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Teduglutide for Safe Reduction of Parenteral Nutrient and/or Fluid Requirements in Adults: A Systematic Review

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Abstract

Background: Teduglutide (Gattex; NPS Pharma, Bedminster, NJ), a recombinant analogue of human glucagon-like peptide 2 (GLP-2), is the first long-term medical therapy approved for the treatment of adults dependent on parenteral nutrition (PN). *Objective*: To assess the efficacy and safety of teduglutide in reducing PN (parenteral nutrient and/or fluid) requirements in PN-dependent adults. *Methods*: Studies were identified using predefined search criteria and multiple databases, including Medline and Embase. The search was completed to November 30, 2014, in the absence of date or study design restrictions. Citation inclusion criteria and methodological quality were assessed by 2 independent reviewers. Outcomes of interest were changes in parenteral nutrient or fluid requirements and adverse event incidence. From 2693 unique citations, 76 abstracts were reviewed. Fourteen reports met the inclusion criteria, including data from 2 phase III, double-blind, placebo-controlled clinical trials and their respective extension studies. Data extraction was performed by 2 reviewers using a standardized form. *Results*: Teduglutide reduced PN requirements compared with placebo, whereas adverse event incidence was similar. *Limitations*: Number of subjects studied and length of follow-up. *Conclusions*: Teduglutide appears to be a safe and well-tolerated means to reduce PN dependence in adults, regardless of PN dependence duration. (*JPEN J Parenter Enteral Nutr*. XXXX;xx:xx-xx)

Keywords

teduglutide; parenteral nutrition; systematic review; intestinal failure

Clinical Relevancy Statement

Patients with intestinal failure (IF) are dependent on parenteral nutrition (PN) for nutrients and/or fluid, and prolonged PN dependence is associated with decreased quality of life and numerous complications. Teduglutide is the first long-term pharmacologic treatment indicated for adult patients with short bowel syndrome who are dependent on parenteral support. This systematic review demonstrates that teduglutide is efficacious for minimizing PN dependence in adults regardless of PN dependence duration, with a therapeutic gain assessed from 32.6%–39.4% compared with placebo in reducing PN volume requirements by ≥20%. Furthermore, longer teduglutide treatment duration is associated with increased clinical gains, and adverse event incidence on teduglutide is similar to that observed with placebo and is consistent with underlying IF.

Introduction

Intestinal failure (IF), caused by disease, congenital defect, or surgical resection, is characterized by the inability to maintain protein, energy, fluid, electrolyte, or micronutrient balance.[1] Parenteral nutrition (PN) is often required in IF to maintain body weight as well as fluid, nutrient, and electrolyte balance. While life-saving, long-term or permanent dependence on PN is associated with decreased quality of life[1–7] and numerous complications, including catheter-related bloodstream infections and sepsis, which are the primary cause of morbidity and hospital readmission in these patients.[8] The risk of PN-related mortality rises with increasing PN dependence duration,[9] but with proper care, PN complications are rarely lethal,[10,11] and most deaths of patients receiving long-term PN are attributable to the underlying disease rather than to the administration of PN.[12]

The goal of IF treatment is to promote enteral autonomy by maximizing the functional capacity of the remnant intestine, which is capable of increasing its absorptive capacity through mucosal surface area expansion and enhancement of absorptive efficiency per unit surface area.[13–16] Capacity for this functional adaptation is maximal in the first 2 years following intestinal failure onset,[17] and if enteral autonomy is not achieved during this

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period, the likelihood of permanent IF and PN dependence is 95%.[18,19] However, enteral autonomy can be achieved beyond this initial 2-year period if effective long-term strategies are employed to maximize intestinal adaptation following resection.[20,21]

