CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203-441
Supplement #:	
Drug Name:	GATTEX® (teduglutide) 0.05 mg/kg/day powder for subcutaneous injection
Indication(s):	The treatment of adult patients with Short Bowel Syndrome (SBS)
Applicant:	NPS Pharmaceuticals, Inc.
Date(s):	Stamp Date: November 30, 2011 PDUFA Goal date: December 30, 2012
Review Priority:	Standard with Major Amendment (13 month review cycle)
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Keywords: NDA review, Clinical Studies

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

There was a sufficient level of evidence to support an efficacy claim for GATTEX® (teduglutide), and the claims currently reflected within the applicant's submitted product label were verified during this NDA review. With further motivation under the current public health circumstances in which Short Bowel Syndrome is a rare, serious and life-threatening condition with an unmet medical need, the reviewer supports the approval of teduglutide for the treatment of adult patients with this condition.

There were no major statistical issues that impacted the overall conclusions from the trials CL-0600-020 and CL-0600-004. Each study's design was adjudicated as being adequate, and the applicant's corresponding analysis plans were deemed appropriate. The change in primary endpoint during the conduct of trial CL-0600-004 could have possibly been an issue, however it ultimately was not. The premise behind this change in primary endpoint was understandable and acceptable. And although it would have been more ideal for the sponsor to have changed their endpoint prior to study enrollment, the decision was conducted with an independent and blinded team of consultants. As seen in section 3.2.4.1, this change in endpoint made no impact on the interpretation of this study's conclusions.

The efficacy of the 0.05 mg/kg/day teduglutide dose, for which the applicant is pursuing labeling, was principally demonstrated in trial CL-0600-020. The primary endpoint, Binary Response, and almost all secondary endpoints were significantly in favor of teduglutide. Consequently, results from trial CL-0600-020 are viewed positively as the formal basis for an efficacy claim to be reflected in the product's label. In trial CL-0600-004, the 0.05 mg/kg/day teduglutide dose showed a numerical advantage over Placebo for both Binary and Graded Response endpoints, and results from trial CL-0600-004 are viewed as supportive. With a sustained efficacy profile during the extension studies and with the Gastrointestinal Drug Advisory Committee's concurrence regarding the clinical meaningfulness of the Binary Response endpoint, overall there is a sufficient level of evidence to support an efficacy claim for teduglutide.

2 INTRODUCTION

2.1 Overview

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations, NPS Pharmaceuticals, Inc. submitted the New Drug Application (NDA) for GATTEX® (teduglutide) on November 30, 2011. The active pharmaceutical ingredient in GATTEX powder [delivery by daily subcutaneous injection] is teduglutide which is a human recombinant analog of glucagon-like peptide-2 (GLP-2). This is the first prescription product to have teduglutide as its active pharmaceutical ingredient thereby making it a New Molecular Entity (NME). Effective on May 27, 1999, GATTEX has officially undergone clinical development under IND 58,213 in patients with short bowel syndrome (SDS), and has been developed specifically to establish safety and efficacy in this patient population. Patients with SDS have a deficiency in the absorption of fluid and nutrients within the small intestine. As a result SDS patients are dependent on parenteral nutrition (PN) to stay alive, however long term PN usage is shown to be dangerous for these patients. GATTEX is utilized to improve intestinal absorption of fluid and nutrients, and decrease the need for total parenteral nutrition. Currently there are no FDA-approved treatment options for patients with SDS, consequently this serious and life threatening condition remains as one with an unmet medical need.

NPS Pharmaceuticals, Inc. obtained permission from the Division of Gastroenterology and Inborn Errors (DGIEP) to file their submission to facilitate a rolling review, and the final component of their rolling submission (which officially started the original PDUFA clock) was delivered on November 30, 2011. The original review cycle established by DGIEP was a standard 10 month cycle; however this was later amended to being a 13 month review cycle in order to aid its Advisory Committee meeting. The application also qualified for Orphan Exception under section 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act, and NPS Pharmaceuticals, Inc. ultimately obtained *Orphan Designation* from the Office or Orphan Products Development (OOPD) on June 29, 2000.

The clinical efficacy and safety of GATTEX has been principally evaluated through two studies: a Phase 3, multicenter, randomized, double-blind, parallel-group placebo-controlled study (CL0600-020) which serves as the lone adequate and well controlled study of this clinical development program as per 21 CFR 314.126; and a Phase 3, multicenter, randomized, double-blind, parallel-group placebo-controlled study (CL0600-004) which acts as the principally supportive study of this clinical development program.

Table 1 below presents information on the two relevant clinical trials contained in the submission.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety; Phase 3	CL-0600-020	Evaluate the efficacy, safety, tolerability and PK of teduglutide compared with placebo in subjects with parenteral nutrition dependent SBS	Multicenter, double-blind, randomized, parallel-group, placebo-controlled	teduglutide 0.05 mg/kg along with matching placebo; daily; subcutaneous injection	0.05 mg/kg: 42 placebo: 43 Total: 85	Male or female subjects with parenteral nutrition-dependent SBS	24 weeks	Complete; Full
Efficacy and Safety; Phase 3	CL-0600-004	Evaluate the efficacy, safety, tolerability and PK of teduglutide compared with placebo in subjects with parenteral nutrition dependent SBS	Multicenter, double-blind, randomized, parallel-group, placebo-controlled	teduglutide 0.10 mg/kg and 0.05 mg/kg along with matching placebo; daily; subcutaneous injection	0.10 mg/kg: 32 0.05 mg/kg: 35 placebo: 16 Total: 83	Male or female subjects with parenteral nutrition-dependent SBS	24 weeks	Complete; Full

Source: Reviewer's Table.

2.2 Data Sources

This NDA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). Its content, including the electronic data sets and labeling information, has been stored in the electronic document room (EDR) at this path location: \\Cdsesub1\evsprod\NDA203441. Sequences 0001, 0004, 0010, and 0021 contain all the contents relevant for this review.

For each of the two aforementioned clinical studies, the applicant's clinical study report (CSR), clinical datasets and analysis datasets were reviewed. Each study's clinical datasets were compliant to CDISC/SDTM v.3.1.2 standards; however, both studies utilized a non-standardized legacy approach for modeling the corresponding analysis data. Adequate data definition files and software code was also submitted for both studies.

3 STATISTICAL EVALUATION

The organization of the sub-sub-sections (and sub-sub-sub-sections if applicable) throughout section 3 will be made by clinical study.

3.1 Data and Analysis Quality

3.1.1 CL-0600-004

This study utilized Case Report Forms (CRF), and the submitted data quality and integrity appeared to be adequate. There were no issues in reproducing the primary analysis dataset (along with the numerical results presented within the CSR), in particular the primary endpoint, from the original data source. It was possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within section 9.6 of their ICH E3 compliant CSR. The blinding/unblinding procedures were well documented within the protocol and in section 9.4.6 of their ICH E3 compliant CSR. The applicant's statistical analysis plan (SAP) was finalized on April 20, 2007. The SAP was submitted and all relevant analysis decisions were made before unblinding. Database hard-lock was on July 27, 2007 with unblinding one week later on August 3, 2007.

3.1.2 CL-0600-020

This study utilized Electronic Data Capture (EDC), and the submitted data quality and integrity appeared to be adequate. There were again no issues in reproducing the primary analysis dataset (along with the numerical results presented within the CSR), in particular the primary endpoint, from the original data source. It was possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within section 9.6 of their ICH E3 compliant CSR. The blinding/unblinding procedures were well documented within the protocol and in section 9.4.6 of their ICH E3 compliant CSR. The applicant's SAP was finalized on December 21, 2010. The SAP was submitted and all relevant analysis decisions were made before unblinding. Database hard-lock was on January 25, 2011 with unblinding one week later on February 1, 2011.

