours per day of PN infusion and enteral feeding volumes were based on patient diary data, which were considered more accurate measures of actual patient infusion time and EN consumption than prescribed data. Families were directed to follow prescriptions as closely as possible. Rare changes in patient diaries were made because of technical impediments (eg, pump failure) or caregiver need. EN calorie and volume data were based on formula-based liquid nutrition received orally or via tube feeding only. Other solid foods and liquids were considered ad lib nutrition and were not included in the calculation of EN calories and volume.

Because of the small pool of eligible patients, the study analysis was descriptive in nature and was not designed or sufficiently powered to determine the statistical significance of safety or PD/efficacy endpoints. The intent-to-treat (ITT) population consisted of all patients who enrolled in the trial. The safety population consisted of all patients in the ITT population who received at least 1 dose of teduglutide or SOC. The ITT population was analyzed for PD/efficacy endpoints except for analysis of percentage change from baseline in EN volume and calories (ie, analysis did not include patients who did not receive EN at baseline [n = 10] or did not have EN volume/calorie data recorded at baseline [n = 1], because it is mathematically impossible to calculate a percentage change when the baseline is zero). Patients with no baseline EN intake were included in calculations of actual change in EN volume and calories. Patient electronic case report forms or diaries were used as sources for data collection and management. All data were entered into a preformatted database, verified, quality-checked, and submitted for statistical evaluation.

Adverse events (AEs) were coded with the *Medical Dictionary for Regulatory Activities*.[18] TEAEs were summarized by system organ class, preferred term, and treatment group by the use of descriptive statistics. TESAEs were tabulated by overall and treatment-related events. Missing safety variables were not imputed. The absolute values and change from baseline in PD/efficacy variables at each scheduled visit for each treatment group were presented as median (min, max) and also summarized by descriptive summary statistics.

Results

During the study period (November 2013-January 2015), 54 patients were screened and 42 patients were enrolled (**Figure 1**): 8 in the 0.0125 mg/kg/d cohort, 14 in the 0.025 mg/kg/d cohort, 15 in the 0.05 mg/kg/d cohort, and 5 in the SOC cohort. Forty patients (95%) completed the study. One patient (0.05 mg/kg/d) withdrew consent, and 1 patient (0.0125 mg/kg/d) was removed from the study because of protocol noncompliance (**Figure 2**; available at www.jpeds.com). Of the 42 enrolled patients, 32 were receiving formula-based liquid EN at baseline (n = 4 in the SOC cohort and n = 28 in the combined teduglutide cohorts). Baseline patient demographics are reported in **Table II**.

Indicators of clinical status remained stable throughout the study period (**Table III**; available at www.jpeds.com). All patients experienced at least 1 TEAE. Most patients reported a mild TEAE (95% and 100% of teduglutide- and SOC-treated patients, respectively) or moderate TEAE (57% and 60%). Severe TEAEs were reported by 30% of patients who received teduglutide and by 20% of patients who received SOC. The most common TEAE (**Table IV**) among all patients receiving teduglutide was vomiting, which was reported more frequently in the 0.05 and 0.025 mg/kg/d cohorts (47% and 36%, respectively, compared with 0% in the 0.0125 mg/kg/d and SOC cohorts). Other commonly reported TEAEs were

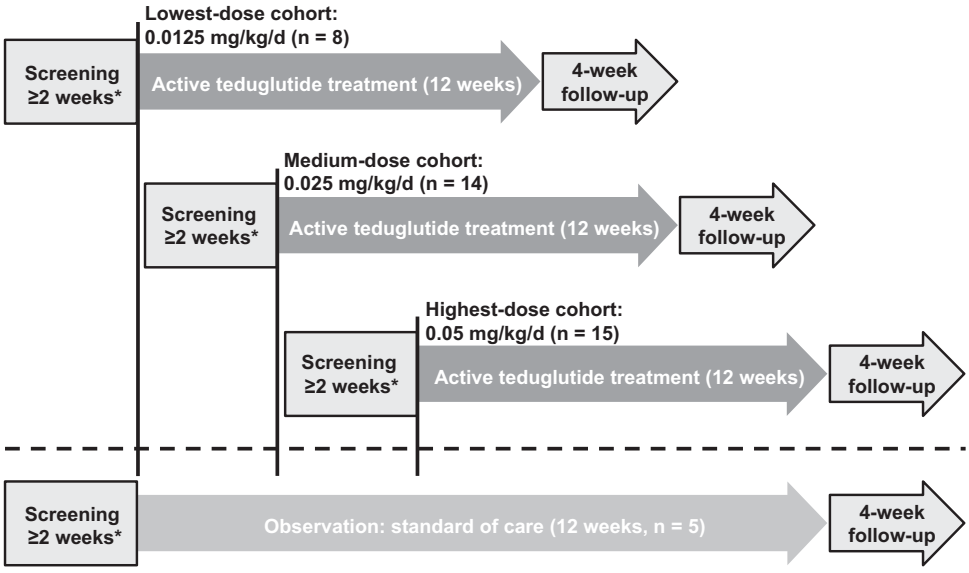


Figure 1. Study design. *Safety data were assessed after ≥28 days of teduglutide treatment before the next dosing cohort could proceed.

Table II. Patient demographics at baseline

Variables	SOC (n = 5)	Teduglutide, mg/kg/d				
		Lowest dose 0.0125 (n = 8)	Medium dose 0.025 (n = 14)	Highest dose 0.05 (n = 15)	Total teduglutide (n = 37)	Total (N = 42)
Age, y						
Median (min, max)	2.0 (2, 3)	3.0 (1, 14)	4.0 (1, 14)	4.0 (1, 14)	4.0 (1, 14)	3.0 (1, 14)
1-3, n (%)	5 (100)	4 (50)	6 (43)	7 (47)	17 (46)	22 (52)
4-12, n (%)	0	3 (38)	7 (50)	7 (47)	17 (46)	17 (40)
13-17, n (%)	0	1 (13)	1 (7)	1 (7)	3 (8)	3 (7)
Sex, n (%)						
Male	3 (60)	6 (75)	11 (79)	8 (53)	25 (68)	28 (67)
Female	2 (40)	2 (25)	3 (21)	7 (47)	12 (32)	14 (33)
Race, n (%)						
White	3 (60)	6 (75)	11 (79)	13 (87)	30 (81)	33 (79)
Black	1 (20)	2 (25)	1 (7)	1 (7)	4 (11)	5 (12)
Asian	1 (20)	0	0	1 (7)	1 (3)	2 (5)
Other/not applicable	0	0	2 (14)	0	2 (5)	2 (5)
Reason for resection, n (%)*						
Necrotizing enterocolitis	2 (40)	1 (13)	2 (14)	3 (20)	6 (16)	8 (19)
Midgut volvulus	2 (40)	2 (25)	4 (29)	7 (47)	13 (35)	15 (36)
Intestinal atresia	1 (20)	1 (13)	4 (29)	2 (13)	7 (19)	8 (19)
Gastroschisis	0	2 (25)	7 (50)	3 (20)	12 (32)	12 (29)
Other	0	2 (25)	0	1 (7)	3 (8)	3 (7)
Estimated residual small intestine length						
n	5	7	13	13	33	38
Median (min, max), cm	35.0 (10, 75)	15.0 (2, 75)	68.0 (15, 145)	26.0 (0, 68)	30.0 (0, 145)	32.5 (0, 145)
Length of remaining anatomy determined by, n (%)						
Surgery	4 (80)	5 (62.5)	7 (50)	12 (80)	24 (65)	28 (67)
Radiology	0	1 (12.5)	3 (21)	1 (7)	5 (13.5)	5 (12)
Other	1 (20)	2 (25)	4 (29)	2 (13)	8 (22)	9 (21)
Ileocecal valve present, n (%)	1 (20)	2 (25)	1 (7)	4 (27)	7 (19)	8 (19)
Intact colon, n (%)	5 (100)	7 (88)	14 (100)	14 (93)	35 (95)	40 (95)
Estimated colon remaining						
n	5	6	11	12	29	34
Median (min, max), %	50 (33, 100)	85 (30, 100)	60 (10, 100)	78 (8, 100)	75 (8, 100)	75 (8, 100)
Colon-in-continuity, n (%)†	5 (100)	7 (100)	12 (86)	14 (100)	33 (94)	38 (95)
Undergone serial transverse enteroplasty procedure, n (%)	1 (20)	0	3 (21)	2 (13)	5 (14)	6 (14)
Fed EN via feeding tube, n (%)‡						
Yes	4 (80)	4 (50)	12 (86)	9 (60)	25 (68)	29 (69)
No	0	0	1 (7)	2 (13)	3 (8)	3 (7)
Concomitant medications, n (%)						
Antipropulsives	1 (20)	2 (25)	6 (43)	6 (40)	14 (38)	15 (36)
Probiotics§	1 (20)	1 (13)	1 (7)	2 (13)	4 (11)	5 (12)
Bile acid preparations	0	1 (13)	0	2 (13)	3 (8)	3 (7)
Bile acid sequestrants	2 (40)	3 (38)	2 (21)	2 (13)	8 (22)	10 (24)
Proton pump inhibitors	1 (20)	1 (13)	7 (50)	7 (47)	15 (41)	16 (38)
H_2 receptor antagonists	4 (80)	0	3 (21)	3 (20)	6 (16)	10 (24)

*Patients may have had ≥1 reason for resection. Each reason has been accounted for and thus sums may not total the n listed in the header and percentages may not total 100%.
†Percentages are based on patients with remaining colon in each treatment arm.
‡Category includes only those patients who received EN at baseline.
§Use of probiotics in this patient population is controversial; listing of probiotics as a concomitant medication is not intended as an endorsement of this practice.

