Supplemental Materials

Susan Hill et al. Safety Findings in Pediatric Patients During Long-Term Treatment With Teduglutide for Short Bowel Syndrome–Associated Intestinal Failure: Pooled Analysis of Four Clinical Studies.

Supplemental Methods

Antibody Analyses

In the core studies, samples for teduglutide-specific antibody analysis were drawn at baseline, final treatment visit, and 4 weeks after treatment was completed. During the extension studies, screening for antibodies to teduglutide was conducted at day 1, week 12, week 24, and week 28 (end of 4-week follow-up period) of each treatment cycle, as well as at the end of the study or early termination of the study. The blood sample drawn on day 1 of the cycle was drawn before administration of teduglutide. After initiation of teduglutide treatment, samples were drawn ≥14 hours after dosing. Patients who had been previously treated with teduglutide and who tested positive for antibodies to teduglutide had follow-up blood draws for antibodies to teduglutide every 12 weeks while on study until a negative result was obtained.

Anti-teduglutide antibodies were assessed using an enhanced chemiluminescence assay with biotin-labeled and SULFO-TAG–labeled teduglutide. In addition, anti-teduglutide -neutralizing antibodies were detected using a cell-based assay based on glucagon-like peptide-2 (GLP-2)–stimulated adenylate cyclase activity in a human 293-EBNA cell line expressing rat GLP-2 receptors. Binding of GLP-2 and related analogues, such as teduglutide, to the GLP-2 receptor stimulates the cellular $G_{\alpha s}$ protein, resulting in activation of adenylate cyclase enzyme activity and increase in cyclic adenosine monophosphate (cAMP) production, which is quantified using the cAMP-Glo™ Assay kit (Promega, Madison, WI, USA).

Supplemental Table S1. Criteria for Initiation of Teduglutide Treatment in the Extension Studies

Teduglutide treatment inclusion criteria: ≥1 of the following	
For patients naive to teduglutide	• Inability to significantly reduce PS or advance enteral feeds (eg, ≤10% change in PS or advance in feeds) for the preceding ≥3 months
For patients treated with teduglutide	• Increasing PS requirements after teduglutide discontinuation • Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation • Deteriorating nutritional status (eg, weight loss, growth failure) despite maximal tolerated enteral nutrition after teduglutide discontinuation • Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake after teduglutide discontinuation • Severe diarrhea related to teduglutide discontinuation
Teduglutide treatment exclusion criteria	
For all patients	• Body weight <10 kg at the pretreatment visit • Unresected gastrointestinal polyp, known polyposis condition, premalignant change, or malignancy in the gastrointestinal tract • History of cancer in the previous 5 years (except surgically curative skin cancers) • Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit • Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle • Clinically significant intestinal stricture or obstruction • Clinically significant, active, or recurrent pancreatic or biliary disease • Active, severe, or unstable clinically significant hepatic impairment or injury, including total bilirubin ≥2× ULN and AST or ALT ≥7× ULN at the pretreatment visit • Estimated glomerular filtration rate <50 mL/min/1.73 m^2 at the pretreatment visit • Unstable cardiac disease, congenital heart disease, or cyanotic disease, with the exception of patients who have undergone ventricular or atrial septal defect repair or patent ductus arteriosus ligation • Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, Smoflipid, or teduglutide) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, before the pretreatment visit and for the duration of the 28-week cycle • Treatment with analogues of GLP-1, GLP-2 (not including teduglutide), insulin-like growth factor-1, or growth hormone within 3 months preceding the teduglutide pretreatment visit • Treatment with octreotide or dipeptidyl peptidase 4 inhibitors within 3 months before the pretreatment visit

	• Known or suspected intolerance or hypersensitivity to teduglutide • Known history of alcohol or other substance abuse within 1 year before the pretreatment visit • Pregnant or lactating female patients • Sexually active female patients of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period • Any condition, disease, illness, or circumstance that in the investigator's opinion puts the patient at any undue risk, prevents completion of the study, or interferes with analysis of the study results

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLP, glucagon-like peptide; PS, parenteral support; ULN, upper limit of normal.

Supplemental Table S2. Exposure to Teduglutide

Parameter	N=89
Treatment exposure,* weeks	
Mean (SD)	47.6 (24.59)
Median	51.7
Range	5.0–94.7
Extent of exposure, n (%), weeks	
≤12	9 (10.1)
>12–≤24	16 (18.0)
>24–≤48	11 (12.4)
>48–≤96	53 (59.6)
Total duration of follow-up,† weeks	
Mean (SD)	74.2 (27.48)
Median	83.0
Range	8.3–161.3

*Exposure to teduglutide in the core studies was defined as the time interval from the first dose date to the last dose date; exposure in the extension to the 12-week core study prospective portion and the extension to the 24-week core study was defined as the sum of exposure in all treatment cycles, counting from the first dose date to the last dose date for each cycle.
†Duration of follow-up in core studies and in the extension to the 24-week core study was defined as the time interval from the informed consent date to the last follow-up date or the interim data cutoff date; duration in the extension to the 12-week core study prospective portion was defined as the time interval from the end of the retrospective portion to the last follow-up date or the interim data cutoff date in the prospective portion.