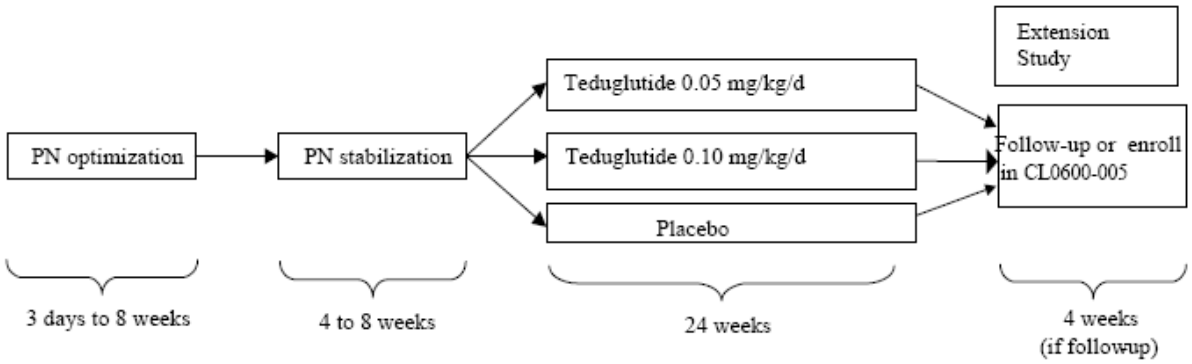
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 CL-0600-004

This Phase 3 efficacy and safety study was the first, in sequence, to be designed and subsequently executed by the applicant to ultimately support an efficacy claim to be reflected by the product label. CL-0600-004 was a 24-week multicenter, double-blind, randomized, parallel group, placebo-controlled trial which was to study two different doses of teduglutide: 0.10 mg/kg/day and 0.05 mg/kg/day. The original protocol for this study was signed off on October 27, 2003. The final version of this protocol, after a series of amendments, was set on September 5, 2007. This last amendment, which occurred after enrollment was finished, was for an administrative change which did not affect trial conduct i.e. study treatment, duration or procedures. Study initiation was on May 25, 2004 while study completion was on July 6, 2007. Figure 1 below diagrams study CL-0600-004.

Figure 1
Study Diagram CL-0600-004



Source: CL-0600-004 CSR - Figure 9-1 on pg. 24.

In order to establish the same relative PN baseline for all patients, the protocol specified a period of fluid optimization followed by stabilization prior to randomization. During optimization, a subject's PN/Intravenous (I.V.) fluid volume was adjusted over one or more 48-hour periods. PN/I.V. was adjusted to keep urine output between 1.0 and 2.0 L/day, while the patient was asked to maintain their oral fluid intake at the same volume as during their previous 48-hour adjustment (or baseline in the case of the first adjustment). During stabilization, PN/I.V. volume was assessed for 'stability' i.e. urine output 1-2 L/day under constant oral intake. PN/I.V. volume at the end of stabilization was taken as the Baseline measurement for all subsequent efficacy assessments.

After stabilization and the Baseline fluid volume assessment, subjects were randomized in a 1:2:2 ratio to placebo, teduglutide 0.05 mg/kg/day, or teduglutide 0.10 mg/kg/day. The randomization was stratified by two multi-level factors/variables:

- participation in the 72-hour nutrient absorption test (2 levels: 'yes', 'no')
- PN at three levels of consumption [3 levels: PN consisting of IV fluid and electrolytes only (3-7 times weekly), PN 3-5 times weekly, and PN 6-7 times weekly].

At that time, those subjects randomized to placebo were further randomized in a 1:1 ratio prospectively for possible inclusion in the 28-week, multicenter, double-blind extension study to assess the long term efficacy and safety (trial CL-0600-005) of the 0.05 or the 0.10 mg/kg/day teduglutide doses. All patients who participated in study CL-0600-004 were eligible to enroll in this follow-up roll-over trial.

Within the original protocol, the following primary and secondary endpoints were pre-specified in the following order.

Primary Endpoint: The number and percentage of subjects who demonstrated a response at Week 20, and who sustained that response through Week 24. Response was defined as the achievement of at least a 20% reduction from Baseline in weekly PN volume [measured in terms of Liters(L)/week]. The applicant refers to this endpoint as 'Binary Response'.

Secondary Endpoints:

- Number and percentage of subjects with at least a 1-day reduction in weekly PN usage
- Absolute reduction from Baseline in weekly PN kilojoules (transformed from kilocalories)
- Absolute reduction from Baseline in weekly volume of PN
- Change from Baseline in plasma citrulline at Dosing Week 24

These secondary endpoints were deemed by the applicant as being supportive to determining the intensity and duration of the response to treatment with teduglutide.

A sample size of 80 randomized subjects (32 subjects in each of the teduglutide treatment groups and 16 subjects in the placebo group) was to provide at least 90% power to detect an increase in the percentage of subjects who had the protocol-defined minimum response (20% decrease for both Weeks 20 and 24), from 5% in the placebo treatment group to 50% in the teduglutide treatment groups (80% power to detect an increase to 44%). The power calculations were based on two-sided tests of significance using Fisher's Exact test at α=0.05.

The two teduglutide treatment groups (0.10 mg/kg/day, 0.05 mg/kg/day) were each to be compared to the placebo group. For the secondary efficacy analyses, all pair-wise comparisons were also performed. The following step-down procedure was pre-specified within the original protocol to be used to adjust for multiple comparisons in the analysis for the primary endpoint, and then, in the order previously shown, for each of the secondary endpoints:

Step 1: The 0.10 mg/kg/day teduglutide group was to be compared with the placebo group using a two-sided test at a 0.05 significance level.

- If the 0.10 mg/kg/day teduglutide group was not significantly different from the placebo group, no further comparisons were to be made.
- If the 0.10 mg/kg/day teduglutide group was significantly different from the placebo group, comparisons were to continue to Step 2.

Step 2: The 0.05 mg/kg/day teduglutide group was to be compared with the placebo group using a two-sided test at a 0.05 significance level.

- If the 0.05 mg/kg/day teduglutide group was not significantly different from the placebo group, no further comparisons were to be made.
- If the 0.05 mg/kg/day teduglutide group was significantly different from the placebo group, comparisons were to continue to Step 3.

Step 3: The 0.10 mg/kg/day teduglutide group was to be compared with the 0.05 mg/kg/day teduglutide group using a two-sided test at a 0.05 significance level.

- If the teduglutide groups were significantly different from one another, comparisons were to move back to Step 1 using the next endpoint in line.

Prior to completion of study enrollment and preparation of the SAP, NPS organized a meeting, on July 28, 2006, with an independent panel of expert clinicians and statisticians in order to discuss the statistical components of this study protocol. The expert panel present at this

Regulatory Expert Consultants meeting was asked to review the protocol and make recommendations regarding the primary endpoint. Subsequently, an expanded primary endpoint was developed which the consultants and NPS agreed to be of greater sensitivity and specificity than the originally proposed primary endpoint previously presented. It was hoped that the utilization of this expanded endpoint would result in greater power to detect a treatment effect for teduglutide in the study. This expanded primary measure assesses intensity and sustained durability of PN reduction, both of which were considered clinically meaningful by the consultants. The expanded primary measure was built on the foundation of the originally proposed primary measure, and thus the transition was viewed as easily supportable from a regulatory perspective. No study data were provided to the consultants, and the study was fully blinded at the time of this meeting. The protocol was officially amended (Amendment 4b) on June 29, 2007 to include this new primary endpoint. It is to be noted, however, that the study's SAP was amended on April 20, 2007 to reflect this change, and this amendment took place prior to the official protocol amendment on June 29, 2007.

The New Primary Endpoint was defined as follows - An ordered categorical (or graded) response variable that accounts for both intensity and duration of response at the end of the 24-week treatment period. The intensity of response relies on a reduction from baseline in weekly PN volume, where the protocol defined reduction is set at a minimum of 20% and a maximum of 100%. Duration of response incorporates the responses at Weeks 16 to 20 and Weeks 20 to 24. Accordingly, the response variable is:

$$y = y_1 + y_2 + y_3 + y_4 + y_5;$$
$$= 0, 1, 2, 3, 4 \text{ or } 5$$

where,

$$y_1 = \begin{cases} 1 & \text{if} \geq 20\% \text{ reduction from baseline in PN volume at Week 20 is sustained to Week 24} \\ 0 & \text{if not} \end{cases}$$

$$y_2 = \begin{cases} 1 & \text{if} \geq 20\% \text{ reduction from baseline in PN volume at Week 16 is sustained to Week 24} \\ 0 & \text{if not} \end{cases}$$

$$y_3 = \begin{cases} 1 & \text{if [} \geq 20\% \text{ reduction from baseline in PN volume at either Week 16 or 20 is sustained to Week 24] and [} \geq 40\% \text{ reduction from baseline in PN volume from Week 16 to Week 20 or from Week 20 to Week 24]} \\ 0 & \text{if not} \end{cases}$$

$$y_4 = \begin{cases} 1 & \text{if} \geq 40\% \text{ reduction from baseline in PN volume at Week 16 is sustained to Week 24} \\ 0 & \text{if not} \end{cases}$$

$$y_5 = \begin{cases} 1 & \text{if 100\% reduction in PN volume (ie, off PN) at week 20 is sustained to Week 24} \\ 0 & \text{if not} \end{cases}$$

It is to be noted that y_1 is equivalent to the previously presented original primary endpoint. Values for the response criterion, y, are presented in Table 2 below.

Table 2
Criterion Values for Graded Response

	Weeks 20 to 24			
Weeks 16 to 20	**< 20% Reduction**	**20%-39% Reduction**	**40%-99% Reduction**	**100% Reduction**
< 20% Reduction	0	1	2	3
20%-39%Reduction	0	2	3	4
≥ 40% Reduction	0	3	4	5

Source: CL-0600-004 Protocol (Amendment 4b) - Table 8-1 on pg. 43.