Table IV. TEAEs occurring in >5% of the pooled teduglutide dose cohorts

Preferred terms, n (%)*	SOC (n = 5)	Teduglutide, mg/kg/d			Total teduglutide (n = 37)
		Lowest dose 0.0125 (n = 8)	Medium dose 0.025 (n = 14)	Highest dose 0.05 (n = 15)	
Vomiting	0	0	5 (36)	7 (47)	12 (32)
Upper respiratory tract infection	2 (40)	2 (25)	4 (29)	4 (27)	10 (27)
Catheter-related complication	1 (20)	3 (38)	4 (29)	2 (13)	9 (24)
Pyrexia	2 (40)	0	2 (14)	7 (47)	9 (24)
Cough	1 (20)	1 (13)	2 (14)	4 (27)	7 (19)
Abdominal pain	1 (20)	1 (13)	1 (7)	4 (27)	6 (16)
Headache	0	1 (13)	2 (14)	2 (13)	5 (14)
Nausea	0	1 (13)	2 (14)	2 (13)	5 (14)
Fatigue	0	0	1 (7)	4 (27)	5 (14)
Blood bicarbonate decreased	2 (40)	1 (13)	1 (7)	3 (20)	5 (14)
Diarrhea	1 (20)	0	1 (7)	3 (20)	4 (11)
Fecal volume increased	0	1 (13)	1 (7)	2 (13)	4 (11)
Central line infection	0	0	3 (21)	1 (7)	4 (11)
Abdominal distension	0	1 (13)	1 (7)	1 (7)	3 (8)
Flatulence	0	2 (25)	1 (7)	0	3 (8)
Hematochezia	0	2 (25)	1 (7)	0	3 (8)
Injection-site hemorrhage	0	0	0	3 (20)	3 (8)
Viral gastroenteritis	1 (20)	1 (13)	0	2 (13)	3 (8)
Nasopharyngitis	0	2 (25)	0	1 (7)	3 (8)
Weight decreased	0	1 (13)	1 (7)	1 (7)	3 (8)
Dizziness	0	0	1 (7)	2 (13)	3 (8)
Rash	0	0	1 (7)	2 (13)	3 (8)
GI stoma complication†	0	0	0	1 (100)	1 (25)

*Percentages are based on the number of patients in each treatment group.
†Percentages are based on the number of patients with a stoma in each treatment group.

upper respiratory infection (27% teduglutide, 40% SOC), catheter-related complication (24% teduglutide, 20% SOC), and pyrexia (24% teduglutide, 40% SOC). The second most common GI-related TEAE was abdominal pain (16% teduglutide, 20% SOC). Overall, GI-related TEAEs occurred in 67% (0.05 mg/kg/d), 71% (0.025 mg/kg/d), 50% (0.0125 mg/kg/d), and 20% (SOC) of patients. AEs of special interest (ie, intestinal obstruction; fluid overload; or gallbladder, biliary, or pancreatic disease [colonic polyp formation not assessed]), which were identified during the adult teduglutide clinical program and reported in the teduglutide prescribing information,[17] were not evident during this smaller pediatric study. There were no discontinuations due to TEAEs. Seventeen patients (46%) in the combined teduglutide cohorts experienced 34 TESAEs, and 3 patients (60%) in the SOC cohort experienced 6 TESAEs (**Table V**; available at www.jpeds.com). TESAEs reported in >2 patients treated with teduglutide were pyrexia (n = 4 [11%] teduglutide; n = 2 [40%] SOC), central line infection (n = 4 [11%] teduglutide; n = 0 SOC), and catheter-related complication (n = 3 [8%] teduglutide; n = 1 [20%] SOC). No deaths or TESAEs related to study drug occurred during the study. No patient developed neutralizing antibodies to teduglutide. One patient (0.025 mg/kg/d) tested positive for non-neutralizing antiteduglutide antibodies at week 16. This patient had no hypersensitivity or injection-site reactions, and PN requirements remained stable during the study. At a 3-month follow-up visit, the patient tested negative for antibodies.

Teduglutide treatment was associated with trends toward decreased PN volume and calorie requirements in the 0.025 and 0.05 mg/kg/d cohorts, which were observed as early as week 4 (**Figure 3**, A and B). At week 12, weekly prescribed PN volume was changed by a median (min, max) of −2.3 (−6.9, 0) L/wk and −1.3 (−11.0, 1.0) L/wk in the 0.025 and 0.05 mg/kg/d cohorts, respectively. In contrast, median PN volume remained near baseline in the 0.0125 mg/kg/d and SOC groups (median change at week 12: 0 [−2.5, 0] L/wk and 0 [−0.3, 1.4] L/wk, respectively). On the basis of patient diary data, the median change in daily PN infusion time at 12 weeks was 0 (0, 2.0), −4.0 (−9.0, 2.0), and −3.0 (−12.0, 0.8) hours per day in the 0.0125, 0.025, and 0.05 mg/kg/d cohorts, respectively; change in PN infusion time was 0 (−2.0, 0.6) hours per day in the SOC cohort. At week 12, PN calories changed by −1 (−5, 5), −2 (−12, 3), −17 (−39, 2), and −17 (−45, 53) kcal/kg/d in the SOC, 0.0125, 0.025, and 0.05 mg/kg/d groups, respectively. Four patients receiving teduglutide achieved independence from PN: 3 of 15 in the 0.05 mg/kg/d cohort (achieved at weeks 4, 8, and 12) and 1 of 14 in the 0.025 mg/kg/d cohort (achieved at week 11) (**Table VI**; available at www.jpeds.com). At week 16 (4 weeks after teduglutide discontinuation), 2 of these 4 patients had resumed PN and 2 remained PN independent.

On the basis of patient diary data from the ITT population, including those patients who did not receive EN, the EN volume changed by a median of +0.5 (0, 1.7) L/wk in the SOC cohort, +1.1 (0, 12.5) L/wk in the 0.0125 mg/kg/d cohort, +2.3 (−0.9, 8.8) L/wk in the 0.025 mg/kg/d cohort, and +0.7 (0, 3.9) L/wk in the 0.05 mg/kg/d cohort. At week 12, EN calorie intake changed by a median of +2 (−3, 20), +9 (−18, 72), and +7 (−1, 63) kcal/kg/d in the 0.0125, 0.025, and 0.05 mg/kg/d groups, respectively, and by +5 (0, 47) kcal/kg/d in the SOC group.

Changes in EN volume and calories from baseline are reported in **Figure 3**, C and D.

