Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome—Associated Intestinal Failure: STEPS-3 Study

Douglas L. Seidner, MD, AGAF, FACC, CNSC; Ken Fujioka, MD; Joseph I. Boullata, PharmD, RPh, BCNSP, FASPEN; Kishore Iyer, MBBS, FRCS, FACS; Hak-Myung Lee, PhD, and Thomas R. Ziegler, MD

Abstract

Background: Patients with intestinal failure associated with short bowel syndrome (SBS−IF) require parenteral support (PS) to maintain fluid balance or nutrition. Teduglutide (TED) reduced PS requirements in patients with SBS−IF in the randomized, placebo (PBO)-controlled STEPS study (NCT00798967) and its 2-year, open-label extension, STEPS-2 (NCT00930644). Methods: STEPS-3 (NCT01560403), a 1-year, open-label extension study in patients with SBS−IF who completed STEPS-2, further monitored the safety and efficacy of TED (0.05 mg/kg/day). Baseline was the start of TED treatment, in either STEPS or STEPS-2. At the end of STEPS-3, patients treated with TED in both STEPS and STEPS-2 (TED−TED) received TED for ≤42 months, and patients treated with TED only in STEPS-2 (no TED treatment [NT]/PBO−TED) received TED for ≤36 months. Results: Fourteen patients enrolled (TED−TED, n = 5; NT/PBO−TED, n = 9) and 13 completed STEPS-3. At the last dosing visit, mean (SD) PS was reduced from baseline by 9.8 (14.4 [50%]) and 3.9 (2.8 [48%]) L/week in TED−TED and NT/PBO−TED, respectively. Mean (SD) PS infusions decreased by 3.0 (4.6) and 2.1 (2.2) days per week from baseline in TED−TED and NT/PBO−TED, respectively. Two patients achieved PS independence; 2 additional patients who achieved independence in STEPS-2 maintained enteral autonomy throughout STEPS-3. All patients reported ≥1 treatment-emergent adverse event (TEAE); 3 patients had TEAEs that were reported as treatment related. No patient had a treatment-related treatment-emergent serious AE. Conclusions: Long-term TED treatment yielded a safety profile consistent with previous studies, sustained efficacy, and a further decline in PS requirements. (Nutr Clin Pract. 2018;33:520–527)

Keywords
glucagon-like peptide-2; intestinal failure; parenteral nutrition; short bowel syndrome; teduglutide

In adults, intestinal failure associated with short bowel syndrome (SBS−IF) is an uncommon but life-altering condition that occurs as a consequence of surgical resection or disease with or without partial or complete colonic resection, typically in patients with inflammatory bowel disease, intestinal obstruction, ischemic events, fistula resection, or malignancy. As a result of reduction in residual small-bowel length and absorptive function, patients with SBS−IF experience generalized protein-energy malnutrition, dehydration, and micronutrient depletion due to a loss in intestinal absorptive capacity and often require long-term parenteral support (PS) in the form of parenteral nutrition and/or intravenous hydration, depending on the extent of bowel resection and the presence of colon-in-continuity. Patients with SBS−IF require PS to maintain hydration and nutrition status, including energy, protein sources (amino acids), vitamins, trace elements, and electrolytes.