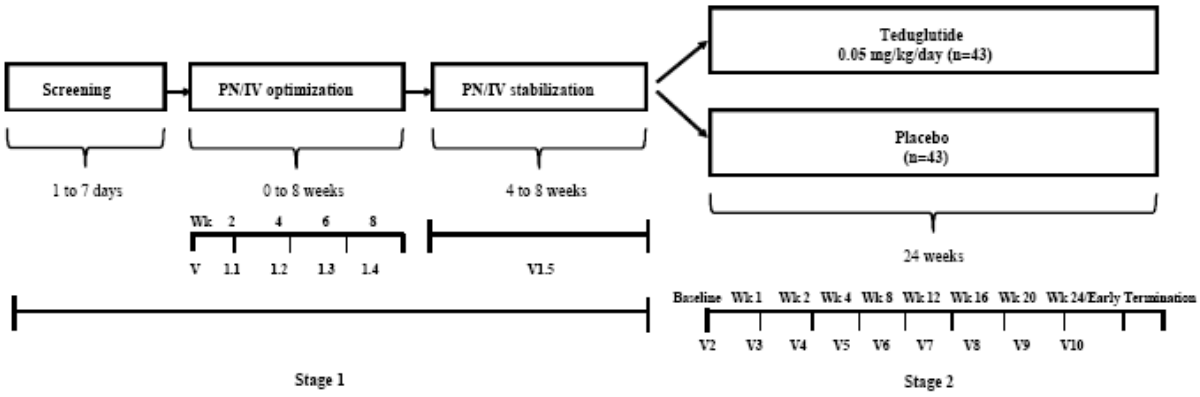
As a result, the original primary endpoint, Binary Response, was demoted one level down to being the key secondary endpoint. The ordering of the other secondary endpoints did not change, and the step-down procedure to adjust for multiple comparisons also stayed as is with the new primary endpoint now being assessed first.

Reviewer Comments:
The premise behind this change in primary endpoint was understandable and acceptable. And although it would have been more ideal for the sponsor to have organized their July 2006 meeting prior to study enrollment, the fact that it was conducted using an independent and blinded team of consultants results in no regulatory review issues. As will be seen in the results section, this change in endpoint made no impact on the interpretation of study results/conclusions. It can be argued that the graded response endpoint itself was actually not technically ordinal as the applicant purports. As an example from Table 2 above, at Weeks 20 to 24, a value of 3 from complete PN stoppage is actually scored worse by the scoring system than a 4 achieved from only a 40% reduction. Many examples of this violation in ordinality can be found in Table 2. Nonetheless, overall the design of study CL-0600-004 was adequate, and the estimated sample size was validated and confirmed as appropriate.

3.2.1.2 CL-0600-020

This Phase 3 efficacy and safety study was designed and executed by the applicant after the completion of trial CL-0600-004. This trial served as the clinical development program's adequate and well-controlled study which made it the basis for an efficacy claim to be reflected by the product label. CL-0600-020 was a 24-week multicenter, double-blind, randomized, parallel group, placebo-controlled trial whose primary objective was to confirm the efficacy of the teduglutide's 0.05 mg/kg/day dose. The original protocol for this study was signed off on September 4, 2008. The final version of this protocol, after a few amendments, was set on January 14, 2010. Study initiation was on November 25, 2008 while study completion was on January 4, 2011. Figure 2 below diagrams study CL-0600-020.

Figure 2
Study Diagram CL-0600-020



Source: CL-0600-020 CSR - pg. 6.

The design and population of study CL-0600-020 was very similar to that of CL-0600-004.

In order to establish the same relative PN baseline for all patients, an important part of the study was to establish consistency in PN/I.V. fluid management among all investigators at entry and

throughout the trial. To this end, the study protocol, like that of CL-006-004, specified a period of fluid optimization followed by a period of stabilization and the criteria to manage fluids.

During optimization, a subject's PN/I.V. fluid volume was adjusted over one or more 48-hour periods. PN/I.V. was adjusted to keep urine output between 1.0 and 2.0 L/day while the patient was asked to maintain their oral fluid intake at the same volume as during their previous 48-hour adjustment (or baseline in the case of the first adjustment).

During stabilization, PN/I.V. volume was assessed for 'stability' i.e. urine output 1-2 L/day under constant oral intake. PN/I.V. volume at the end of stabilization was taken as the Baseline measurement for all subsequent efficacy assessments. If stability was not achieved the first time through Stage 1 (see Figure 2 above), patients returned to the optimization phase again, followed again by stabilization. If stability was still not achieved, i.e. the second time through the sequence, the subject was not randomized or allowed to continue the trial.

After stabilization is finally achieved along with the Baseline fluid volume assessment made, subjects were randomized in a 1:1 ratio to placebo or teduglutide 0.05 mg/kg/day. The randomization was stratified by one two-level factor/variable i.e. Baseline PN/I.V. fluid volume (≤6 L/week, >6 L/week).

It is to be noted that all subjects randomized into this study were later given the opportunity to roll over into the currently ongoing 2-year, multicenter, open-label, un-controlled extension study (trial CL-0600-021) which assesses the long term efficacy and safety of the 0.05 mg/kg/day teduglutide treatment.

The following primary and secondary endpoints were pre-specified in the following order.

Primary Endpoint: Binary Response i.e. the number and percentage of subjects who demonstrated a response at Week 20, and who sustained that response through Week 24. Response was defined as the achievement of at least a 20% reduction from Baseline in weekly PN volume.

Reviewer Comments:
It is to be noted that this primary endpoint is the same as the original primary endpoint (which later became the key secondary endpoint) of the CL-0600-004 study. NPS went back to utilizing this more simplistic endpoint as the primary endpoint for this confirmatory study. A Gastroenterology Drug Advisory Committee meeting regarding this marketing application was held on October 16, 2012, and this endpoint was deemed as clinically meaningful by all members of the committee.

Secondary Endpoints:

- Percent change in PN volume between baseline and last dosing visit, where the last dosing visit is the last scheduled visit (including early termination visits) for which there was at least 14 days since the previously scheduled study visit
- Absolute change in PN volume between baseline and last dosing visit

- Duration of response (number of consecutive visits with at least 20% reduction)
- Proportion of patients with at least 20% reduction or at least a 2 L reduction from baseline in weekly PN at Week 20 and maintained through Week 24
- Number of subjects who stop PN altogether, and the time of stopping PN
- Graded (or ordered categorical) response i.e. the CL-006-004 study's new primary endpoint as previously described

These secondary endpoints were premised on reductions in PN/I.V. volume or the direct effects of improved intestinal absorption of fluid. The applicant felt that these endpoints were clinically meaningful.

A sample size of 86 subjects (43 subjects in the teduglutide treatment group and 43 subjects in the placebo group) was to provide at least 90% power to detect a difference in responder rates between the active and placebo arms of 35% vs. 6%, respectively. This power calculation was based on a two-sided test of significance using Fisher's Exact test at α=0.05.

The standard step-down procedure was pre-specified by the applicant to adjust for multiple comparisons in the analysis for the primary endpoint, and then, in the order previously shown, for each of the secondary endpoints.

Reviewer Comments:
The estimated sample size was validated and confirmed as appropriate. Overall, the design of study CL-0600-020 was deemed adequate.

3.2.2 Statistical Methodologies

3.2.2.1 CL-0600-004

3.2.2.1.1 Analysis Sets

The primary analysis set, i.e. the analysis set used for all primary and secondary endpoint analyses, is the Intent-to-Treat (ITT) analysis set which includes all randomized subjects who receive at least one dose of study drug. In this analysis set, patients are included in the treatment group that they were randomized to receive regardless of actual treatment received.

All analyses are re-conducted, for sensitivity analysis purposes, utilizing the Per-Protocol (PP) analysis set which includes all subjects in the ITT set who completed the study while being compliant with the study medication along with not having any major protocol deviations.

Reviewer Comment:
Due to the fact that this is a double-blind study, the utilization of the applicant defined ITT analysis set as the primary analysis set is acceptable per ICH E9. Ideally an All-Randomized analysis set, i.e. patients who were randomized into the double-blind study period, would be optimal. This All-Randomized analysis set is most compliant to the Intent-to-Treat Principle which, when conducting superiority tests (which is the case for the statistical tests conducted in

this protocol), avoids overly optimistic estimates of efficacy. Ultimately, only one patient was randomized into the CL-0600-004 study without dosing (into the 0.10 mg/kg/day teduglutide dose group). And because, as you will see below in Section 3.2.4.1, the 0.10 mg/kg/day teduglutide group was shown not to be significantly different than placebo for every tested endpoint (except plasma citrulline), further inclusion of this lone patient through more conservative analysis approaches (e.g. inclusion as a "non-responder") was not necessary. Consequently, the applicant defined ITT analysis set was sufficient.