Adaptation of the remnant intestine can be stimulated through a variety of interventions, including both dietary and pharmacologic strategies.[22] Until recently, pharmacological treatments have focused largely on antisecretory, antimotility, and antidiarrheal medications. One promising pharmacologic intervention is the provision of exogenous glucagon-like peptide 2 (GLP-2). GLP-2 is a 33–amino acid peptide secreted from the enteroendocrine L cells of the distal intestine in response to luminal nutrients. First reported to stimulate enterocyte proliferation in 1996,[23] GLP-2 has gained widespread support as an intestinotrophic mediator capable of increasing absorptive surface area, preventing mucosal atrophy, and increasing DNA, RNA, and protein concentrations in intestinal cells of animals sustained on PN.[24–26] Furthermore, GLP-2 enhances nutrient and fluid absorption,[27] increases intestinal barrier function,[28] and inhibits gastric emptying and stimulates intestinal blood flow.[29–31] In a proof-of-concept study, GLP-2 increased intestinal wet weight absorption and decreased diarrhea in patients with short bowel syndrome (SBS).[32]

GLP-2 has demonstrated consistent therapeutic promise for IF treatment. However, the half-life of GLP-2 is extremely short due to rapid degradation by dipeptidyl peptidase IV. Thus, teduglutide, a GLP-2 analogue that substitutes glycine for alanine in the second N-terminus position, was created, which extends the half-life from 7 minutes to 1.3–2 hours.[33–35] The US Food and Drug Administration (FDA) granted teduglutide orphan drug designation in 2000 and approved it for marketing for treatment of PN-dependent adult patients with SBS in December 2012.[35] Teduglutide has also been approved for marketing in Europe under the trade name Revestive.[36]

Given the complications and decreased quality of life associated with prolonged PN dependence, the potential for duplicate publication bias, and that extension study data are only yet available in abstract form, which may change substantially or never reach publication, the objective of this systematic review is 2-fold: (1) to distill the available data on teduglutide safety and efficacy in reducing PN requirements to original results and (2) to measure the impact of teduglutide via calculation of summary measures, including the number needed to treat to benefit (NNTB) or harm (NNTH), the odds ratio (OR), and therapeutic gain so that treatment decisions can be evidence based and well informed, taking into consideration both benefits and potential harms of teduglutide treatment.

Methods

This study was conducted according to the procedures outlined by the Cochrane Collaboration for systematic reviews[37] to assess the safety and efficacy of teduglutide in reducing PN requirements in PN-dependent adults. A standard protocol for study identification, inclusion, and data abstraction was developed and followed after establishment of the following study (population, intervention, comparison, and outcome [PICO]) question: "In PN-dependent adult humans, would adding teduglutide to standard intestinal rehabilitation therapies safely result in reduced PN requirements when compared with standard intestinal rehabilitation therapies alone?" These standard rehabilitation strategies include individualized treatments based on patients' residual anatomy and SBS status and may include optimization of PN and/or conventional medications such as antisecretory agents or antidiarrheals.

Multiple databases (Suppl. Table S1), clinical trial and adverse event registries, and pharmaceutical industry databases were searched from database inception through November 30, 2014, in the absence of date or study design restrictions using the following search terms: *alx-0600, gattex, gly(2)-GLP-2, (gly2)GLP-2, revestive*, and *teduglutide*. Results were restricted to English-language studies that enrolled PN-dependent adult humans and employed teduglutide, alone or in combination with additional therapies, to investigate the efficacy and/or safety of teduglutide in reducing PN requirements. References from identified citations were cross-referenced for completeness. The outcomes of interest were changes in PN requirements and adverse event (AE) incidence. No restrictions were applied to the ways in which changes in PN requirements were expressed in study results. Hits were assessed for inclusion criteria and methodological quality by the 2 authors, including multiples domains of selection, performance, detection, attrition, reporting, and other biases. In the event where a risk of bias was unclear, attempts were made to clarify by contacting the senior study authors. Methodological quality of studies was graded per the Cochrane Collaboration, and discrepancies in trial bias assessments between reviewers were resolved by consensus. A data extraction form was developed and piloted jointly by the authors using a representative sample of the studies to be reviewed, after which both authors performed data extraction. Qualitative data synthesis, rather than meta-analysis, was performed due to variations in length, timing, and dosing strategies of the included trials. Summary statistics, including NNTB (NNTB = 1/[teduglutide responder rate – placebo responder rate], rounded up to the next whole number), NNTH (NNTH = 1/[teduglutide event rate – placebo event rate], rounded up to the next whole number), OR (OR = [number of teduglutide-treated subjects experiencing event/number of event-free teduglutide treated subjects]/[number of placebo-treated subjects experiencing event/number of event-free placebo-treated subjects]), and therapeutic gain (teduglutide responder rate – placebo responder rate), were calculated as described by The Cochrane Collaboration[37] to directly compare the safety and clinical efficacy of teduglutide with that of placebo.