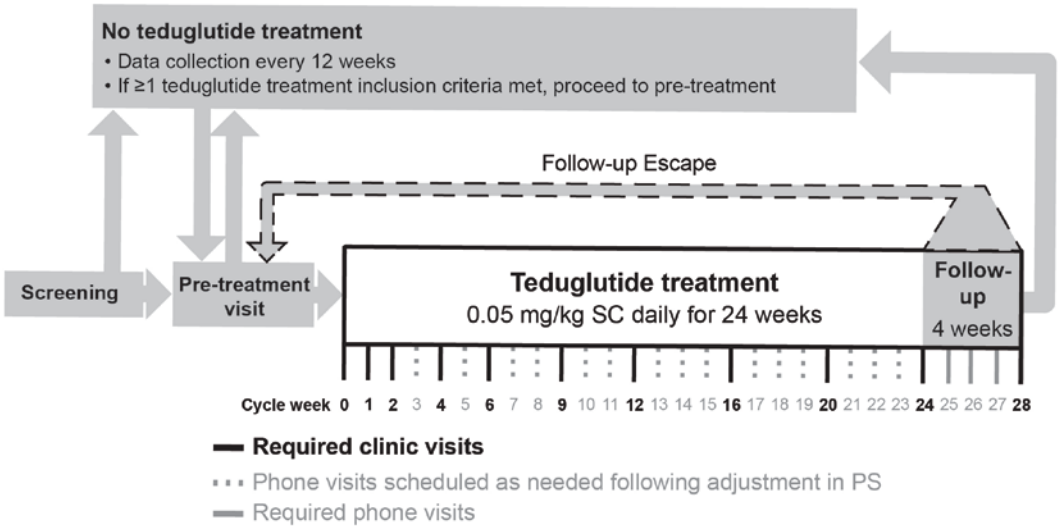
Supplemental Table S3. Abnormal Laboratory Findings

Laboratory Finding	N=89 n (%)
Liver enzymes/liver function	
ALT >8× ULN	12 (13.5)
AST >8× ULN	1 (1.1)
Alkaline phosphatase >5× ULN	1 (1.1)
Direct bilirubin >34.208 µmol/L	1 (1.1)
Bilirubin >3× ULN	1 (1.1)
Kidney function	
BUN >12.495 mmol/L	5 (5.6)
Pancreatic enzymes	
Lipase >3× ULN	12 (13.5)
Amylase >3× ULN	4 (4.5)
CRP ≥100 mg/L	4 (4.5)
Glucose	
High glucose (>13.875 mmol/L; >250.0 mg/dL)	3 (3.4)
Low glucose (<2.22 mmol/L; >40.0 mg/dL)	1 (1.1)
Electrolytes	
High phosphorus (>2.254 mmol/L; >7.0 mg/dL)	6 (6.7)
Low phosphorus (<0.644 mmol/L; <2.0 mg/dL)	2 (2.2)
Low magnesium (<0.4114 mmol/L; <1.0 mg/dL)	2 (2.2)
High potassium (>6.5 mmol/L; (>6.5 mEq/L)	1 (1.1)
Low potassium (<2.5 mmol/L; <2.5 mEq/L)	1 (1.1)
High calcium (>3 mmol/L; >12 mg/dL)	1 (1.1)
High triglycerides (>5.65 mmol/L; >500.0 mg/dL)	1 (1.1)
Hematology	
Leukocytes $<2 \times 10^9$/L	4 (4.5)
Platelet count $<75 \times 10^9$/L	3 (3.4)
Neutrophils $<0.5 \times 10^9$/L	3 (3.4)
Hemoglobin <70 g/L (<7 g/dL)	1 (1.1)

Platelets >700 $\times$ 10^9/L	1 (1.1)
Leukocytes >30 $\times$ 10^9/L	1 (1.1)

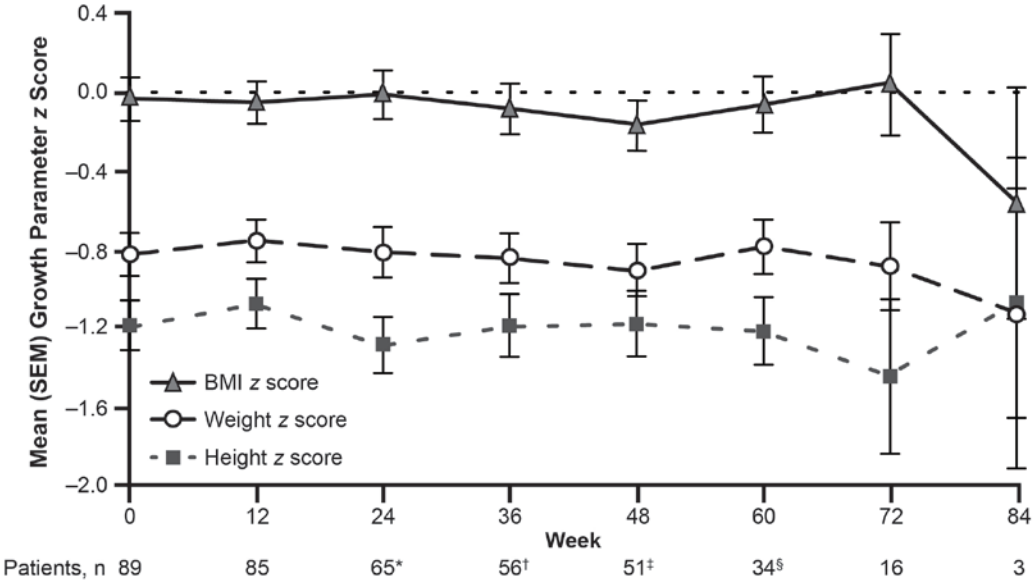
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ULN, upper limit of normal.

Supplemental Figure S1. Design of the extension studies.



PS, parenteral support; SC, subcutaneous

Supplemental Figure S2. Growth Parameters Over Time.



*n=66 for weight *z* score; †n=57 for weight *z* score; ‡n=55 for weight *z* score; §n=36 for weight *z* score.
BMI, body mass index.