Although PS provides vital fluid and nutrient support for patients with SBS−IF, this therapeutic approach is associated with potentially serious or life-threatening complications (eg, risk for catheter-related infection and liver failure). Patients with SBS−IF also have impaired health-related quality of life characterized by feelings of social isolation, a disruption of activities of daily living, and gastrointestinal (GI) symptoms (eg, diarrhea, abdominal pain). Teduglutide (TED) is a synthetic analog of endogenous glucagon-like peptide-2, which is synthesized in the ileum and colon of healthy individuals. Subcutaneous TED administration promotes intestinal adaptation, enhances intestinal absorptive capacity, and enables reduction of PS in patients with SBS−IF. TED is approved in the United States (adults) and Europe (adults and children aged ≥1 year) for the treatment of patients...
who are PS dependent. In the pivotal, phase III, 24 week, multinational, placebo (PBO)-controlled STEPS study (NCT00798967; EudraCT: 2008-006193-15), the primary study endpoint (≥20% reduction in PS volume at Week 20 that was maintained at Week 24) was met in 63% of adult patients treated with subcutaneous TED 0.05 mg/kg/day compared with 30% of patients treated with PBO (P < 0.01). In the open-label, 2-year, multinational extension study (STEPS-2; NCT00930644; EudraCT: 2009-011679-65), treatment with subcutaneous TED 0.05 mg/kg/day for ≥24 months was well tolerated and resulted in additional reductions in weekly PS volume and number of days of PS infusions per week while maintaining patients’ nutrition status. The objective of STEPS-3 (NCT01560403) was to further assess the long-term safety and efficacy of TED in patients with SBS–IF who had completed the STEPS-2 study.

Methods

Study Design and Population

STEPS-3 was an additional 1-year, open-label extension of the STEPS-2 open-label TED extension study, designed primarily to assess the long-term safety of TED in patients with SBS–IF. In addition, efficacy outcome data using measures from the original STEPS study were collected. STEPS-3 was conducted in the United States, and 5 of the 7 STEPS-2 study sites participated (ie, of the 88 patients who participated in STEPS-2, 24 patients came from the United States [7 sites; 18 patients] and Canada [3 sites; 6 patients]); the majority were from Europe (7 countries; 64 patients). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation and Good Clinical Practice, and the study protocol was approved by institutional review boards.

Eligible adult participants in STEPS-3 had completed 24 months of TED treatment in STEPS-2, regardless of whether they had been weaned from PS, and they had provided written informed consent before the initiation of study-related procedures. All patients received TED 0.05 mg/kg/day by subcutaneous injection.

The STEPS-3 study population was stratified into 2 subgroups for the purpose of data analysis, depending on length of TED treatment (Figure 1). The TED–TED subgroup was composed of patients who received TED in the initial PBO-controlled trial (STEPS) and in the open-label STEPS-2 study. The no teduglutide treatment (NT)/PBO–TED subgroup included patients who received NT (entered STEPS-2 directly) or PBO in the initial PBO-controlled trial (STEPS) and TED in STEPS-2. Compliance with the dosing regimen, a prespecified endpoint, was monitored by counting used and unused vials of study drug on return patient visits and was considered to have been achieved if ≥80% of planned doses were administered (ie, [vials dispensed–vials returned intact]/days on treatment). Baseline demographics, patient characteristics, and efficacy parameters were based on the intent-to-treat (ITT) population. Baseline for the parameters assessed in STEPS-3 was defined as the start of TED treatment in the STEPS study for patients in TED–TED or the start of TED treatment in STEPS-2 for patients in the NT/PBO–TED subgroup (Figure 1). As such, observations collected for the patients who received PBO in the initial STEPS trial were not included in the analysis of the NT/PBO–TED subgroup. The safety analysis population included all patients who

From the 1Vanderbilt University Medical Center, Nashville, TN, USA; 2Scripps Clinic, La Jolla, CA, USA; 3Hospital of the University of Pennsylvania and Drexel University, Philadelphia, PA, USA; 4Mount Sinai Medical Center, New York, NY, USA; 5Shire Human Genetic Therapies, Inc., Lexington, MA, USA; and 6Emory University School of Medicine, Atlanta, GA, USA.

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Conflicts of interest: D.L. Seidner received research support from and served as a study investigator, consultant, and advisory board member for NPS Pharmaceuticals, Inc., and as a consultant for Shire; K. Fujioka served as a consultant and study investigator for NPS Pharmaceuticals, Inc., and as a speaker for Shire; J.I. Boullata served as a study investigator and advisory board member for NPS Pharmaceuticals, Inc.; K. Iyer served as a consultant, study investigator, and advisory board member for and received research support from NPS Pharmaceuticals, Inc., and has served as a consultant for Shire; H.-M. Lee is an employee of Shire; and T.R. Ziegler served as a study investigator for NPS Pharmaceuticals, Inc.