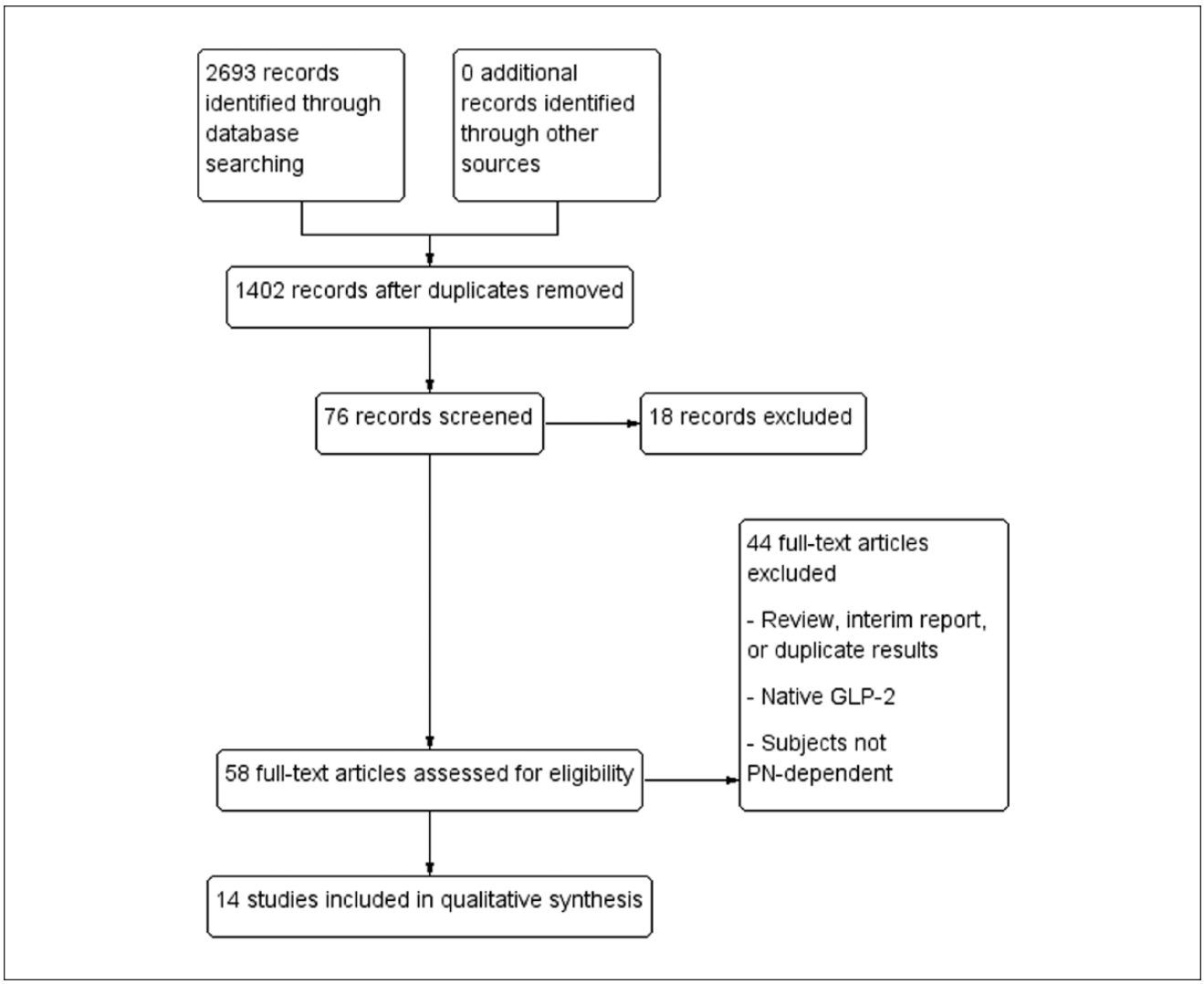

Figure 1. Study flowchart. GLP-2, glucagon-like peptide 2.