Overall, trends suggestive of PN reductions and EN improvements over baseline values persisted during the first 4 weeks of treatment (**Figure 3**). Point estimates of median change in PN weekly volume requirements were increased at week 16 (ie, 4 weeks after teduglutide discontinuation) compared with week 12 (ie, at end of treatment) but remained lower than baseline values in the 2 highest teduglutide dose cohorts: −2.2 (−6.9, 0.3) L/wk for the 0.025 mg/kg/d cohort and −0.9 (−9.0, 1.9) L/wk for the 0.05 mg/kg/d cohort. In contrast, point estimates for median change in PN volume at week 16 were closer to baseline values in the 0.0125 mg/kg/d and SOC cohorts: −0.2 (−2.5, 0) and 0.0 (−0.9, 1.4) L/wk, respectively. A similar pattern was observed for prescribed PN calories. At week 16, PN calories were changed by −1 (−10, 1), −9 (−39, 8), and −15 (−40, 6) kcal/kg/d from baseline in the 0.0125, 0.025, and 0.05 mg/kg/d cohorts, respectively. In the SOC cohort at week 16, prescribed PN calories were near baseline (median change, 0 [−13, 1] kcal/kg/d). After 4 weeks off teduglutide, point estimates of EN volume and calories were maintained or increased compared with baseline. Median EN volume changed by +0.9 (0, 1.7), +3.2 (0, 10.5), +3.5 (−1.9, 8.7), and +0.8 (0, 3.5) L/wk vs baseline in the SOC, 0.0125, 0.025, and 0.05 mg/kg/d cohorts, respectively. Prescribed EN calories changed by +6 (0, 48) kcal/kg/d vs baseline with SOC, by +5 (−5, 27) kcal/kg/d with 0.0125 mg/kg/d, by +11 (−20, 72) kcal/kg/d with 0.025 mg/kg/d, and by +2 (−3, 64) kcal/kg/d with 0.05 mg/kg/d teduglutide.

Median plasma citrulline levels at baseline, week 12, and week 16 (4 weeks after teduglutide discontinuation) are reported in **Table VII** (available at www.jpeds.com). Broad variability in baseline citrulline values was observed, but median change from baseline in citrulline levels increased in all teduglutide cohorts at week 12.

Discussion

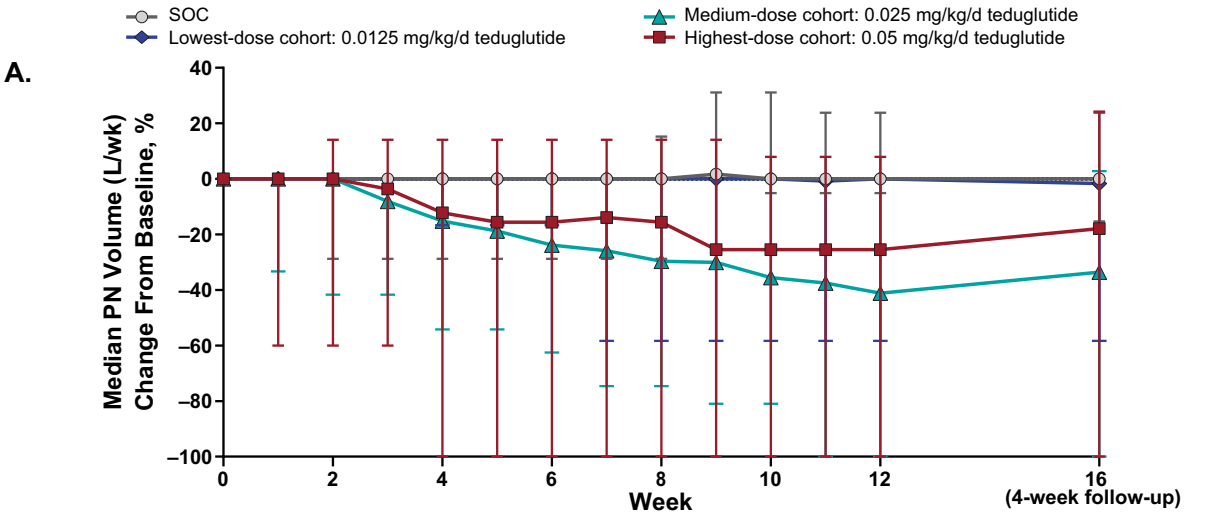
Population pharmacokinetic modeling and simulation data indicated that pediatric patients >1 year of age would likely require the same teduglutide dosage approved for adult patients (ie, 0.05 mg/kg/d).[17] Preliminary modeling also suggested that lower doses may show some benefit in children. Therefore, a conservative approach was taken, and 2 lower doses were investigated first.

Teduglutide had a generally good safety profile and was well tolerated by pediatric patients at the doses tested. GI events were reported at a relatively low frequency overall, but most were more common in the 0.025 mg/kg/d and 0.05 mg/kg/d teduglutide dose cohorts than in the SOC cohort (**Table IV**). Despite GI events, most patients treated with teduglutide completed the study. The overall safety profile was consistent with the adult SBS population. The most commonly reported TEAEs in the teduglutide-treated population were GI-related AEs, upper respiratory tract infection, catheter-related complications, and pyrexia, all of which were observed in the short-term studies of teduglutide in adult patients.[19,20] The study protocol included frequent study visits because of the potential for treatment-associated AEs identified in the adult clinical trial program and reported as AEs of special interest in the teduglutide US prescribing information.[17] None of these AEs were observed.

Teduglutide treatment was associated with trends toward decreases in PN requirements and increases in EN intake in a study population that had not experienced any clinically meaningful reductions in PN and minimal or no advance in EN feedings for ≥3 months. Trends suggestive of improvements in EN feedings also were observed in the SOC cohort during this study, in terms of a median 11% increase in EN volume and a 41% increase in EN kcal/kg/d at week 12 vs baseline. Patients receiving SOC in this study likely benefited from intensive, high-frequency patient management at experienced intestinal rehabilitation centers, which are associated with improved outcomes in patients with pediatric SBS.[21] The SOC cohort also was a younger population (2 vs 4 years of age in the pooled teduglutide cohorts) and, therefore, perhaps more capable of endogenous intestinal adaptation.

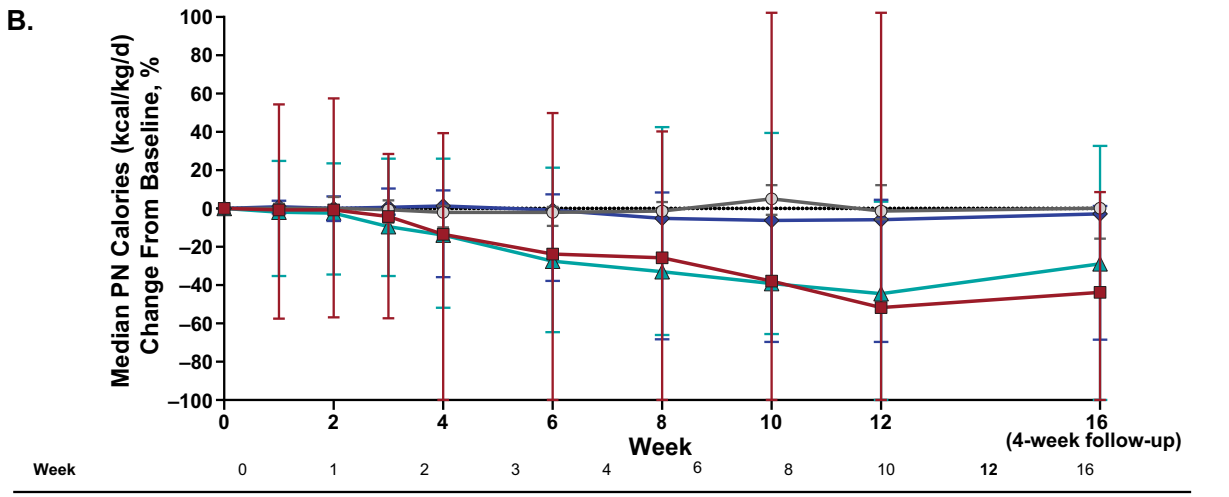
Citrulline levels also were assessed during this study, but the results were clouded by wide variability of baseline values. In the 0.05 mg/kg/d teduglutide cohort, point estimates showed a median increase in the change of plasma citrulline between baseline and week 12, but the absolute median values for plasma citrulline levels virtually were unchanged. In adults with SBS-IF, treatment with teduglutide has been associated with significant ($P < .0001$ vs placebo) increases in plasma citrulline.[22] Additional studies with larger sample sizes will need to be conducted to determine whether the same correlation is noted in pediatric patients or to determine whether children need longer courses or greater doses of teduglutide than adults to achieve a consistent effect on plasma citrulline.