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Corresponding Author:
Douglas L. Seidner, MD, AGAF, FACG, CNSC, Vanderbilt University Medical Center, 1211 21st Avenue South, Ste 514 MAB, Nashville, TN 37232-2713, USA.
Email: douglas.seidner@vanderbilt.edu

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Figure 1. Flow diagram of patients across the STEPS studies. NT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2. TED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2. *Patients who completed fluid optimization and stabilization but were not randomized in STEPS because of full study enrollment were eligible for direct enrollment into STEPS-2. NT, no teduglutide treatment; PBO, placebo; TED, teduglutide.

received ≥1 dose of study drug in this extension study and was identical to the ITT population.

**Efficacy and Safety Measures**

Study visits were conducted every 3 months. Prespecified efficacy parameters included absolute and relative change from baseline in actual PS volume received, reduction in days of PS infusions per week, and number of patients who achieved independence from PS in the STEPS-3 study. Prespecified safety parameters included duration of exposure to TED; incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs); physical examinations; vital signs; electrocardiogram results; colonoscopy evaluations; clinical laboratory testing (including serum chemistries for liver and kidney biochemical values, pancreatic enzymes, and electrolytes); and assessment of TED-specific antibody formation. Body weight and body mass index (BMI) were determined as post hoc analyses because of a data correction to 1 patient’s weight. Electrocardiograms and colonoscopies were performed at the first and final study visits; all other safety parameters were assessed at every study visit.

**Data Analysis**

Descriptive statistics were used to summarize the baseline and demographic characteristics, efficacy endpoints, and TEAEs; the study was not designed or sufficiently powered to determine the statistical significance of safety or efficacy endpoints.

**Results**

Of the 14 patients who completed treatment with TED in STEPS-2 and enrolled in STEPS-3 (ITT population), 13 patients completed the study (ie, were receiving TED at the time the study concluded). One patient was lost to follow-up after being treated with TED for 8 months; however, available data from this patient were included in the analysis. The confluence of the rolling start dates and the study end date meant that all patients did not receive 12 months of TED treatment. The mean (SD) duration of exposure to TED during STEPS-3 was 38.9 (9.8) weeks for the overall population, 41.5 (8.4) weeks for NT/PBO–TED, and 34.3 (11.3) weeks for TED–TED. Combined with the TED treatment in the STEPS-2 study, the total TED exposure time was ≤36 months for NT/PBO–TED and ≤42 months for TED–TED. Of the 14 patients enrolled in STEPS-3, 8 (57%) received ≥80% of the planned dose: 67% (n = 6/9) in the NT/PBO–TED and 40% (n = 2/5) in the TED–TED subgroups. Patient demographics and baseline characteristics are summarized in Table 1.

**Efficacy**

At baseline, the mean (SD) PS volume requirements were 13.4 (11.6) and 10.5 (7.5) L/week for patients in the TED–TED and NT/PBO–TED subgroups, respectively. From study baseline to the final dosing visit, mean (SD) total PS volume was reduced during the STEPS-3 study period by 9.8 (14.4) and 3.9 (2.8) L/week for patients in the TED–TED and NT/PBO–TED subgroups, respectively. The mean (SD) percentage reduction from baseline in PS volume was 49.7% (72.4%) for the TED–TED subgroup and 47.8% (42.9%) for the NT/PBO–TED subgroup. In addition, patients in the TED–TED subgroup compared with the NT/PBO–TED subgroup exhibited greater reductions in actual mean PS volume at all visits (Figure 2). In addition to the mean volume reduction with time during STEPS-3 compared with baseline, patients reduced the frequency of required PS infusions. For patients in the TED–TED subgroup, the reduction from baseline in mean (SD) days per week receiving PS at the last dosing study visit in this extension study was 3.0 (4.6) days. Patients in the NT/PBO–TED subgroup had a reduction of 2.1 (2.2) days per week receiving PS. Eight of 14 patients had a ≥1-day reduction in PS, and 6 of 14 patients had a ≥3-day reduction. At the completion of the STEP-3 study,
Table 1. Demographics and Baseline Characteristics.