Results

Included Studies

A total of 2693 citations were identified, and 1402 unique results remained after removal of duplicates. Potentially relevant citations were evaluated for inclusion after cross-referencing index terms and titles. Seventy-six abstracts were reviewed, after which the remaining 58 full-text articles and meeting abstracts were assessed for inclusion. Fourteen met the inclusion criteria (Figure 1). Reasons for article exclusion included duplicate data, review articles or articles that provided interim findings when final results were available, use of native rather than analogue GLP-2, and enrollment of subjects who were not PN dependent. Five of the included citations are full-text articles, and 9 are meeting abstracts. These citations describe 3 trials as well as their respective extension and substudies. Characteristics of included studies, including study durations, populations, and outcomes of interest, are found in Table 1.

Risk of Bias in Included Studies

All included studies had a low risk of bias in the following domains: (1) random-sequence generation (selection bias), (2) incomplete outcome data (attrition bias), (3) selective reporting (reporting bias), and (4) other bias (Figure 2). Risk of allocation concealment (selection) bias in the Gilroy et al[38] study, risks of blinding of participants and personnel (performance) and blinding of outcome assessment (detection) bias in the Jeppesen et al[39–41] studies, and risks of blinding of outcome assessment (detection bias) in the Jeppesen et al,[42,43] Iyer et al,[44] and Fujioka et al[45] studies were determined to be

Table 1. Characteristics of Included Studies.

Study[a]	Description	Outcomes
Jeppesen et al[48]	Phase III clinical trial. SBS males and females ≥18 y receiving PN ≥3 d/wk for ≥12 mo. Randomized to teduglutide 0.05 mg/kg/d (n = 35), teduglutide 0.10 mg/kg/d (n = 32), or placebo (n = 16) for 6 mo.	1. PN volume 2. Responder rate[b] 3. Complete PN weaning 4. Intestinal adaptation 5. Safety
Jeppesen et al[39,40,41,c]	*Subset of Jeppesen et al[48] subjects.* Teduglutide 0.05 mg/kg/d (n = 10), teduglutide 0.10 mg/kg/d (n = 7), or placebo (n = 4) for 6 mo.	1. Intestinal adaptation
Tappenden et al[52]	*Subset of Jeppesen et al[48] subjects.* Teduglutide 0.05 mg/kg/d (n = 32), teduglutide 0.10 mg/kg/d (n = 30), or placebo (n = 15) for 6 mo.	1. Safety
O'Keefe et al[49] Gilroy et al[38,c]	*Extension of Jeppesen et al.[48]* Subjects previously on teduglutide 0.05 mg/kg/d (n = 25) or teduglutide 0.10 mg/kg/d (n = 27) received 7 additional mo of same dose. Previously placebo-treated subjects randomized to teduglutide 0.05 mg/kg/d (n = 6) or 0.10 mg/kg/d (n = 7) for 7 mo.	1. PN infusion frequency[d] 2. Responder rate 3. Complete PN weaning 4. Safety
Compher et al[46]	*Extension of Jeppesen et al.[48]* Subjects with stable (n = 15) or decreased (n = 7) PN requirement by 12 mo off teduglutide compared with those with increased PN requirement (n = 15).	1. PN volume 2. Complete PN weaning 3. Safety
Jeppesen et al[50] (STEPS)	Phase III clinical trial. SBS males and females ≥18 y on PN ≥3 d/wk for ≥12 mo. Previously teduglutide-treated subjects not eligible. Subjects randomized to receive teduglutide 0.05 mg/kg/d (n = 43) or placebo (n = 43) for 6 mo.	1. PN volume 2. PN infusion frequency 3. Responder rate 4. Safety
Jeppesen et al,[42,c] Jeppesen et al,[43,c] Fujioka et al[45,c] (STEPS-2)	*Open-label extension of STEPS.* Treatment in STEPS/STEPS-2: teduglutide/teduglutide 0.05 mg/kg/d (n = 30), placebo/teduglutide 0.05 mg/kg/d (n = 29), or not randomized/teduglutide 0.05 mg/kg/d (n = 6) for 18–24 mo.	1. PN volume 2. PN infusion frequency 3. Responder rate 4. Complete PN weaning 5. Safety
Iyer et al[44,c] (STEPS-3)	*Open-label extension of STEPS/STEPS-2.* Teduglutide 0.05 mg/kg/d (n = 14), with STEPS/STEPS-3 treatment of teduglutide/teduglutide (n = 5; treatment duration ≤42 mo), placebo/teduglutide (n = 6; treatment duration ≤36 mo), or not treated/teduglutide (n = 3; treatment duration ≤36 mo).	1. PN volume 2. PN infusion frequency 3. Complete PN weaning 4. Safety
Ukleja et al[47,c]	Retrospective chart review of patients with SBS (n = 6) following FDA approval of teduglutide. Teduglutide 0.05 mg/kg/d administered for 1–12 mo.	1. PN volume 2. Responder rate 3. Complete PN weaning 4. Safety