Although not directly comparable, the PN decreases (−41% and −25% in the 0.025 and 0.05 mg/kg/d cohorts, respectively) were in range with reductions observed in adults receiving teduglutide 0.05 mg/kg/d in the pivotal phase 3 clinical trial (−32%).[20] In the current study, 4 patients were weaned successfully from PN with teduglutide after up to 12 years of PN dependence. PN had to be resumed in 2 of these patients at week 16 (4 weeks after teduglutide discontinuation), suggestive of a treatment-related improvement while on treatment. Considering the safety profile observed in this study at all doses and trends suggesting decreased PN requirements and EN advancements at the 2 greater teduglutide doses, the benefit/risk profile for teduglutide was more favorable with 0.025 and 0.05 mg/kg/d teduglutide. Patients in the 0.025 and 0.05 mg/kg/d cohorts reduced PN volume (L/wk) by 25% to 41% and PN calories (kcal/kg/d) by 45% to 52% while increasing EN volume by 32% to 40% and EN calories by 26% to 63%. In addition, 4 of 29 patients in these 2 cohorts achieved PN independence during the treatment period. Nonetheless, these results are tempered by the recognized limitations of this short-term, open-label study. The treatment period of this study was only 12 weeks; in adult patients with SBS-IF, teduglutide administered over 30 months yielded continued PN reductions throughout extended treatment.[23] The relatively short study



Week	0	1	2	3	4	5	6	7	8	9	10	11	**12**	16
Median PN Volume (L/wk), % Change From Baseline (min, max)														
SOC*	0 (0, 0)	0 (0, 0)	0 (–29, 0)	0 (–29, 0)	0 (–29, 0)	0 (–29, 0)	0 (–29, 0)	0 (–29, 0)	0 (–29, 15)	1.7 (0, 31)	0 (–5, 31)	0 (–5, 24)	**0 (–5, 24)**	0 (–15, 24)
0.0125 mg/kg/d†	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (–17, 0)	0 (–17, 1)	0 (–17, 0)	0 (–58, 0)	0 (–58, 0)	0 (–58, 0)	0 (–58, 0)	–1 (–58, 0)	**0 (–58, 0)**	–2 (–58, 0)
0.025 mg/kg/d‡	0 (0, 0)	0 (–33, 0)	0 (–42, 0)	–8 (–42, 0)	–15 (–54, 0)	–19 (–54, 0)	–24 (–63, 0)	–26 (–75, 0)	–30 (–75, 0)	–30 (–81, 0)	–36 (–81, 0)	–38 (–100, 0)	**–41 (–100, 0)**	–34 (–100, 3)
0.05 mg/kg/d§	0 (0, 0)	0 (–60, 0)	0 (–60, 14)	–4 (–60, 14)	–12 (–100, 14)	–16 (–100, 14)	–16 (–100, 14)	–14 (–100, 14)	–16 (–100, 14)	–25 (–100,14)	–25 (–100, 8)	–25 (–100, 8)	**–25 (–100, 8)**	–18 (–100, 24)

*n = 5 (except n = 4 at week 5).
†n = 8 (except n = 6 at week 11 and n = 7 at weeks 1, 4–10, 12, and 16).
‡n = 14 (except n = 13 at week 12).
§n = 15 (except n = 14 at weeks 7, 9–12, and 16).

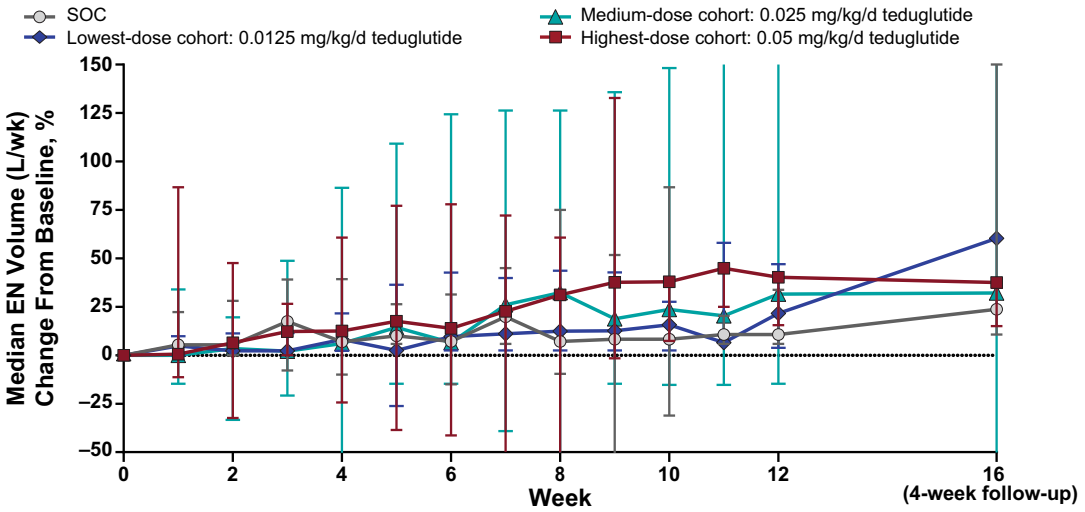


Week	0	1	2	3	4	6	8	10	**12**	16
Median PN Calories (kcal/kg/d), % Change From Baseline (min, max)										
SOC*	0 (0, 0)	0 (–3, 3)	0 (–1, 6)	–1 (–7, 4)	–2 (–10, 1)	–2 (–9, 1)	–1 (–3, 3)	5 (–3, 12)	**–1 (–6, 12)**	0 (–16, 2)
0.0125 mg/kg/d†	0 (0, 0)	1 (–3, 4)	0 (–7, 6)	1 (–3, 10)	–1 (–36, 9)	–1 (–38, 7)	–5 (–68, 8)	–6 (–70, 5)	**–6 (–70, 5)**	–3 (–69, 1)
0.025 mg/kg/d‡	0 (0, 0)	2 (–35, 25)	–2 (–35, 24)	–10 (–35, 26)	–14 (–52, 26)	–28 (–65, 21)	–33 (–66, 43)	–39 (–66, 39)	**–45 (–100, 4)**	–29 (–100, 33)
0.05 mg/kg/d§	0 (0, 0)	–1 (–58, 54)	–1 (–57, 58)	–4 (–57, 29)	–14 (–100, 39)	–24 (–100, 50)	–26 (–100, 40)	–38 (–100, 102)	**–52 (–100, 102)**	–44 (–100, 9)

*n = 5 (except n = 4 at week 10).
†n = 8 (except n = 7 at weeks 1 and 4–16).
‡n = 14 (except n = 12 at week 12 and n = 13 at week 16).
§n = 15 (except n = 14 at weeks 10 and 16 and n = 13 at week 12).

Figure 3. Median percentage change from baseline in prescribed weekly **A,** PN volume and **B,** PN calories and median percentage change from baseline in **C,** weekly EN volume per patient diary data and **D,** prescribed EN calories during 12 weeks of teduglutide administration and for 4 weeks after treatment discontinuation (weeks 13-16). Analyses of percentage change in EN volume and calories did not include patients who did not receive EN at baseline (n = 11). Error bars represent min, max values. *(Continues)*

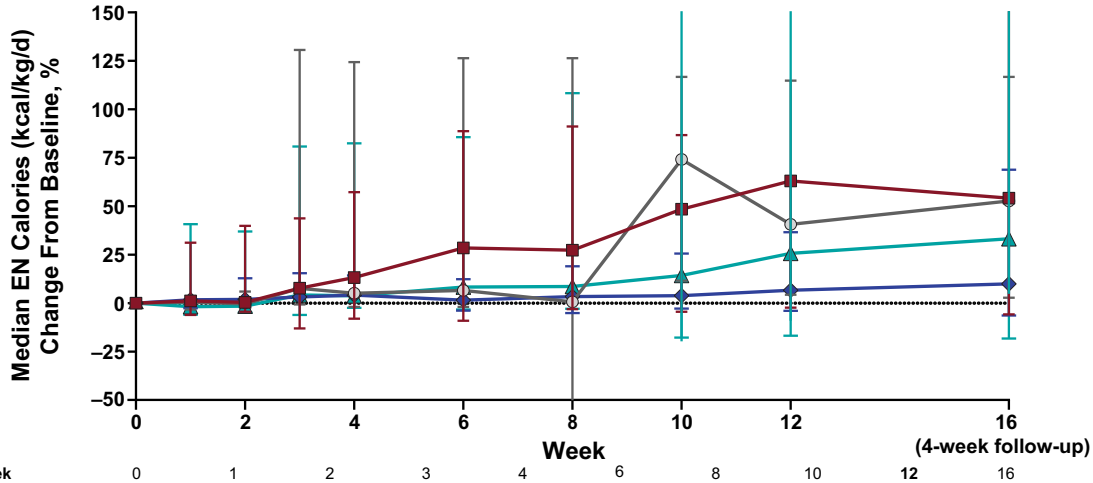
C.