| Characteristic                        | NT/PBO–TED\(^a\) (n = 9) | TED–TED\(^b\) (n = 5) | All Patients (n = 14) |
|---------------------------------------|---------------------------|------------------------|----------------------|
| Mean (SD) age, \(c\) years            |                           |                        |                      |
| \(<45\) years                         | 55.9 (12.2)               | 55.8 (10.7)            | 55.9 (11.3)          |
| \(45–<65\) years                      | 6 (67)                    | 3 (60)                 | 9 (64)               |
| \(\geq65\) years                      | 1 (11)                    | 1 (20)                 | 2 (14)               |
| Women, n (%)                          | 6 (67)                    | 4 (80)                 | 10 (71)              |
| Race, n (%)                           |                           |                        |                      |
| White                                 | 7 (78)                    | 5 (100)                | 12 (86)              |
| Black                                 | 2 (22)                    | 0                      | 2 (14)               |
| Ethnicity, n (%)                      |                           |                        |                      |
| Not Hispanic or Latino                | 9 (100)                   | 5 (100)                | 14 (100)             |
| Mean (SD) body weight, kg             | 68.5 (14.2)               | 58.4 (14.2)            | 64.9 (14.5)          |
| Mean (SD) BMI, kg/m\(^2\)             | 24.4 (4.2)                | 21.8 (3.2)             | 23.5 (3.9)           |
| Reason for resection, n (%)           |                           |                        |                      |
| Vascular disease                      | 1 (11)                    | 3 (60)                 | 4 (29)               |
| Crohn's disease                       | 2 (22)                    | 0                      | 2 (14)               |
| Injury                                | 1 (11)                    | 1 (20)                 | 2 (14)               |
| Volvulus                              | 1 (11)                    | 0                      | 1 (7)                |
| Cancer                                | 0                         | 0                      | 0                    |
| Other                                 | 4 (44)                    | 1 (20)                 | 5 (36)               |
| Colon remaining, n (%)                | 7 (78)                    | 3 (60)                 | 10 (71)              |
| Colon-in-continuity, n (%)            | 5 (56)                    | 3 (60)                 | 8 (57)               |
| Mean (SD) percentage of colon remaining\(^d\) | 52.6 (39.9)             | 50.0 (0.0)             | 51.8 (32.6)          |
| Median (range) estimated remaining small intestine,\(^c\) cm | 55 (17–100)               | 76 (30–190)            | 66 (17–190)          |
| Stoma, n (%)                          | 2 (22)                    | 3 (60)                 | 5 (36)               |
| Mean (SD) time since start of PS dependence, years | 6.5 (9.1)               | 5.0 (3.5)              | 6.0 (7.4)            |

BMI, body mass index; NT, no teduglutide treatment; PBO, placebo; PS, parenteral support (parenteral nutrition and/or intravenous hydration); TED, teduglutide.

\(^a\)NT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2.

\(^b\)TED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2.

\(^c\)Age at informed consent in initial PBO-controlled trial (STEPS).

\(^d\)Includes only patients with a colon (NT/PBO–TED, n = 7; TED–TED, n = 3; all patients, n = 10).

\(^e\)Includes only patients with known residual small intestine length (NT/PBO–TED, n = 7; TED–TED, n = 5; all patients, n = 12).

4 patients were independent from PS. Two female patients (aged 43 and 41 years) with no stoma, colon-in-continuity, and baseline PS volumes of 4.5 and 4.7 L/week achieved enteral autonomy after 126 and 130 weeks, respectively, with TED treatment. The other 2 patients had achieved independence from PS during the STEPS-2 study and maintained long-term enteral autonomy in STEPS-3. These 2 patients were women (aged 61 and 60 years) with no stoma and baseline PS volumes of 4.1 and 6.3 L/week, respectively.