3.2.2.1.2 Primary Endpoint Analysis

The analysis of the primary endpoint, i.e. the graded response endpoint, utilizes a rank-based ANCOVA adjusted by PN consumption level (two binary indicators; one each for PN 3-5 times weekly and PN 6-7 times weekly, and with IV fluids 3-7 times weekly serving as the reference category) and Baseline PN volume. Treatment group is an independent factor in this model.

Reviewer Comments:
The rank-ANCOVA approach is less reliant on parametric model assumptions. This is beneficial in this relatively small sample environment. However, as previously commented on, it can be argued that the Graded Response endpoint itself was actually not technically ordinal, as the applicant purported, thereby potentially hurting the case for a rank-based approach. Although this argument may have some merit, the presented rank-ANCOVA is still a sufficient analytical approach. In addition, any variable utilized for stratification when randomizing patients should subsequently be incorporated into the primary analysis as covariates for adjustment purposes. This will ensure more powerful statistical testing without loss of statistical sufficiency for any estimated parameter e.g. treatment effect. Consequently, the primary analysis was re-conducted by the statistical review team by further incorporating/adjusting the analysis by the two-level (i.e. 'yes' or 'no') 72-hour nutrient absorption test participation variable.

3.2.2.1.3 Secondary Endpoint Analyses

For the original primary endpoint (now the key secondary endpoint), Binary Response, and for the number and percentage of subjects with at least a 1-day reduction in weekly PN usage, pair-wise differences between treatment group rates and the corresponding 95% Confidence Intervals (CI) is presented. Pair-wise comparisons between the treatment groups are made using the Fisher's Exact test. For Binary Response, the aforementioned analysis is additionally conducted on a subgroup of clinical interest i.e. those patients who had a Baseline PN/I.V. volume >6 L vs. those who had a volume of ≤6 L. This additional subgroup testing is exploratory in nature with no impact on Type I Error control.

For the change from Baseline in weekly PN kilojoules and weekly PN volume, a mixed model repeated measures (MMRM) is utilized. Covariates include Baseline PN consumption level along with either Baseline PN kilojoules or Baseline PN volume depending on the endpoint being analyzed. Treatment group is an independent factor in these MMRM models.

For the change from Baseline in plasma citrulline, a linear regression is utilized with Baseline PN consumption level and baseline citrulline included as covariates in the model. Treatment group along with visit and treatment by visit interaction are independent factors in this model.

3.2.2.1.4 Handling of Dropouts/Missing Data

For the analysis of the responder endpoints, i.e. the primary and top two secondary endpoints based on the applicant's pre-specified ordering, a worst-case imputation is administered. Thus any patient dropping out of the study prior to study week 24 is imputed as a zero or failure.

For the analysis of the change-from-Baseline endpoints, a no-change-from-baseline imputation is administered for any patient dropping out of the study prior to study week 24.

3.2.2.2 CL-0600-020

3.2.2.2.1 Analysis Sets

The primary analysis set, i.e. the analysis set used for all primary and secondary endpoint analyses, is the ITT analysis set which includes all randomized subjects. In this analysis set, patients are included in the treatment group that they were randomized to receive regardless of actual treatment received.

All analyses are re-conducted, for sensitivity analysis purposes, utilizing the PP analysis set which includes all subjects in the ITT set who completed the study while being compliant with the study medication along with not having any major protocol deviations.

3.2.2.2.2 Primary Endpoint Analysis

The number and percentage of subjects who demonstrate at least a 20% reduction in PN volume at Week 20 and sustain at least a 20% reduction in weekly PN volume through Week 24 is presented by treatment group. The analysis compares the event rates for the two treatment groups using a Cochran-Mantel-Haenszel (CMH) test adjusted for the randomization stratification variable which was Baseline PN/I.V. fluid volume (≤6 L/week, >6 L/week).

Reviewer Comments:
In tandem with the CMH test, a Breslow-Day test is conducted by the statistical review team in order to test for the homogeneity of the treatment effect across the different randomization strata. This accompanying test is exploratory, and, hence, does not impact the study's overall Type 1 error; however, it is a necessary and useful accessory to the CMH test. For example, if the resulting CMH test is statistically significant in favor of teduglutide, a confirmation of homogeneity across the strata will further support and add value to the CMH test result in that the treatment effect would be found to be consistent across both Baseline weekly PN volume strata. If, however, the resulting CMH test is not statistically significant in favor of teduglutide, a finding of heterogeneity can also be valuable in that the treatment effects could be going in opposite directions between the Baseline weekly PN volume strata thereby contributing to the non-significant CMH test result.

3.2.2.2.3 Secondary Endpoint Analyses

For percent and absolute change from Baseline in weekly PN volume, treatment group differences are compared using an ANCOVA model with treatment and the interaction of

treatment by Baseline PN volume as effects, and Baseline PN volume as a covariate. In addition, 95% confidence intervals are presented.

For duration of response, the number and percentage of subjects for each number of days are presented for each treatment group. The two treatment groups are compared using extended CMH test statistics (with standardized mid-ranks) adjusted for the randomization stratification variable.

The number and percentage of subjects achieving at least a 20% reduction or at least a 2 L reduction from baseline in weekly PN volume at Week 20 and sustained through Week 24 are presented for each treatment group. The analysis will compare the event rates for the two treatment groups using the CMH test adjusted for the randomization stratification variable.

The number and percentage of subjects who stop PN administration are presented by treatment group. Treatment group comparisons are assessed using Fisher's Exact tests.

For the Graded (or ordered categorical) Response, the analysis will compare the two treatment groups utilizing extended CMH test statistics (with standardized mid-ranks) adjusted for the randomization stratification variable.

3.2.2.2.4 Handling of Dropouts/Missing Data

For the analysis of the responder endpoints, i.e. the Binary and Graded response endpoints, a worst-case imputation is administered. Thus any patient dropping out of the study prior to study week 24 is imputed as a failure or zero.

For the duration of response, the last observed number of days is imputed for any patient achieving response that later dropped out of the study prior to study week 24.

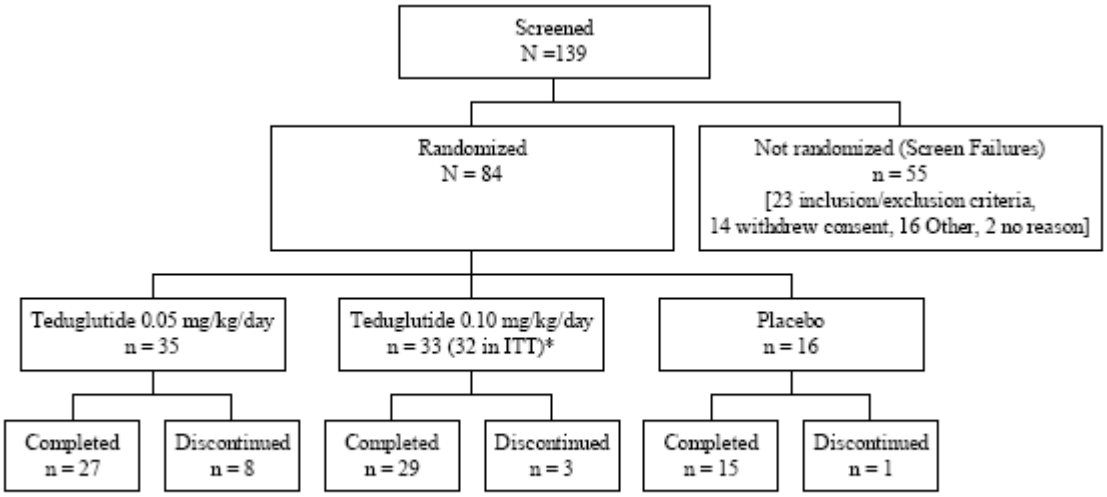
For the analysis of the change-from-Baseline endpoints, a no-change-from-baseline imputation is administered for any patient dropping out of the study prior to study week 24.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 CL-0600-004

The disposition information for all randomized patients is presented in Figure 3 and Table 3 below.

Figure 3
Disposition CL-0600-004



*A total of 83 subjects were randomized and received study drug. One subject (# 0132-0003) who was randomized to teduglutide 0.10 mg/kg/day group did not receive the study drug.

Source: CL-0600-004 CSR - Figure 10-1 on pg. 48.