FDA, Food and Drug Administration; PN, parenteral nutrition; SBS, short bowel syndrome; STEPS, Study of Teduglutide Effectiveness in Parenteral Nutrition–Dependent SBS Subjects.
[a]Parent studies are in gray. Associated/extension studies are directly below each parent study.
[b]Responder rate refers to subjects that achieved ≥20% volume reduction in PN requirement.
[c]Denotes meeting abstract.
[d]PN infusion frequency expressed as d/wk PN required.

unclear since these domains were not specifically addressed in these citations. High risk of allocation concealment (selection) and blinding of participants and personnel (performance) bias were noted in the open-label Jeppesen et al,[42,43] Iyer et al,[44] and Fujioka et al[45] studies. Risk of blinding of outcome assessment (detection) bias was also high in the Gilroy et al,[38] Compher et al,[46] and Ukleja et al[47] studies since the treatments were known by the outcome assessors.

Outcomes of Interest

Efficacy

Responder rate. Table 2 shows the proportion of subjects classified as responders across studies, achieving ≥20% reduction by volume in weekly PN requirements. In Jeppesen et al,[48] response rate at 20 and maintained at 24 weeks of treatment was higher ($P = .005$) in teduglutide 0.05 mg/kg/d (0.05 group) vs placebo subjects (NNTB = 3, OR = 12.63, therapeutic gain

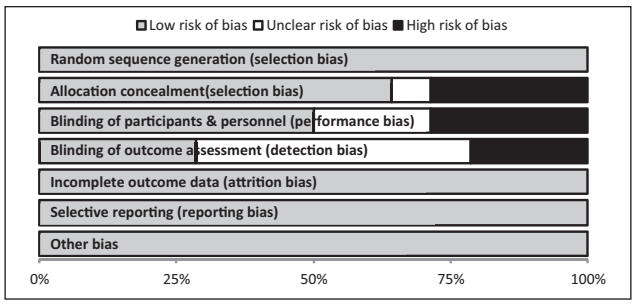

Figure 2. Risk of bias assessment. Results of each bias domain are presented as percentages across all included studies.

= 39.4%). Response rate of teduglutide 0.10 mg/kg/d (0.10 group) subjects did not differ (P = .17) from placebo (NNTB = 6, OR = 5.00, therapeutic gain = 18.7%) Seventeen of 25 (68.4%) 0.05 subjects and 14 of 27 (52.2%) 0.01 subjects were responders by 52 weeks of treatment.[49] Compared with week 24, by week 52, 4 of the 24 responders become nonresponders, and 11 of 19 nonresponders became responders. Twelve of the 18 subjects who became responders by week 24 and remained so through week 52 were treated with teduglutide 0.05 and 6 with teduglutide 0.10.[49] Of subjects receiving placebo in the initial study[48] but teduglutide in the extension study,[49] 6 of 6 (100.0%) and 2 of 7 (28.6%) responded to teduglutide 0.05 and 0.10, respectively.[38]

Similarly, in the Jeppesen et al[50] (Study of Teduglutide Effectiveness in Parenteral Nutrition–Dependent SBS Subjects [STEPS]) study, more (P = .002) teduglutide 0.05 vs placebo subjects were responders at week 24 (Table 2; NNTB = 4, OR = 3.89, therapeutic gain = 32.6%). In the extension study in which all subjects received teduglutide 0.05 (STEPS-2),[43,45] subjects previously treated with teduglutide 0.05, placebo, or not randomized achieved responder rates of 28 of 30 (93.3%), 16 of 29 (55.2%), and 4 of 6 (66.7%), respectively. Teduglutide response was observed regardless of subject characteristics (age, remnant anatomy, baseline PN requirements, or disease etiology).[43] Importantly, teduglutide efficacy was demonstrated in responder rate ORs of >1 in both phase III trials.[48,50] In the Ukleja et al[47] study, all 6 patients (100.0%) experienced >20% reduction in PN volume while taking teduglutide.