**Safety**

TED-specific antibody-positive samples were reported in 3 of 14 patients (21%), all of whom were in the NT/PBO–TED subgroup. In 1 of these patients, neutralizing antibodies specific for TED were detected at the first visit in STEPS-3, but the Month 3 visit sample was negative for such antibodies. Subsequent sample results collected at Months 6 and 9 did not detect neutralizing TED antibodies.

TEAEs were reported by 100% of patients; most were mild to moderate in severity and none led to study discontinuation. There were no deaths during the study. There were no reports of pancreatic-related events or GI stenosis/obstruction in this extension study. Among the overall study population, the most common TEAEs were asthenic conditions (an adverse event [AE] grouping consisting of medically similar terms including asthenia, decreased activity, fatigue, and lethargy) and diarrhea (Table 2). Five patients (36%) reported ≥1 TESAE during the study. None of the 14 TESAEs reported were considered by the study investigators to be related to treatment with TED (Table S1). There were no electrocardiogram abnormalities reported as a TEAE or TESAE. There was 1 reported
Table 2. Treatment-Emergent Adverse Events Reported in ≥2 Patients Sorted by Incidence in Overall Population.

| Adverse Event Group or Preferred Term | NT/PBO–TEDa (n = 9) | TED–TEDb (n = 5) |
|--------------------------------------|---------------------|-----------------|
| Asthenic conditions                  | 2 (22), 2           | 1 (20), 1       |
| Diarrhea                             | 1 (11), 1           | 2 (40), 3       |
| Abdominal pain                       | 2 (22), 2           | 0               |
| Benign neoplasms gastrointestinal    | 2 (22), 2           | 0               |
| Catheter sepsis                      | 0                   | 2 (40), 2       |
| Cognition and attention disorders and disturbances | 2 (22), 3 | 0 |
| Dyspnea                              | 0                   | 2 (40), 2       |
| Hypersensitivity                     | 2 (22), 2           | 0               |
| Viral infection                      | 2 (22), 2           | 0               |
| Weight decreased                     | 0                   | 2 (40), 3       |

NT, no teduglutide treatment; PBO, placebo; TED, teduglutide.

aNT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2.

bTED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2.

Patients maintained their nutrition status, as demonstrated by the lack of substantial changes in mean (SD) body weight (TED–TED, −3.0 [6.7] kg; NT/PBO–TED, −0.9 [4.6] kg) or BMI (TED–TED, −1.0 [2.4] kg/m²; NT/PBO–TED, −0.3 [1.6] kg/m²) at the last dosing visit compared with baseline (Table S2). In addition, patients exhibited stable electrolyte levels (ie, calcium, magnesium, and phosphate), as reflected in the absence of meaningful changes from baseline at the end of study visit.

One patient in the NT/PBO–TED subgroup reported an elevation in serum creatinine levels (126 μmol/L; NT/PBO–TED, −3.4 [12.7] μmol/L), serum sodium (TED–TED, −1.6 [7.3] mmol/L; NT/PBO–TED, 0.6 [3.0] mmol/L), or urine sodium (TED–TED, 56.2 [43.2] mmol/L; NT/PBO–TED, −22.3 [64.8] mmol/L) in patients at the end of study visit compared with baseline. One patient in the NT/PBO–TED subgroup reported an elevation in serum creatinine levels (126 μmol/L; upper limit of normal, 115 μmol/L) that returned to 116 μmol/L by the 6 month visit and remained within normal limits through the end of study visit; this event was considered to be unrelated to treatment by the site investigator. Stable serum albumin levels were maintained in all patients, and mean decreases in serum concentrations of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were reported in all patients at the end of study visit compared with baseline.