Week	0	1	2	3	4	5	6	7	8	9	10	11	**12**	16
Median EN Volume (L/wk), % Change From Baseline (min, max)														
SOC*	0 (0, 0)	5 (0, 22)	5 (0, 28)	17 (–8, 39)	7 (–10, 39)	10 (6, 26)	7 (–15, 31)	20 (6, 45)	7 (–10, 75)	8 (–55, 52)	8 (–31, 87)	11 (6, 20)	**11 (6, 34)**	24 (11, 150)
0.0125 mg/kg/d†	0 (0, 0)	5 (0, 10)	2 (0, 11)	2 (1, 12)	8 (2, 22)	3 (–26, 36)	10 (3, 43)	11 (3, 40)	12 (3, 44)	13 (3, 43)	16 (3, 28)	7 (4, 58)	**22 (4, 47)**	60 (60, 60)
0.025 mg/kg/d‡	0 (0, 0)	0 (–15, 34)	3 (–33, 20)	2 (–21, 49)	6 (–65, 86)	14 (–15, 109)	7 (–15, 124)	26 (–39, 126)	32 (–76, 126)	19 (–15, 136)	24 (–15, 148)	20 (–15, 162)	**32 (–15, 177)**	32 (–95, 180)
0.05 mg/kg/d§	0 (0, 0)	1 (–11, 87)	6 (–32, 48)	12 (0, 27)	13 (–24, 61)	18 (–39, 77)	14 (–41, 78)	23 (–60, 72)	31 (–64, 61)	38 (–2, 133)	38 (7, 159)	45 (25, 156)	**40 (16, 154)**	38 (15, 224)

*n = 4 (except n = 3 at weeks 5, 11, and 12).
†n = 4 (except n = 1 at week 16 and n = 3 at weeks 1–3, 5, and 11).
‡n = 13 (except n = 11 at week 16 and n = 12 at weeks 4, 7, 8, and 12).
§n = 10 (except n = 8 at weeks 1 and 12 and n = 9 at weeks 2–4, 9–11, and 16).

D.



Week	0	1	2	3	4	6	8	10	**12**	16
Median EN Calories (kcal/kg/d), % Change From Baseline (min, max)										
SOC*	0 (0, 0)	0 (–3, 3)	0 (–2, 6)	8 (–1, 131)	5 (–2, 124)	7 (–2, 126)	1 (–100, 126)	74 (12, 117)	**41 (4, 115)**	53 (3, 117)
0.0125 mg/kg/d†	0 (0, 0)	2 (–3, 4)	2 (1, 13)	3 (1, 15)	4 (1, 14)	2 (–4, 12)	3 (–5, 19)	4 (–3, 26)	**7 (–4, 37)**	10 (–6, 69)
0.025 mg/kg/d‡	0 (0, 0)	–2 (–6, 41)	–2 (–5, 37)	4 (–6, 81)	4 (–2, 82)	8 (–3, 86)	9 (–3, 108)	14 (–18, 165)	**26 (–17, 169)**	33 (–18, 183)
0.05 mg/kg/d§	0 (0, 0)	1 (–6, 31)	0 (–5, 40)	8 (–13, 44)	13 (–8, 57)	28 (–9, 89)	27 (–3, 91)	48 (–5, 87)	**63 (–2, 167)**	54 (–6, 169)

*n = 4 (except n = 3 at week 10).
†n = 4.
‡n = 13 (except n = 12 at week 12).
§n = 10 (except n = 9 at weeks 10 and 16 and n = 8 at week 12).

Figure 3. Continued.

period did not allow us to evaluate the effects of teduglutide on long-term outcomes such as growth.

Furthermore, analyses of EN calorie and volume data were based on liquid nutrition only and did not encompass other ad lib enteral consumption. If teduglutide, as anticipated, enhanced ad lib intake and subsequent nutritional absorption, then the assessments of EN volume and calories may have underestimated the potential beneficial impact of teduglutide. In addition, the analyses of actual change in EN calorie and volume data during the study were calculated for the ITT population and thus included those patients who did not receive EN. Reported changes in PN infusion time at week 12 could represent either adjustments in PN volume or modifications of the infusion schedule (ie, cycling), but the accompanying PN volume time course data support trends for reduced PN volume with greater doses of teduglutide. The pool of eligible patients for this study was small, and, as such, the sample size was based on the available patient population rather than on a statistical power calculation. More patients were assigned to the 2 greater-dose cohorts, which were hypothesized to be more likely to elicit clinically relevant effects, than to the 0.0125 mg/kg/d and SOC cohorts. Moreover, recruitment into the SOC cohort in this open-label study was hindered by lack of interest or perceived benefit among patients and guardians, and this cohort included no patients older than 3 years of age. Thus, the study was not powered sufficiently to determine the statistical significance of safety or PD/efficacy endpoints, and only descriptive statistics were used. Finally, 3 study centers enrolled ≥5 patients (n = 5, 6, and 7, respectively), leading to the possibility of a "center effect," in which the specific practice patterns of those centers may have exerted a disproportionate influence on study results. Many of the aforementioned limitations can be attributed to the fact that pediatric SBS is an orphan condition, making impossible the stratification of the small number of patients enrolled by age, diagnosis, bowel length, or baseline intestinal function.

Effects of teduglutide treatment persisted for at least 4 weeks following drug discontinuation. Although point estimates for PN volume increased at 4 weeks after teduglutide discontinuation compared with end of treatment, median PN volumes remained lower than baseline levels in the 2 greater-dose cohorts (0.025 and 0.05 mg/kg/d). Similarly, compared with end of treatment, trends suggesting advancements in EN feeds were maintained during the 4 weeks after teduglutide discontinuation. Of the 4 patients who achieved enteral autonomy with teduglutide treatment, 2 maintained PN independence at the 4-week follow-up. Study data were not collected past week 16.

In this initial, 3-month, open-label study, teduglutide treatment was associated with trends toward reductions in PN needs and advancements in EN in children with SBS-IF, particularly at the greater doses tested, 0.025 and 0.05 mg/kg/d. Teduglutide had a favorable safety profile and was well tolerated across all dosing cohorts. A 24-week study that compared the safety and efficacy of 0.025 and 0.05 mg/kg/d teduglutide vs SOC treatment in pediatric patients with SBS-IF (ClinicalTrials.gov, NCT02682381) will yield additional data regarding optimal teduglutide dosing. ■

We thank the patients and their families who participated in this study, as well as the study coordinators and research assistants at all the study centers, including Brooke Bessard, Tess Buccigrosso, Heather Godwin, Jani Klein, Ila McDonald, Heather Nielson, Kate Reeve, Crystal Slaughter, and those in the Department of Surgery-Office of Clinical Research at the University of Wisconsin School of Medicine and Public Health. Editorial support was provided by Heather Heerssen, PhD (Complete Healthcare Communications, LLC, Chadds Ford, PA) and was funded by NPS Pharmaceuticals, Inc, Lexington, MA, a wholly owned indirect subsidiary of Shire.

Submitted for publication Jun 7, 2016; last revision received Aug 8, 2016; accepted Oct 6, 2016

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References

1. Wales PW, Christison-Lagay ER. Short bowel syndrome: epidemiology and etiology. Semin Pediatr Surg 2010;19:3-9.
2. Duro D, Kamin D, Duggan C. Overview of pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr 2008;47:S33-6.
3. Cole CR, Hansen NI, Higgins RD, Ziegler TR, Stoll BJ, Eunice Kennedy Shriver NICHD Neonatal Research Network. Very low birth weight preterm infants with surgical short bowel syndrome: incidence, morbidity and mortality, and growth outcomes at 18 to 22 months. Pediatrics 2008;122:e573-82.
4. Diamanti A, Bizzarri C, Basso MS, Gambarara M, Cappa M, Daniele A, et al. How does long-term parenteral nutrition impact the bone mineral status of children with intestinal failure? J Bone Miner Metab 2010;28:351-8.
5. Modi BP, Jaksic T. Pediatric intestinal failure and vascular access. Surg Clin North Am 2012;92:729-43, x.
6. Nehra D, Fallon EM, Puder M. The prevention and treatment of intestinal failure-associated liver disease in neonates and children. Surg Clin North Am 2011;91:543-63.
7. Sanchez SE, McAteer JP, Goldin AB, Horslen S, Huebner CE, Javid PJ. Health-related quality of life in children with intestinal failure. J Pediatr Gastroenterol Nutr 2013;57:330-4.
8. Torres C, Sudan D, Vanderhoof J, Grant W, Botha J, Raynor S, et al. Role of an intestinal rehabilitation program in the treatment of advanced intestinal failure. J Pediatr Gastroenterol Nutr 2007;45:204-12.
9. Khan FA, Squires RH, Litman HJ, Balint J, Carter BA, Fisher JG, et al. Predictors of enteral autonomy in children with intestinal failure: a multicenter cohort study. J Pediatr 2015;167:29-34, e1.
10. Salvia G, Guarino A, Terrin G, Cascioli C, Paludetto R, Indrio F, et al. Neonatal onset intestinal failure: an Italian Multicenter Study. J Pediatr 2008;153:674-6, e1-2.
11. Sigalet D, Boctor D, Brindle M, Lam V, Robertson M. Elements of successful intestinal rehabilitation. J Pediatr Surg 2011;46:150-6.
12. Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. J Pediatr 2012;161:723-8, e2.
13. Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. Annu Rev Physiol 2014;76:561-83.
14. Drucker DJ, Shi Q, Crivici A, Sumner-Smith M, Tavares W, Hill M, et al. Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV. Nat Biotechnol 1997;15:673-7.
15. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut 2005;54:1224-31.
16. Tappenden KA, Edelman J, Joelsson B. Teduglutide enhances structural adaptation of the small intestinal mucosa in patients with short bowel syndrome. J Clin Gastroenterol 2013;47:602-7.