Changes in PN volume requirements. Using a strict parenteral weaning algorithm that allowed for reductions in PN volumes of ≤10% at 4-week intervals, both the teduglutide 0.05 and teduglutide 0.10 groups in the Jeppesen et al[48] trial had reduced PN volume requirements compared with baseline at weeks 8, 12, 16, 20, and 24 (all P < .05). The placebo group also achieved significant reductions at weeks 12 and 24 (P = .02 and 0.03, respectively). At week 24, both teduglutide dose groups achieved mean PN volume requirement reductions of 2.5 L/wk, while the placebo group achieved a 0.91-L/wk reduction (P = .08). At week 24, the teduglutide 0.05, teduglutide 0.10, and placebo groups also achieved reductions (P = .001, P = .03, and P = .056, respectively) in parenteral energy intake compared with baseline, but reductions in either teduglutide-treated group did not differ (P = .11) from placebo. By 52 weeks of treatment,[49] the teduglutide 0.05 and teduglutide 0.10 groups decreased their PN volume requirements by 4.9 L/wk (52%) and 3.3 L/wk (26%), respectively, compared with baseline. However, 4 weeks after stopping treatment, PN requirements of both the teduglutide 0.05 and 0.10 groups increased compared with study end (from 4.0 ± 3.4 to 5.5 ± 4.4 L/wk and 8.5 ± 5.1 to 7.9 ± 3.7 L/wk, respectively). There were no significant changes in 7-day urine outputs or oral intakes over the 52-week study period.

Subjects with increased (INC) PN requirements by 12 months after stopping teduglutide[46] had a greater (P = .04) PN volume reduction while on drug compared with those with stable (STABLE) or decreased (DEC) requirements at 12 months off drug (−4.7 vs −1.9 L/wk, respectively). INC had increased (P < .001) PN requirements at 3, 6, and 12 months off drug vs study end while STABLE/DEC requirements did not change. Furthermore, INC PN requirements were higher (P = .001) than STABLE/DEC (11.9 vs 5.7 L/wk) at 12 months off drug. Similar trends were observed in the subset of drug responders, in that INC had increased (P < .001) PN volume requirements at 3, 6, and 12 months compared with study end, while STABLE/DEC PN requirements did not change, and INC requirements were greater (P = .003) than those of STABLE/DEC subjects at 12 months off drug.

In STEPS,[50] using a weaning algorithm that allowed for 10%–30% PN volume reductions of baseline PN levels at 4-week intervals, teduglutide 0.05 and placebo subjects achieved mean L/wk reductions in PN volume requirements of 4.4 ± 3.8 (baseline 12.9 ± 7.8) and 2.3 ± 2.7 (baseline 13.2 ± 7.4), respectively, after 24 weeks of treatment. The difference in absolute change in PN volume requirements between these groups was significant by week 8 (P < .01) and remained so through week 24 (P < .001). Similarly, the difference in percentage reduction in PN volume from baseline to week 24 between groups became significant (P < .03) at week 12 and remained significant (P < .03) through week 24. By STEPS[50]/STEPS-2[43,45] treatment, the mean PN volume requirement reduction from baseline was 7.6 (66%), 3.1 (28%), and 4.0 (39%) L/wk in the groups treated with teduglutide/teduglutide, placebo/teduglutide, and not randomized/teduglutide, respectively. By STEPS[50]/STEPS-3[44] treatment, teduglutide/teduglutide, placebo/teduglutide, and not-treated/teduglutide subjects reduced their PN requirements from baseline by 9.8 (50%), 3.3 (35%), and 5.2 (73%) L/wk, respectively. In Ukleja et al,[47] 6 of 6 (100.0%) subjects experienced >20% reduction in PN volume requirements from baseline requirements of 1–8 L/wk.

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