Serious cardiac AE in a patient with bilateral pneumonia and acute congestive heart failure; the events were deemed by the investigator to be unrelated to treatment with TED.

Colonoscopy procedures were scheduled at the first STEPS-3 study baseline visit (ie, the end of STEPS-2) and at the end of STEPS-3 study visit (ie, Month 12 or early termination). Per the study protocol, polyps were removed at the baseline study visit before the patient could continue in the STEPS-3 extension study. Four of the 10 patients with remnant colon had colonoscopies at both the first visit and the end-of-study visit. Of these 4 patients, 1 patient had hyperplastic colon polyps at the first study visit and colon polyps at the final study visit (no additional histology reported), and 1 patient had a tubular adenoma at the final study visit only (normal baseline colonoscopy). Three of the 10 patients with remnant colon had only the first visit colonoscopy; 1 patient had cecal polyps with histology of tubular adenoma. The remaining 3 of 10 patients with remnant colon had only a single, unscheduled visit colonoscopy; 1 of these patients was initially evaluated for possible polyps, but follow-up histology showed that no polyp was present. Collectively, of the 10 patients with remnant colon, 3 patients had adenoma or polyps based on the colonoscopy and/or histology evaluations.
Table 3. Change in Serum Albumin Level and Liver Enzymes From Baseline to Last Dosing Study Visit.

| Liver Function Tests/Liver Enzymes | NT/PBO–TED\(^a\) (n = 9) | TED–TED\(^b\) (n = 5) |
|-----------------------------------|--------------------------|----------------------|
| Serum albumin level (normal range, 32–50 g/L) |                          |                      |
| Baseline, g/L, mean (SD)          | 39.1 (3.2)               | 41.4 (4.3)           |
| Change from baseline, g/L, mean (SD) | 0.7 (3.2)               | −2.8 (3.6)           |
| > 10% increase from baseline at EOT, n (%) | 1 (11)                  | 0                    |
| > 10% decrease from baseline at EOT, n (%) | 1 (11)                  | 1 (20)               |
| Alkaline phosphatase (normal range, 37–147 U/L) |                          |                      |
| Baseline, U/L, mean (SD)          | 124.8 (50.1)             | 130.4 (50.8)         |
| Change from baseline, U/L, mean (SD) | −18.7 (25.7)            | −17.0 (39.9)         |
| > 10% increase from baseline at EOT, n (%) | 0                      | 1 (20)               |
| > 10% decrease from baseline at EOT, n (%) | 4 (44)                  | 2 (40)               |
| ALT (normal range, 0–55 U/L)      |                          |                      |
| Baseline, U/L, mean (SD)          | 34.7 (22.6)              | 24.8 (4.9)           |
| Change from baseline, U/L, mean (SD) | −22 (6.6)               | −14.1 (8.1)          |
| > 10% increase from baseline at EOT, n (%) | 3 (33)                  | 2 (40)               |
| > 10% decrease from baseline at EOT, n (%) | 6 (67)                  | 2 (40)               |
| AST (normal range, 0–45 U/L)      |                          |                      |
| Baseline, U/L, mean (SD)          | 31.0 (10.8)              | 25.4 (5.6)           |
| Change from baseline, U/L, mean (SD) | −2.2 (6.6)              | −1.4 (8.1)           |
| > 10% increase from baseline at EOT, n (%) | 2 (22)                  | 1 (20)               |
| > 10% decrease from baseline at EOT, n (%) | 5 (56)                  | 2 (40)               |
| Bilirubin (normal range, 5.1–25.7 \(\mu\)mol/L) |                          |                      |
| Baseline, \(\mu\)mol/L, mean (SD) | 8.7 (7.5)                | 8.5 (4.0)            |
| Change from baseline, \(\mu\)mol/L, mean (SD) | −2.5 (6.2)              | −3.4 (4.4)           |
| > 10% increase from baseline at EOT, n (%) | 1 (11)                  | 0                    |
| > 10% decrease from baseline at EOT, n (%) | 4 (44)                  | 3 (60)               |
| GGT (normal range, 0–30 U/L)      |                          |                      |
| Baseline, U/L, mean (SD)          | 79.0 (56.1)              | 57.8 (82.4)          |
| Change from baseline, U/L, mean (SD) | −9.9 (26.7)             | −4.4 (11.7)          |
| > 10% increase from baseline at EOT, n (%) | 3 (33)                  | 1 (20)               |
| > 10% decrease from baseline at EOT, n (%) | 5 (56)                  | 3 (60)               |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; GGT, \(\gamma\)-glutamyl transferase; NT, no teduglutide treatment; PBO, placebo; TED, teduglutide.