17. GATTEX® (teduglutide [rDNA origin]). Full Prescribing information, Shire-NPS Pharmaceuticals, Inc., Lexington, MA, 2016. http://www.shirecontent.com/PI/PDFS/Gattex_USA_ENG.pdf. Accessed October 26, 2016.
18. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20:109-17.
19. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut 2011;60:902-14.
20. Jeppesen PB, Pertkiewicz M, Messing B, Iyer K, Seidner DL, O'Keefe SJ, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology 2012;143:1473-81.
21. Stanger JD, Oliveira C, Blackmore C, Avitzur Y, Wales PW. The impact of multi-disciplinary intestinal rehabilitation programs on the outcome of pediatric patients with intestinal failure: a systematic review and meta-analysis. J Pediatr Surg 2013;48:983-92.
22. Seidner DL, Joly F, Youssef NN. Effect of teduglutide, a glucagon-like peptide 2 analog, on citrulline levels in patients with short bowel syndrome in two phase III randomized trials. Clin Transl Gastroenterol 2015;6:e93.
23. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape U-F, et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol 2016;7:e142.

50 Years Ago in *The Journal of Pediatrics*

Cerebral Lesions in Congenital Rubella Syndrome

Rorke LB, Spiro AJ. J Pediatr 1967;70:243-55

Before the release of the rubella vaccine in 1969, more than 20 000 infants in the US were born with congenital rubella syndrome.[1] Affected infants had neurosensory deficits including microcephaly, intellectual disabilities, cataracts, glaucoma, and hearing loss. As with the Zika virus today, there was controversy and a bit of mystery regarding how the virus affected the central nervous system in utero. In 1967, before the availability of advanced neuroimaging, pathologists were the specialists who evaluated brain development and injury.

Fifty years ago in *The Journal*, pediatric neuropathologists Rorke and Spiro reported a case series of 9 infants who died before age 1 year with confirmed or presumed congenital rubella. The brains of the infants exhibited widespread vascular injury with resulting ischemic lesions in watershed areas, including the periventricular white matter, but no structural malformations of the brain or inflammation were evident. Older infants had poor myelination. The pediatric neuropathologists had rarely seen this constellation of findings. They also found vascular injury to the pulmonary, renal, hepatic, and pancreatic vessels, and speculated that vascular degeneration and resulting ischemia was the primary cause of brain injury with fetal rubella infection. This report was one of many that established the sensorineural consequences of congenital infection with rubella and provided the impetus for public health campaigns that have eliminated endemic rubella in the US.[1]

Today, the Zika virus presents a new threat to the fetus. As with congenital rubella, when Zika virus infection first emerged as a threat, there was controversy about whether and how it caused brain injury in the fetus. Our current research toolkit is enhanced by the availability of fetal neuroimaging and identification of the viral genome in brain tissue,[2] but now, as in 1967, careful neuropathologic evaluation of suspected cases continues to be important in establishing disease pathogenesis.

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References

1. Reef SE, Cochi SL. The evidence for the elimination of rubella and congenital rubella syndrome in the United States: a public health achievement. Clin Infect Dis 2006;43(Suppl 3):S123-5.
2. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. N Engl J Med 2016;374:951-8.

Appendix

Sponsored by NPS Pharmaceuticals, Inc, a wholly owned indirect subsidiary of Shire. In addition, B.C. has served as an advisory board member for Shire; M.C. serves on a data safety monitoring board for Nestle; S.Hi has served as a consultant for Abbott Nutrition. R.M. is a retiree of Abbott Laboratories; and is a stockholder in Abbott, AbbVie, and Johnson & Johnson. P.N. is an investor and chair of the scientific advisory board for MedAware Systems. S.K. has served as a consultant for NPS Pharmaceuticals, Inc., and on the Abbott Nutrition Speakers Bureau. B.L. and N.Y. were employees of NPS Pharmaceuticals, Inc, at the time of data collection and analysis—B.L. was the lead statistician for the analysis and provided data analysis and interpretation, and N.Y. was the medical monitor for the study. C.D. serves on the Editorial Board of *The Journal of Pediatrics*. C.C. declares no conflicts of interest.

Table I. Guidance for PN and nutritional support adjustments

Types of adjustment	Measurement	Action taken
Fluid	Intake exceeds output by >400 mL/m^2	PN volume decreased and oral/enteral volume increased
	Intake exceeds output by 0-400 mL/m^2	No action taken
	Intake less than output by >400 mL/m^2	PN volume increased; oral/enteral volume not changed
Calorie	Weight loss >5% of body weight	PN calories increased
	Weight increased beyond expected weight gain* between 2 study visits	PN calories decreased and oral/enteral calories increased
	Weight change <5% of body weight	No change to PN calories; oral/enteral calories increased

*Expected weight gain: > 5-10 g/d for toddlers aged 1-2 y and >3-5 g/d for children aged >2 y.

