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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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;