Table 3
Disposition CL-0600-004 – n (%)
(All Randomized)

	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 33)	Total (N = 84)
Randomized	16 (100%)	35 (100%)	33 (100%)	84 (100%)
Randomized and Dosed i.e. ITT	16 (100%)	35 (100%)	32 (97.0%)	83 (98.8%)
Per-Protocol (PP)	15 (93.8%)	26 (74.3%)	29 (87.9%)	70 (83.3%)
Completed Study	15 (93.8%)	27 (77.1%)	29 (87.9%)	71 (84.5%)
Discontinued Study Early	1 (6.3%)	8 (22.9%)	3 (9.1%)	12 (14.3%)
Adverse Event	1 (6.3%)	5 (14.3%)	2 (6.1%)	8 (9.5%)
Death	0	0	0	0
Lost to follow-up	0	0	0	0
Subject decision (withdrew consent)	0	3 (8.6%)	1 (3.0%)	4 (4.8%)
Investigator's decision	0	0	0	0
Other	0	0	0	0

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group or overall.

The demographics and baseline characteristics for all randomized patients is presented in Table 4 below.

Table 4
Demographic and Baseline Characteristics CL-0600-004
(All Randomized)

	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 33)	Total (N = 84)
Age (years)				
n	16	35	33	84
Mean (SD)	49.4 (15.14)	47.1 (14.17)	50.3 (13.82)	48.8 (14.13)
Median	53.5	51.0	52.0	52.0
Min, Max	20, 72	20, 68	19, 79	19, 79
Age Group – n (%)				
≥ 65	2 (12.5%)	4 (11.4%)	3 (9.1%)	9 (10.7%)
< 65	14 (87.5%)	31 (88.6%)	30 (90.9%)	75 (89.3%)
Gender – n (%)				
Female	9 (56.3%)	18 (51.4%)	20 (60.6%)	47 (56.0%)
Male	7 (43.8%)	17 (48.6%)	13 (39.4%)	37 (44.0%)
Race – n (%)				
Caucasian	15 (93.8%)	32 (91.4%)	31 (93.9%)	78 (92.9%)
African American	1 (6.3%)	3 (8.6%)	2 (6.1%)	6 (7.1%)
PN consumption level n (%) [1]				
Level 1: IV fluids 3-7 x weekly	4 (25.0%)	8 (22.9%)	4 (12.1%)	16 (19.0%)
Level 2: PN 3-5 x weekly	8 (50.0%)	19 (54.3%)	18 (54.5%)	45 (53.6%)
Level 3: PN 6-7 x weekly	4 (25.0%)	8 (22.9%)	11 (33.3%)	23 (27.4%)
72-hour nutrient absorption test n (%)				
Yes	4 (25.0%)	10 (28.6%)	7 (21.2%)	21 (75.0%)
No	12 (75.0%)	25 (71.4%)	26 (78.8%)	63 (25.0%)
PN/I.V. Weekly Volume (L)				
n	16	34	32	82
Mean (SD)	10.7 (6.12)	9.6 (4.47)	12.7 (7.06)	11.0 (6.01)
Median	9.0	9.6	11.6	9.9
Min, Max	5, 27	2, 18	3, 33	2, 33
PN/I.V. Volume – n (%)				
> 6L	10 (62.5%)	26 (74.3%)	27 (81.8%)	63 (75.0%)
≤ 6L	6 (37.5%)	9 (25.7%)	6 (18.2%)	21 (25.0%)
Geographic Region				
North America	8 (50.0%)	13 (37.1%)	15 (45.5%)	36 (42.9%)
Europe	8 (50.0%)	22 (62.9%)	18 (54.5%)	48 (57.1%)

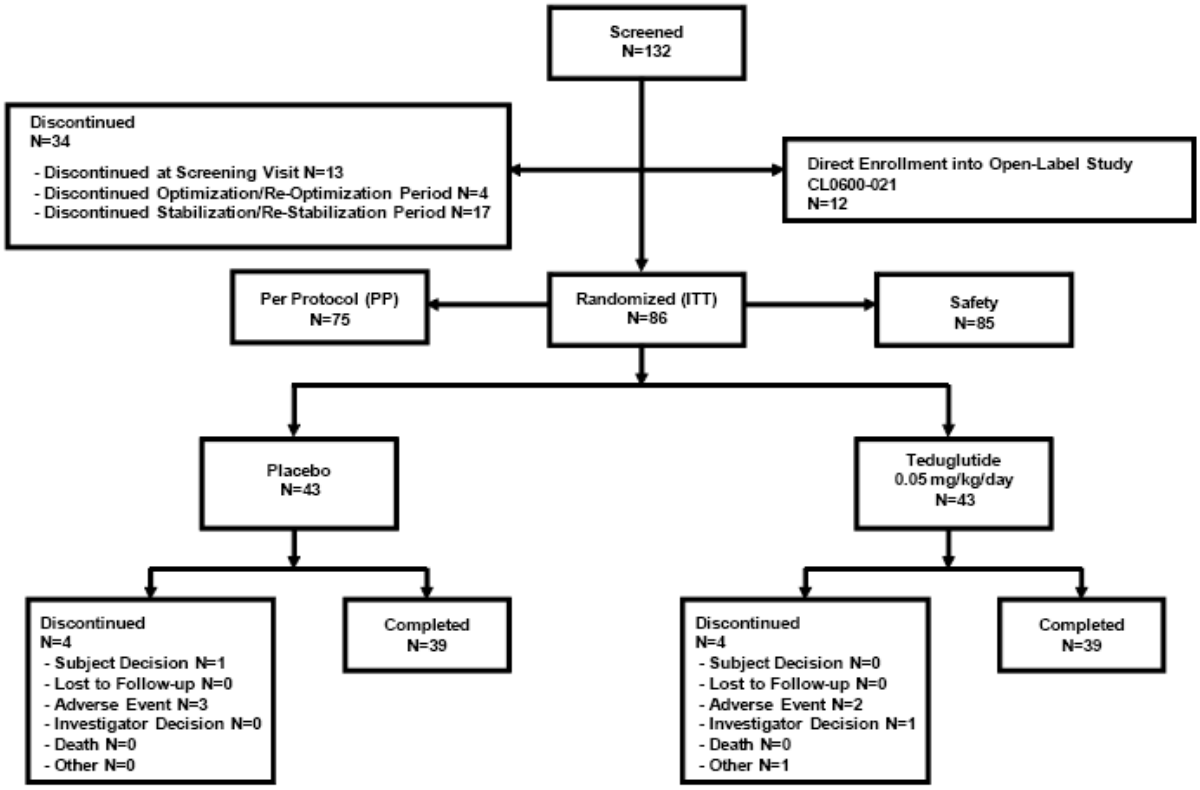
Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group or overall.
[1]: PN consumption level at study entry i.e. before optimization and stabilization.

Reviewer Comments:
There is only one significant imbalance between the treatment groups regarding the presented demographic and baseline characteristics, and this pertains to weekly PN/I.V. volume. The difference is between the 0.10 mg/kg/day and 0.05 mg/kg/day teduglutide dose groups. It is to be noted that this patient sample consists of primarily Caucasians under the age of 65. In addition, a good majority of the patient sample also had a Baseline PN/I.V. weekly volume of greater than 6 Liters.

3.2.3.2 CL-0600-020

The disposition information for all randomized patients (i.e. ITT patients) is presented in Figure 4 and Table 5 below.

Figure 4
Disposition CL-0600-020



Source: CL-0600-020 CSR - Figure 10-1 on pg. 90.

Table 5
Disposition CL-0600-020 – n (%)
(ITT)

	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)	Total (N = 86)
Randomized i.e. ITT	43 (100%)	43 (100%)	86 (100%)
Randomized and Dosed	43 (100%)	42 (97.7%)	85 (98.8%)
Per-Protocol (PP)	38 (88.4%)	37 (86.0%)	75 (89.3%)
Completed Study	39 (90.7%)	39 (90.7%)	78 (90.7%)
Discontinued Study Early	4 (9.3%)	4 (9.3%)	8 (9.3%)
Adverse Event	3 (7.0%)	2 (4.7%)	5 (5.8%)
Death	0	0	0
Lost to follow-up	0	0	0
Subject decision (withdrew consent)	1 (2.3%)	0	1 (1.2%)
Investigator's decision	0	1 (2.3%)	1 (1.2%)
Other	0	1 (2.3%)	1 (1.2%)

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group or overall.

The demographics and baseline characteristics for all randomized patients is presented in Table 6 below.