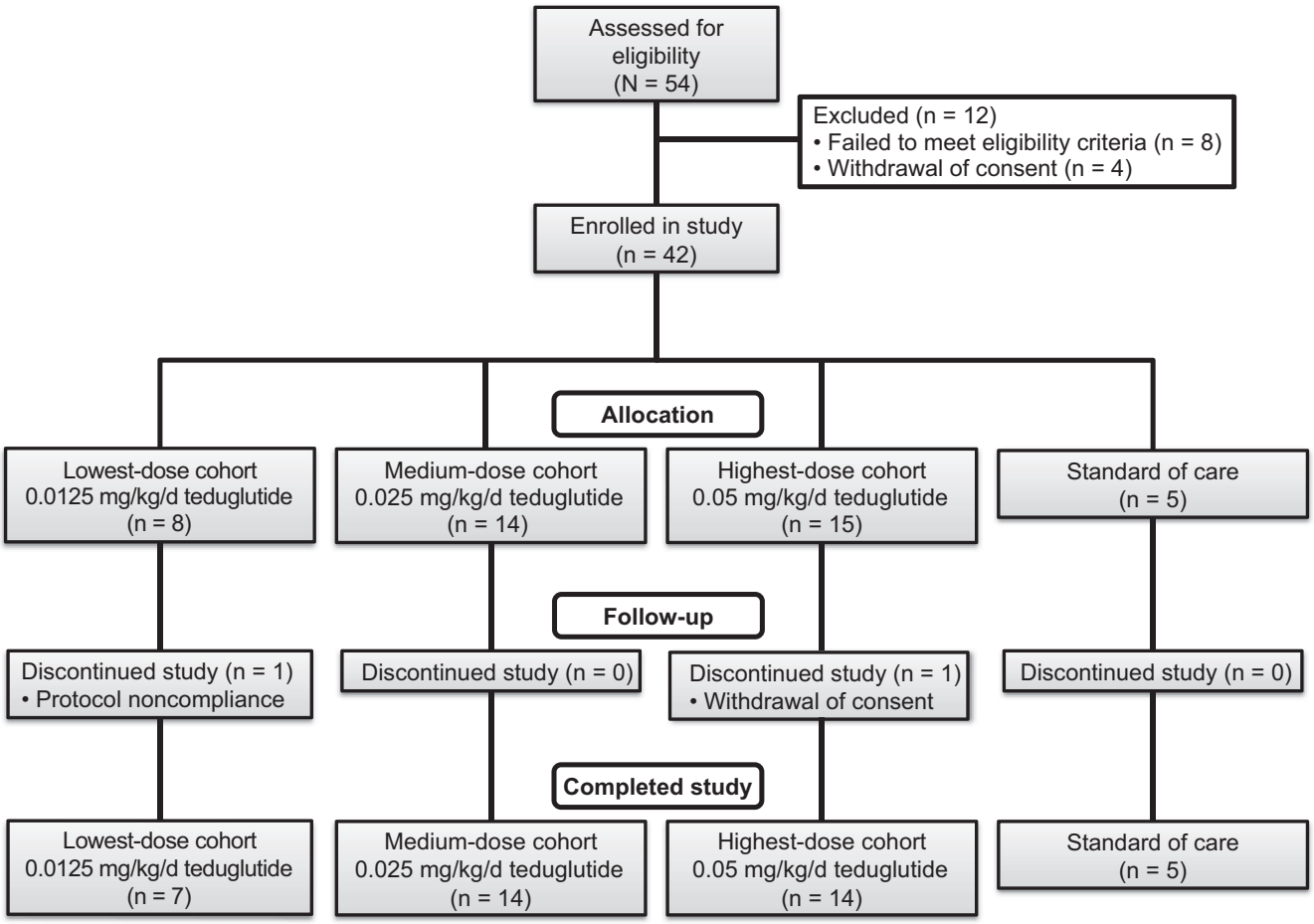

Figure 2. Patient disposition.

Table III. Clinical status

Variables	SOC (n = 5)	Teduglutide, mg/kg/d		
		Lowest dose 0.0125 (n = 8)	Medium dose 0.025 (n = 14)	Highest dose 0.05 (n = 15)
Height, cm				
Baseline				
n	5	8	14	15
Median (min, max)	92.0 (82.0, 95.0)	95.2 (80.0, 160.3)	100.4 (80.6, 158.8)	99.6 (76.1, 145.5)
Week 12				
n	5	7	12	13
Median (min, max)	91.7 (84.7, 94.2)	103.0 (84.0, 161.5)	104.5 (81.2, 161.0)	99.5 (87.1, 147.9)
Change				
n	5	7	12	13
Median (min, max)	2.1 (–3.3, 2.7)	1.2 (–0.2, 4.0)	1.9 (–0.6, 6.7)	1.7 (0.1, 11.0)
Weight, kg				
Baseline				
n	5	8	14	15
Median (min, max)	12.3 (11.2, 14.8)	13.3 (10.1, 48.7)	17.4 (10.3, 44.3)	16.1 (10.5, 38.5)
Week 12				
n	5	7	12	13
Median (min, max)	13.1 (11.7, 15.7)	16.0 (11.2, 50.4)	17.2 (10.2, 53.4)	16.1 (10.8, 35.8)
Change				
n	5	7	12	13
Median (min, max)	0.5 (0.1, 0.9)	0.8 (0.3, 2.1)	0.4 (–0.7, 9.1)	0.3 (–2.7, 2.0)
Weight, z score				
Baseline				
n	5	7	9	14
Median (min, max)	–0.5 (–1.6, 0.5)	–1.2 (–1.6, 0.1)	–0.3 (–0.9, 2.4)	–0.2 (–1.7, 1.2)
Week 12				
n	5	7	10	12
Median (min, max)	–0.5 (–1.2, 1.3)	–0.2 (–0.9, 0.3)	0.04 (–1.0, 2.8)	–0.5 (–3.0, 1.5)
Change				
n	5	7	8	12
Median (min, max)	0.4 (0, 1.2)	0.3 (–0.1, 1.2)	0.3 (–1.7, 2.1)	–0.03 (–3.1, 1.3)
Serum electrolytes				
Calcium, mmol/L				
Baseline				
n	5	8	14	15
Median (min, max)	2.4 (2.2, 2.5)	2.4 (2.0, 2.7)	2.4 (2.2, 2.6)	2.3 (2.3, 2.5)
Week 12				
n	5	7	13	13
Median (min, max)	2.3 (2.1, 2.4)	2.3 (2.1, 2.5)	2.3 (2.2, 2.5)	2.3 (2.1, 2.5)
Change				
n	5	7	13	13
Median (min, max)	–0.1 (–0.3, 0.1)	–0.1 (–0.1, 0.4)	–0.1 (–0.2, 0.0)	0.0 (–0.3, 0.2)
Phosphate, mmol/L				
Baseline				
n	5	8	14	15
Median (min, max)	1.6 (1.6, 1.8)	1.7 (1.3, 1.8)	1.5 (1.1, 1.9)	1.6 (1.2, 1.9)
Week 12				
n	5	7	13	13
Median (min, max)	1.7 (1.5, 1.7)	1.6 (1.1, 1.7)	1.6 (0.9, 1.9)	1.6 (0.9, 1.9)
Change				
n	5	7	13	13
Median (min, max)	–0.1 (–0.2, 0.1)	–0.1 (–0.2, 0.0)	–0.1 (–0.6, 0.6)	0.0 (–0.6, 0.3)
Magnesium, mmol/L				
Baseline				
n	5	8	14	15
Median (min, max)	0.8 (0.8, 0.8)	0.8 (0.6, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)
Week 12				
n	5	7	13	13
Median (min, max)	0.8 (0.7, 0.8)	0.8 (0.8, 0.9)	0.8 (0.6, 0.9)	0.8 (0.5, 0.9)
Change				
n	5	7	13	13
Median (min, max)	0.0 (–0.1, 0.0)	0.0 (–0.1, 0.2)	0.0 (–0.4, 0.1)	0.0 (–0.2, 0.1)
Liver function tests and liver enzymes				
Albumin, g/L				
Baseline				
n	5	8	14	15
Median (min, max)	39.0 (36, 40)	39.0 (37, 44)	38.5 (31, 44)	39.0 (35, 46)
Week 12				

(*continued*)

Table III. Continued

		Teduglutide, mg/kg/d		
	SOC (n = 5)	Lowest dose 0.0125 (n = 8)	Medium dose 0.025 (n = 14)	Highest dose 0.05 (n = 15)
n	5	7	13	13
Median (min, max)	36.0 (32, 40)	39.0 (33, 44)	38.0 (33, 43)	38.0 (27, 44)
Change				
n	5	7	13	13
Median (min, max)	–3.0 (–4, 2)	–1.0 (–6, 3)	–1.0 (–9, 4)	–2.0 (–12, 3)
Alkaline phosphatase, U/L				
Baseline				
n	5	8	14	15
Median (min, max)	221.0 (167, 649)	338.0 (181, 423)	227.0 (120, 396)	288.0 (120, 482)
Week 12				
n	5	7	13	13
Median (min, max)	186.0 (119, 424)	296.0 (172, 388)	203.0 (89, 247)	248.0 (84, 482)
Change				
n	5	7	13	13
Median (min, max)	–44.0 (–225, –12)	–15.0 (–131, 32)	–9.0 (–120, 66)	–51.0 (–135, 194)
Alanine aminotransferase, U/L				
Baseline				
n	5	8	14	15
Median (min, max)	25.0 (21, 51)	71.0 (19, 140)	35.0 (11, 179)	50.0 (24, 136)
Week 12				
n	5	7	13	13
Median (min, max)	35.0 (21, 40)	58.0 (24, 142)	30.0 (11, 77)	46.0 (23, 98)
Change				
n	5	7	13	13
Median (min, max)	0.0 (–11, 13)	–8.0 (–82, 44)	–3.0 (–102, 19)	–3.0 (–91, 34)
Aspartate aminotransferase				
Baseline				
n	5	8	14	15
Median (min, max)	36.0 (35, 76)	54.5 (20, 72)	39.0 (16, 85)	43.0 (22, 69)
Week 12				
n	5	7	13	13
Median (min, max)	46.0 (30, 64)	49.0 (30, 161)	37.0 (20, 75)	39.0 (29, 116)
Change				
n	5	7	13	13
Median (min, max)	–2.0 (–20, 21)	–1.0 (–15, 89)	5.0 (–27, 22)	–6.0 (–22, 47)
Bilirubin, μmol/L				
Baseline				
n	5	8	14	15
Median (min, max)	2.0 (2, 7)	3.0 (2, 10)	3.0 (2, 9)	3.0 (2, 19)
Week 12				
n	5	7	13	13
Median (min, max)	2.0 (2, 15)	3.0 (2, 14)	3.0 (2, 9)	3.0 (2, 11)
Change				
n	5	7	13	13
Median (min, max)	0.0 (–2, 10)	0.0 (–3, 4)	0.0 (–1, 5)	0.0 (–8, 5)
Blood urea nitrogen, mmol/L				
Baseline				
n	5	8	14	15
Median (min, max)	4.0 (3, 6)	5.0 (1, 8)	5.2 (3, 8)	4.70 (3, 8)
Week 12				
n	5	7	13	13
Median (min, max)	3.7 (2, 7)	4.4 (3, 7)	4.9 (3, 6)	4.5 (3, 6)
Change				
n	5	7	13	13
Median (min, max)	–0.6 (–1, 2)	–0.3 (–3, 1)	–1.4 (–3, 2)	–0.4 (–1, 2)
Gamma glutamyl transferase, U/L				
Baseline				
n	5	8	14	15
Median (min, max)	23.0 (10, 99)	33.5 (8, 112)	18.0 (10, 82)	21.0 (10, 78)
Week 12				
n	5	7	13	13
Median (min, max)	16.0 (11, 93)	14.0 (5, 115)	13.0 (5, 35)	27.0 (8, 108)
Change				
n	5	7	13	13
Median (min, max)	–6.0 (–7, 2)	–2.0 (–54, 49)	–5.0 (–47, 14)	6.0 (–30, 70)