\(^a\)NT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2.

\(^b\)TED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2.

but 2 patients at the end of study visit compared with baseline (Table 3). Furthermore, for each liver enzyme measured, more patients experienced a > 10% decrease between baseline and end of treatment than experienced a > 10% increase in these measures (Table 3).

Two patients had mild hepatobiliary-related laboratory findings reported at baseline that continued throughout the study. The increases in ALT and \(\gamma\)-glutamyl transferase (GGT) reported in these 2 patients were not deemed to be clinically significant and were not considered by the site investigator to be related to treatment with TED. During the study, increased serum lipase concentrations (> 3 times upper limit of normal) were reported in 3 patients, and increased serum amylase concentrations (≥ 350 U/L) were reported in 1 patient, without reported clinical evidence of pancreatitis. An additional patient had decreased amylase levels (≤ 15 U/L) postbaseline.

**Discussion**

The findings from the open-label STEPS-3 extension study provide general support for the safety, tolerability, and clinical utility of TED in the treatment of adults with SBS–IF for ≥ 36 months.

The safety data in patients with extended exposure to TED indicated that the drug was well tolerated, and data were in line with the expectations based on previous studies. No indication of new adverse safety signals emerged in the STEPS-3 long-term extension study. The development of anti-TED-specific antibodies was reported in some patients, but this finding had no apparent effect on the efficacy of TED, as determined by PS adjustments during the course of this study among these individuals. Although the intestinotrophic properties of TED may account for the favorable effects of intestinal adaptation observed in
patients with SBS,12 the development of GI polyps is a previously identified safety concern.8,11 In this small open-label, 1-year STEPS-3 study, 10 patients had remnant colon and underwent colonoscopy procedures. In total, 3 patients were reported to have polyps at either the first study visit and/or the final study visit, 2 of whom had histologically confirmed adenoma. In the preceding open-label, 2-year STEPS-2 study, 9 patients had reported polyps with no case of overt malignancy related to polyps reported, 5 of whom had histologically confirmed adenoma.11,13 Collectively, when the overlap in the STEPS-2 final visit and the STEPS-3 baseline visit is considered, 10 patients were reported to have polyps throughout the STEPS study series. Together, these colonoscopy results support the safety-related recommendation in the U.S. and European prescribing information stating that patients receiving TED have regular colonoscopy for signs of neoplastic growth.9,10

The ongoing global registry study for patients with SBS (ClinicalTrials.gov identifier: NCT01990040) will provide needed data regarding the incidence of colorectal polyps in the SBS population overall, as well as among patients treated with TED, during a follow-up period of at least 10 years. Any available results from routine colonoscopies will be captured as part of the clinical outcomes data collection registry, and may permit a more comprehensive analysis of the potential risk of polyp formation associated specifically with TED therapy.

Patients maintained and improved nutrition status in the presence of PS volume reductions, as evidenced by the reported vital signs and chemistry laboratory tests during the course of the study. Although 2 patients experienced episodes of decreased body weight that were reported as TEAEs, these episodes appeared to be transient; mean body weight and BMI remained relatively stable during the course of the study. Furthermore, electrolyte levels remained steady or improved during the course of the study, and mean serum kidney biochemical values generally remained stable between baseline and the end of the study. In addition, mean serum albumin levels were relatively unchanged at the end of the study compared with baseline, indicating that stable nutrition status was maintained during the course of the study.14,15 It is notable that stable or improved nutrition status found in this 1-year extension study is similar to that reported in the previous 2-year STEPS-2 study,11 further supporting the conclusion that extended exposure to TED is well tolerated.