Table 6
Demographic and Baseline Characteristics CL-0600-020
(ITT)

	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)	Total (N = 86)
Age (years)			
n	43	43	86
Mean (SD)	49.7 (15.63)	50.9 (12.57)	50.3 (14.11)
Median	50.0	50.0	50.0
Min, Max	18, 82	22, 78	18, 82
Age Group – n (%)			
≥ 65	6 (14.0%)	7 (16.3%)	13 (15.1%)
< 65	37 (86.0%)	36 (83.7%)	73 (84.9%)
Gender – n (%)			
Female	24 (55.8%)	22 (51.2%)	46 (53.5%)
Male	19 (44.2%)	21 (48.8%)	40 (46.5%)
Race – n (%)			
Caucasian	41 (95.3%)	42 (97.7%)	83 (96.5%)
African American	1 (2.3%)	0	1 (1.2%)
Asian	1 (2.3%)	1 (2.3%)	2 (2.3%)
PN/I.V. Volume – n (%)			
> 6L	36 (83.7%)	35 (81.4%)	71 (82.6%)
≤ 6L	7 (16.3%)	8 (18.6%)	15 (17.4%)
PN/I.V. Weekly Volume (L)			
n	43	42	85
Mean (SD)	13.2 (7.40)	12.9 (7.75)	12.9 (7.55)
Median	12.3	10.5	11.2
Min, Max	2, 34	1, 33	1, 34
Geographic Region			
North America	15 (34.9%)	9 (20.9%)	24 (27.9%)
Europe	28 (65.1%)	34 (79.1%)	62 (72.1%)

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group or overall.

Reviewer Comments:
There is no significant imbalance between the treatment groups regarding the presented demographic and baseline characteristics. It is to be noted that this patient sample is primarily Caucasians under the age of 65. In addition, a good majority of the patient sample also had a Baseline PN/I.V. weekly volume of greater than 6 Liters.

3.2.4 Results and Conclusions

3.2.4.1 CL-0600-004

The results displayed in this section correspond to the endpoint order previously specified in section 3.2.1.1 above.

Table 7
Number and Percent of Patients by Graded Response CL-0600-004
(ITT)

	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 32)	Statistic (p-value)
Response Score – n (%)				
0 (Non-Responder)	15 (93.8%)	19 (54.3%)	24 (75.0%)	
1	0	6 (17.1%)	2 (6.3%)	
2	1 (6.3%)	6 (17.1%)	4 (12.5%)	
3	0	0	0	
4	0	2 (5.7%)	2 (6.3%)	
5	0	2 (5.7%)	0	
Rank ANCOVA Test [1]				
0.10 mg/kg/day - Placebo				1.96 (0.161)
0.05 mg/kg/day - Placebo				7.32 (0.007)
0.10 mg/kg/day - 0.05 mg/kg/day				3.06 (0.080)

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group.
[1]: Test statistic is based on Pair-wise rank ANCOVA after adjustment for the baseline PN consumption level and baseline PN volume as a covariate.

Reviewer Comments:
By failing to reject the null hypothesis of 'no treatment difference' corresponding to the initial test (i.e. 0.10 mg/kg/day vs. Placebo), all subsequent comparisons and corresponding results within Table 7 and this entire section, 3.2.4.1, are deemed as exploratory due to the step-down multiplicity adjustment procedure pre-specified above in section 3.2.1.1. The 0.05 mg/kg/day teduglutide dose does show a difference with Placebo. The analysis was re-conducted by further incorporating/adjusting by the two-level (i.e. 'yes' or 'no') 72-hour nutrient absorption test participation variable, however there were no changes to the conclusions. In addition, the analysis was also re-conducted utilizing the PP analysis set with, again, no changes to the conclusions.

Table 8
Number and Percent of Patients with Binary Response CL-0600-004 (ITT)

	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 32)
Overall [1]			
Non-Responder - n (%)	15 (93.8%)	19 (54.3%)	24 (75.0%)
Responder – n (%)	1 (6.3%)	16 (45.7%)	8 (25.0%)
Difference from Placebo for % Responders		39.5%	18.8%
95% CI for Difference		[19.1%, 59.8%]	[-0.4%, 37.9%]
p-value for Treatment Comparison [3]		0.0089	0.238
Baseline PN/I.V. Volume >6L [2]	n = 10	n = 26	n = 26
Non-Responder - n (%)	9 (90.0%)	13 (50.0%)	19 (73.1%)
Responder – n (%)	1 (10.0%)	13 (50.0%)	7 (26.9%)
Difference from Placebo for % Responders		40.0%	16.9%
95% CI for Difference		[13.3%, 66.7%]	[-9.0%, 40.8%]
p-value for Treatment Comparison [3]		0.0536	0.404
Baseline PN/I.V. Volume ≤6L [2]	n = 6	n = 9	n = 6
Non-Responder - n (%)	6 (100%)	6 (66.7%)	5 (83.3%)
Responder – n (%)	0	3 (33.3%)	1 (16.7%)
Difference from Placebo for % Responders		33.3%	16.7%
95% CI for Difference		[2.5%, 64.1%]	[-13.2%, 46.5%]
p-value for Treatment Comparison [3]		0.229	1.000

Source: Reviewer's Table.
[1]: Denominators for percentages are N, the number of patients in each treatment group.
[2]: Denominators for percentages are n, the number of subgroup patients in each treatment group.
[3]: Treatment comparisons for difference from Placebo are based on Fisher's Exact Test.

Reviewer Comments:
Overall, it can be seen that the 0.05 mg/kg/day teduglutide dose is significantly better than Placebo, but it's clear from the subgroup analysis that the patients whose Baseline PN/I.V. weekly volumes that are greater than 6 Liters are driving the overall results. The 0.10 mg/kg/day teduglutide dose is not significantly better than Placebo in any analysis. These analyses were re-conducted utilizing the PP analysis set with no changes to the conclusions.

For sensitivity analysis purposes, an additional missing data imputation strategy was utilized in exploratory testing between the 0.05 mg/kg/day teduglutide dose and Placebo. In this strategy, the Placebo patients who dropped out of the study (categorized as "failures" by the applicant's worst-case missing data handling strategy) are now categorized as "successes". This ultra-worst-case approach is the most conservative imputation strategy that can be espoused. Ultimately only one Placebo patient dropped out of the study, hence this imputation strategy results in one additional responder within the Placebo group i.e. 2 responders and 14 non-responders in total. The Fisher's Exact Test was re-conducted, and this resulted in an

exploratory p-value of 0.0281 which is larger than 0.0089 but still less than 0.05. This result further strengthens the efficacy conclusion for the 0.05 mg/kg/day teduglutide dose.

Table 9
Number and Percent of Patients with at least a 1-day Reduction in weekly PN Usage
CL-0600-004
(ITT)

	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 32)
No - n (%)	12 (75.0%)	24 (68.6%)	29 (90.6%)
Yes – n (%)	4 (25.0%)	11 (31.4%)	3 (9.4%)
Difference from Placebo for % Responders		6.4%	-15.6%
95% CI for Difference		[-19.8%, 32.6%]	[-39.1%, 7.9%]
p-value for Treatment Comparison [1]		0.749	0.201

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group.
[1]: Treatment comparisons for difference from Placebo are based on Fisher's Exact Test.

Reviewer Comments:
In this analysis, neither teduglutide dose is significantly better than Placebo. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

Table 10
Change from Baseline in Weekly PN kilojoules CL-0600-004
(ITT)

	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 32)
LS Mean	-3544.6	-6993.9	-1587.3
SE LS Mean	1889.8	1345.9	1379.0
95% CI of LS Mean	[-7317.6, 228.5]	[-9681.1, -4306.7]	[-4340.6, 1166.1]
Difference from Placebo in LS Mean (p-value) [1]		-3449.3 (0.136)	1957.3 (0.423)

Source: Reviewer's Table.
[1]: Treatment comparisons for difference from Placebo are based on a Mixed Model with treatment, visit, and treatment by visit interaction as factors, and with Baseline PN kilojoules and Baseline PN consumption level (as indicator variables) as covariates.

Reviewer Comments:
In this analysis, neither teduglutide dose is significantly better than Placebo. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

Table 11
Change from Baseline in Weekly PN Volume CL-0600-004
(ITT)

	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 32)
Baseline PN/I.V. Weekly Volume (L)			
n	16	34	32
Mean (SD)	10.7 (6.12)	9.6 (4.47)	12.7 (7.06)
Median	9.0	9.6	11.6
Min, Max	5, 27	2, 18	3, 33
Week 24 PN/I.V. Weekly Volume (L)			
n	15	27	29
Mean (SD)	8.7 (4.08)	6.9 (4.22)	10.8 (5.96)
Median	7.0	6.1	10.7
Min, Max	5, 16	0, 18	0, 29
Absolute Change from Baseline to Week 24			
n	15	27	29
Mean (SD)	-0.9 (1.41)	-2.5 (2.34)	-2.5 (3.33)
Median	-0.53	-1.7	-1.9
Min, Max	-4, 1	-7, 1	-15, 3
Percentage Change from Baseline to Week 24			
n	15	27	29
Mean (SD)	-8.1 (12.07)	-28.3 (28.25)	-18.2 (25.66)
Median	-7.41	-25.7	-17.3
Min, Max	-28, 14	-100, 11	-100, 31
LS Mean	-0.8681	-2.276	-2.294
SE LS Mean	0.6324	0.4607	0.4648
95% CI of LS Mean	[-2.136, 0.3993]	[-3.197, -1.354]	[-3.225, -1.364]
Difference from Placebo in LS Mean (p-value) [1]		-1.408 (0.0768)	-1.426 (0.0755)

Source: Reviewer's Table.
[1]: Treatment comparisons for difference from Placebo are based on a Mixed Model with treatment, visit, and treatment by visit interaction as factors, and with Baseline PN Volume and Baseline PN consumption level (as indicator variables) as covariates.