(*continued*)

Table III. Continued

	SOC (n = 5)	Teduglutide, mg/kg/d		
		Lowest dose 0.0125 (n = 8)	Medium dose 0.025 (n = 14)	Highest dose 0.05 (n = 15)
Kidney function tests and pancreatic enzymes				
Creatinine, μmol/L				
Baseline				
n	5	8	14	15
Median (min, max)	28.0 (23, 31)	34.0 (16, 57)	29.5 (19, 53)	27.0 (19, 43)
Week 12				
n	5	7	13	13
Median (min, max)	26.0 (21, 27)	35.0 (16, 61)	27.0 (19, 51)	27.0 (19, 78)
Change				
n	5	7	13	13
Median (min, max)	–4.0 (–5, 3)	0.0 (–8, 5)	–1.0 (–10, 11)	4.0 (–4, 55)
Amylase, U/L				
Baseline				
n	5	8	14	15
Median (min, max)	41.0 (21, 45)	54.0 (20, 83)	57.0 (21, 178)	48.0 (40, 115)
Week 12				
n	5	7	13	13
Median (min, max)	37.0 (25, 41)	53.0 (21, 75)	52.0 (25, 226)	58.0 (40, 73)
Change				
n	5	7	13	13
Median (min, max)	0.0 (–8, 4)	1.0 (–17, 5)	4.0 (–23, 48)	3.0 (–42, 15)
Triacylglycerol lipase, U/L				
Baseline				
n	5	8	14	15
Median (min, max)	29.0 (14, 42)	29.0 (14, 135)	23.5 (13, 66)	19.0 (13, 48)
Week 12				
n	5	7	13	13
Median (min, max)	21.0 (15, 71)	21.0 (16, 49)	21.0 (10, 51)	19.0 (10, 31)
Change				
n	5	7	13	13
Median (min, max)	0.0 (–14, 29)	–2.0 (–15, 7)	1.0 (–20, 14)	0.0 (–23, 13)

Table V. Summary of TESAEs

Preferred terms, n (%)*	SOC (n = 5)	Teduglutide, mg/kg/d			Total teduglutide (n = 37)
		Lowest dose 0.0125 (n = 8)	Medium dose 0.025 (n = 14)	Highest dose 0.05 (n = 15)	
Pyrexia	2 (40)	0	1 (7)	3 (20)	4 (11)
Central line infection	0	0	3 (21)	1 (7)	4 (11)
Catheter-related complication	1 (20)	0	2 (14)	1 (7)	3 (8)
Parainfluenza virus infection	0	0	1 (7)	1 (7)	2 (5)
Pancytopenia	0	0	0	1 (7)	1 (3)
Abdominal distension	0	0	1 (7)	0	1 (3)
Frequent bowel movements	0	0	0	1 (7)	1 (3)
Hematochezia	0	0	1 (7)	0	1 (3)
Fatigue	0	0	0	1 (7)	1 (3)
Irritability	0	0	0	1 (7)	1 (3)
Anaphylactic reaction	0	0	0	1 (7)	1 (3)
Adenovirus infection	0	1 (13)	0	0	1 (3)
Catheter-related infection	0	1 (13)	0	0	1 (3)
Catheter sepsis	0	0	0	1 (7)	1 (3)
Influenza	0	1 (13)	0	0	1 (3)
Rhinovirus infection	0	0	1 (7)	0	1 (3)
Blood creatinine increased	0	0	1 (7)	0	1 (3)
Dehydration	0	0	0	1 (7)	1 (3)
Depressed level of consciousness	0	0	0	1 (7)	1 (3)
Grand mal convulsion	0	0	1 (7)	0	1 (3)
Rash	0	0	1 (7)	0	1 (3)
Hypovolemic shock	0	0	1 (7)	0	1 (3)
Fungemia	1 (20)	0	0	0	0
Viral gastroenteritis	1 (20)	0	0	0	0
Viral infection	1 (20)	0	0	0	0

*Percentages are based on the number of patients in each treatment group; a single patient may have reported ≥1 TESAE.

Table VI. Characteristics of patients weaned from PN/intravenous fluids

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Cohort, teduglutide mg/kg/d	Medium dose, 0.025	Highest dose, 0.05	Highest dose, 0.05	Highest dose, 0.05
Age, y	14	8	6	14
Sex	Male	Female	Male	Male
Etiology	Gastroschisis	Intestinal atresia	Hirschsprung disease	Midgut volvulus
Remaining small bowel length, cm	145	23	51	0
Stoma present (stoma type, if applicable)	No	No	Yes (ileostomy)	No
Colon remaining, %	100	100	0	100
Time since last surgical resection, y	1.0	8.4	4.3	12.2
Remaining anatomy determined by	Surgery or operative report/parental history	Surgery or operative report	Surgery or operative report	Surgery or operative report
GI symptoms				
Abnormal or irregular bowel movements	Moderate	None	None	None
Diarrhea, loose	Moderate	Mild	Severe	None
Gas, bloating	Mild	None	None	None
Heartburn, reflux, spit up	None	None	None	Mild
Nausea, feeling queasy	Moderate	None	None	None
Vomiting	Moderate	None	None	None
Teduglutide exposure at weaning, wk	10.7	4.1	12.1	8.1
Time on PN at baseline, y	1.3	8.3	6.7	12.2
Prescribed PN volume at screening, L/wk	6.9	4	9.5	11
Prescribed PN calorie at screening, kcal/wk	6747	3788	6701	4767
Prescribed number of days per week of PN at screening	7	4	7	5
Time on EN at baseline, y	14.3	N/A	N/A	N/A
Prescribed EN volume at screening, L/wk	10.1	N/A	N/A	N/A
Prescribed EN calorie at screening, kcal/wk	6720	N/A	N/A	N/A
Hours per day feeding tube used	24	N/A	N/A	N/A
Change in actual EN volume at week 12, L/wk (%)	8.4 (82.9)	N/A	N/A	N/A
Resumed PN after teduglutide discontinuation	No	No	Yes	Yes

N/A, not applicable (ie, patient did not receive EN).

Table VII. Plasma citrulline levels during and after teduglutide treatment

	Teduglutide, mg/kg/d		
	0.0125	0.025	0.05
Variables	(n = 8)	(n = 14)	(n = 15)
Median (min, max)			
Baseline, μmol/L	14.7 (3.8, 25.3)	16.1 (6.4, 29.8)	16.8* (4.5, 30.6)
Week 12, μmol/L	18.6† (6.2, 48.2)	22.0‡ (7.8, 47.0)	16.7* (4.2, 72.9)
Change from baseline at week 12, μmol/L	1.0† (–0.8, 22.9)	5.4‡ (1.1, 17.2)	7.5‡ (–13.9, 56.5)
Change from baseline at week 12, %	12† (–4, 91)	34‡ (10, 91)	78‡ (–51, 345)
Week 16 (4 weeks after end of study drug treatment), μmol/L	15.1† (6.5, 50.6)	17.5 (6.8, 35.8)	9.5* (2.9, 48.2)
Change from baseline at week 16, μmol/L	1.0† (–4.2, 25.3)	1.9 (–2.4, 6.8)	0.4‡ (–19.1, 28.2)
Change from baseline at week 16, %	8† (–30, 100)	12 (–21, 50)	5‡ (–67, 172)

*n = 14.
†n = 7.
‡n = 13.