Long-term PS is associated with increased risk of liver damage, and advanced liver disease has been reported in 0%–50% of patients receiving chronic PS; the greatest risk is in patients with ultrashort bowel (<50 cm).16,17 During the preceding STEPS-2 study, serum concentrations of liver enzymes either declined or remained stable during 2.0–2.5 years of TED treatment in the study group as a whole. In the subgroup of patients who experienced ≥50% reductions in PS volume, liver enzymes decreased by a mean of 6%–44% from baseline values.11 The improvement in liver biochemical values seen in STEPS-2 continued in this study, with mean decreases from baseline in ALP, ALT, AST, GGT, and bilirubin levels observed at the end of treatment. In addition, for each liver enzyme measured, more patients experienced >10% decreases from baseline than experienced >10% increases from baseline at end of treatment. Together, the results of this study support previous findings indicating that in patients receiving TED, chronic PS can be reduced with corresponding improvements in liver function.

TED has been shown to enhance intestinal absorption in patients with SBS—IF.18 Therefore, it is important that patients who achieve improvements in intestinal fluid absorption during treatment with TED also achieve balanced reductions in the need for PS to minimize the risk for fluid overload. In this study, long-term treatment with TED for ≤42 months was associated with sustained efficacy and a further decline in PS requirements in patients with SBS—IF. It is also noteworthy that some patients who achieved PS autonomy in STEPS-2 maintained such independence with continuous long-term TED in STEPS-3. However, the finding that other patients reached enteral autonomy for the first time after approximately 2 years of treatment with TED in STEPS-3 suggests that some patients may need longer exposure to TED to achieve PS independence.

Limitations of the study include the open-label design and lack of a control arm; additionally, our study population was a small selected cohort that met inclusion requirements for longer-term follow-up. This extension study, undertaken at the end of the clinical development program for drug approval, had a study design and a data analysis plan that was descriptive and was not intended to be sufficiently powered for statistical significance analysis. Even with this limitation, this type of study design can provide important information on outcomes, and as reported here for the STEPS-3 data, observed results that were in line with those of previous studies.8,11 These factors may limit the applicability of the current findings to patients in the real-world clinical setting with a broader range of disease and clinical characteristics and require further study. Although the ongoing global registry study will add valuable real-world experience in broader populations of patients with SBS, this small extension study provides additional new data that long-term treatment with TED has a safety profile similar to that reported in previous studies and supports the overall conclusion that TED is well tolerated. However, the ideal time for response was not determined and may, in fact, be undeterminable because, as this study shows, PS reductions can be further enhanced with continuous treatment.
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Statement of Authorship
D. L. Seidner, K. Fujioka, J. I. Boullata, K. Iyer, and T. R. Ziegler contributed to the conception and design of the research; D. L. Seidner, K. Fujioka, J. I. Boullata, K. Iyer, and T. R. Ziegler contributed to the acquisition, analysis, and interpretation of the data; H.-M. Lee contributed to the analysis and interpretation of data; D. L. Seidner, K. Fujioka, J. I. Boullata, K. Iyer, H.-M. Lee, and T. R. Ziegler drafted the manuscript; D. L. Seidner, K. Fujioka, J. I. Boullata, K. Iyer, H.-M. Lee, and T. R. Ziegler critically revised the manuscript; D. L. Seidner, K. Fujioka, J. I. Boullata, K. Iyer, H.-M. Lee, and T. R. Ziegler agree to be fully accountable for ensuring the integrity and accuracy of the work; and all authors read and approved the final manuscript.

Supplementary Information
Additional supporting information may be found online in the supporting information tab for this article.

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