Reviewer Comments:
In this analysis, neither teduglutide dose is significantly better than Placebo. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

Table 12
Change from Baseline in Plasma Citrulline CL-0600-004
(ITT)

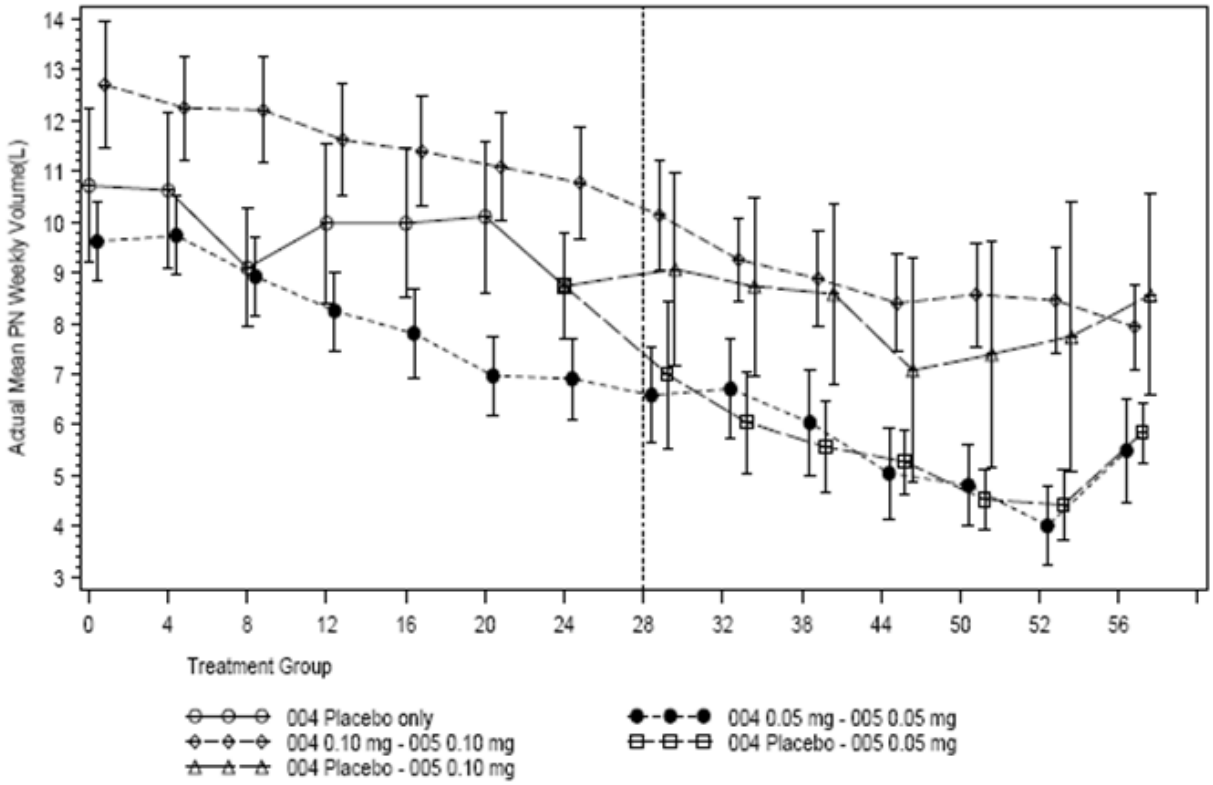
	Placebo (N = 16)	Teduglutide 0.05 mg/kg/day (N = 35)	Teduglutide 0.10 mg/kg/day (N = 32)
Change from Baseline at Dosing Week 24			
n	16	31	32
Mean (SD)	1.99 (5.048)	10.85 (11.463)	15.77 (12.177)
Median	0.95	6.50	13.35
Min, Max	-9.3, 10.5	-1.4, 39.4	-2.9, 47.4
Difference from Placebo p-value [1]		<0.0001	<0.0001

Source: Reviewer's Table.
[1]: Treatment comparisons for difference from Placebo are based on a linear regression with treatment as a factor, and with Baseline citrulline and Baseline PN consumption level (as indicator variables) as covariates.

Reviewer Comments:
In this analysis, both teduglutide doses are significantly better than Placebo. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

As stated previously in section 3.2.1.1, all patients participating in study CL-0600-004 were eligible to roll over into the long term efficacy and safety trial CL-0600-005. Figure 5 below displays the long term weekly PN volume across cumulative weeks of treatment exposure.

Figure 5
Mean (± SE) PN Weekly Volume by Treatment Group – CL-0600-004/CL-0600-005 (ITT)



Source: CL-0600-005 CSR - Figure 14.4.2 on pg. 844.

Reviewer Comments:
As can be seen from Figure 5, weekly PN volume continues to decline during further teduglutide treatment exposure thereby suggesting a positive long-term efficacy profile.

Reviewer Summary Comments:
As stated previously, by failing to reject the initial null hypothesis of 'no treatment difference', which corresponded to the test between the 0.10 mg/kg/day teduglutide dose and Placebo for the primary endpoint (Graded Response), all subsequent comparisons and corresponding results presented in this entire section, 3.2.4.1, were deemed as exploratory due to the applicant's pre-specified step-down multiplicity adjustment procedure. Albeit exploratory, it is to be noted that the 0.05 mg/kg/day teduglutide dose did suggest a difference with Placebo when tested for the Graded and Binary Response endpoints. This result motivated the applicant to study this dose exclusively in what served as the confirmatory trial, CL-0600-020, within this development program. Consequently, regarding overall level of evidence, the 0.05 mg/kg/day teduglutide dose results within trial CL-0600-004 are viewed as supportive.

The applicant's reasoning, in which the reviewer concurs and as previously indicated, regarding why the 0.10 mg/kg/day dose failed pertained to patients within that treatment group having larger Baseline weekly PN/I.V. volumes. The 0.10 mg/kg/day group had a mean Baseline weekly

PN/I.V. volume of 12.7 L/week while the 0.05 mg/kg/day group and Placebo group had mean Baseline weekly PN/I.V. volumes of 9.6 L/week and 10.7 L/week respectively. The differences in these mean Baseline weekly PN/I.V. volumes are not large; however, patients in the 0.10 mg/kg/day group had Baseline volumes that were larger by just enough to end up being less sensitive to calculations for percentage change from Baseline at Week 24. Consequently, given a fixed absolute change from Baseline at Week 24, the corresponding percentage change from Baseline at Week 24 would be smaller for patients in the 0.10 mg/kg/day group relative to patients in the other treatment groups. It ended up being smaller by just enough to result in failure to reject the null hypotheses associated with the Graded and Binary Response endpoints.

3.2.4.2 CL-0600-020

The results displayed in this section correspond to the endpoint order previously specified in section 3.2.1.2 above.

Table 13
Number and Percent of Patients with Binary Response CL-0600-020
(ITT)

	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)
Overall [1]		
Non-Responder - n (%)	30 (69.8%)	16 (37.2%)
Responder – n (%)	13 (30.2%)	27 (62.8%)
p-value for Treatment Comparison [3]		0.002
p-value for Test for Homogeneity across Randomization Strata [4]		0.022
Baseline PN/I.V. Volume >6L [2]	n = 36	n = 35
Non-Responder - n (%)	26 (72.2%)	10 (28.6%)
Responder – n (%)	10 (27.8%)	25 (71.4%)
p-value for Treatment Comparison [5]		0.0003
Baseline PN/I.V. Volume ≤6L [2]	n = 7	n = 8
Non-Responder - n (%)	4 (57.1%)	6 (75.0%)
Responder – n (%)	3 (42.9%)	2 (25.0%)
p-value for Treatment Comparison [5]		0.608

Source: Reviewer's Table.
[1]: Denominators for percentages are N, the number of patients in each treatment group.
[2]: Denominators for percentages are n, the number of subgroup patients in each treatment group.
[3]: Treatment comparisons for difference from Placebo are based on a Cochran-Mantel-Haenszel test adjusted for the randomization stratification variable Baseline PN/I.V. fluid weekly volume (≤6 L/week, >6 L/week).
[4]: Based on a Breslow-Day test. This test is exploratory, and hence will not impact the study's overall Type 1 error.
[5]: Treatment comparisons for difference from Placebo are based on Fisher's Exact Test. These tests are exploratory, and hence will not impact the study's overall Type 1 error.

Reviewer Comments:
Overall, it can be seen that the 0.05 mg/kg/day teduglutide dose is significantly better than Placebo. However, the exploratory test for homogeneity across the two randomization strata is rejected which motivates subsequent testing within each randomization stratum. It's clear from these subgroup analyses, albeit exploratory, that there is heterogeneity across the two randomization strata. The patients whose Baseline PN/I.V. weekly volumes that are greater than 6 Liters are driving the overall results. These analyses were all re-conducted utilizing the PP analysis set with no changes to the conclusions.

For sensitivity analysis purposes, an additional missing data imputation strategy was utilized in exploratory testing between the 0.05 mg/kg/day teduglutide dose and Placebo. In this strategy, the Placebo patients who dropped out of the study (categorized as "failures" by the applicant's worst-case missing data handling strategy) are now categorized as "successes". This ultra-worst-case approach is the most conservative imputation strategy that can be espoused. Ultimately four Placebo patients dropped out of the trial, hence this imputation strategy results in four additional responders in the Placebo group i.e. 17 responders and 26 non-responders in total. It is to be noted that all four Placebo drop-outs were in the >6L/week Baseline PN/I.V. weekly volume strata. The Fisher's Exact Test was re-conducted, and this resulted in an exploratory p-value of 0.0271 which is larger than 0.002 but still less than 0.05. This result further strengthens the case for the efficacy of the 0.05 mg/kg/day teduglutide dose.

Table 14
Percent Change from Baseline to Last Dosing Visit in Weekly PN Volume CL-0600-020 (ITT)

	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)
Baseline PN/I.V. Weekly Volume (L)		
n	43	42
Mean (SD)	13.2 (7.40)	12.9 (7.75)
Median	12.3	10.5
Min, Max	2, 34	1, 33
Week 24 PN/I.V. Weekly Volume (L)		
n	43	40
Mean (SD)	11.0 (7.22)	8.4 (5.28)
Median	10.3	7.0
Min, Max	0, 29	2, 23
Absolute Change from Baseline to Last Dosing Visit		
n	43	40
Mean (SD)	-2.3 (2.79)	-4.4 (3.81)
Median	-1.8	-3.1
Min, Max	-8, 3	-14, 2
LS Mean	-2.35	-4.42
SE LS Mean	0.39	0.41
95% CI of LS Mean	[-3.13, -1.57]	[-5.23, -3.61]
p-value [1]		<0.001
Percentage Change from Baseline to Last Dosing Visit		
n	43	40
Mean (SD)	-21.1 (24.35)	-32.1 (18.71)
Median	-18.24	-33.6
Min, Max	-100, 33	-85, 20
LS Mean	-21.27	-32.26
SE LS Mean	3.29	3.42
95% CI of LS Mean	[-27.82, -14.71]	[-39.05, -25.46]
p-value [1]		0.023

Source: Reviewer's Table.
[1]: The treatment comparison with Placebo for the absolute and percent change is based on an ANCOVA model with treatment and the interaction of treatment by Baseline PN volume as effects, and Baseline PN volume as a covariate.

Reviewer Comments:
In each analysis the 0.05 mg/kg/day teduglutide dose is significantly better than Placebo. These analyses were re-conducted utilizing the PP analysis set with no changes to the conclusions.

Table 15
Duration of Response CL-0600-020
(ITT)

	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)
Duration of Response – n (%)		
0 visits	25 (58.1%)	13 (30.2%)
1 visit	5 (11.6%)	3 (7.0%)
2 visits	1 (2.3%)	3 (7.0%)
≥3 visits	12 (27.9%)	24 (55.8%)
p-value [1]		0.005

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group. Response is defined as at least a 20% reduction from baseline in weekly PN volume. Subjects must have a response at Week 24 in order to have a minimum of 1 visit for the duration.
[1]: The treatment comparison is based on an extended Cochran-Mantel-Haenszel test with standardized mid-ranks adjusted for the randomization stratification variable Baseline PN/I.V. fluid weekly volume (≤6 L/week, >6 L/week).

Reviewer Comments:
In this analysis the 0.05 mg/kg/day teduglutide dose is significantly better than Placebo. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

Table 16
Patients with 20% or 2L Reduction in PN Volume at Week 20, Maintained to Week 24
CL-0600-020
(ITT)

	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)
Non-Responder - n (%)	27 (62.8%)	13 (30.2%)
Responder – n (%)	16 (37.2%)	30 (69.8%)
p-value for Treatment Comparison [1]		0.002

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group.
[1]: Treatment comparisons for difference from Placebo are based on a Cochran-Mantel-Haenszel test adjusted for the randomization stratification variable Baseline PN/I.V. fluid weekly volume (≤6 L/week, >6 L/week).

Reviewer Comments:
In this analysis the 0.05 mg/kg/day teduglutide dose is significantly better than Placebo. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

Table 17
Patients who stop PN Usage CL-0600-020
(ITT)

	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)
Stopped PN as of Week 24 – n (%)		
No	42 (97.7%)	43 (100%)
Yes	1 (2.3%)	0
p-value for Treatment Comparison [1]		>0.999
Patients who Stopped PN by Week 20 – n (%)	0	0
Number of Days to Stopping PN – n (%)		
176	1 (2.3%)	0

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group.
[1]: Treatment comparisons for difference from Placebo are based on a Fisher's Exact Test.

Reviewer Comments:
In this analysis there is no significant difference between the 0.05 mg/kg/day teduglutide dose and Placebo. By failing to reject the null hypothesis of 'no treatment difference' corresponding to this test, all subsequent comparisons and corresponding results within this results section are deemed as exploratory due to the step-down multiplicity adjustment procedure pre-specified above in section 3.2.1.2. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

Table 18
Number and Percent of Patients by Graded Response CL-0600-020
(ITT)

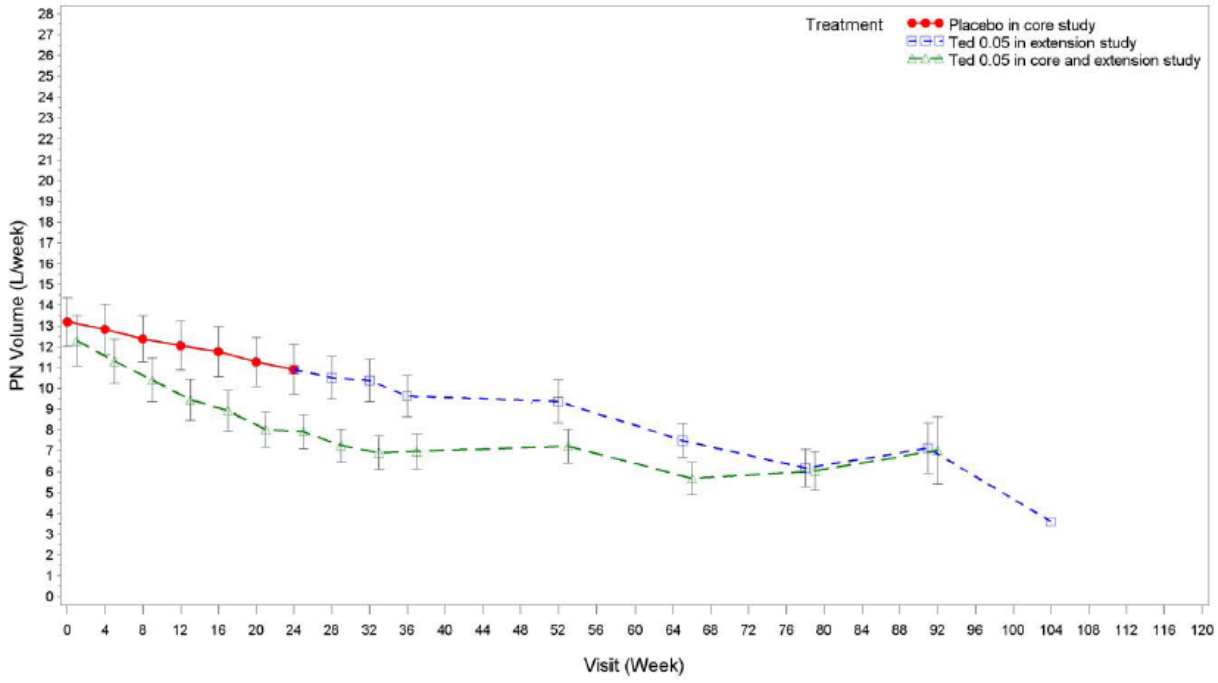
	Placebo (N = 43)	Teduglutide 0.05 mg/kg/day (N = 43)
Response Score – n (%)		
0 (Non-Responder)	30 (69.8%)	16 (37.2%)
1	1 (2.3%)	3 (7.0%)
2	6 (14.0%)	13 (30.2%)
3	2 (4.7%)	4 (9.3%)
4	4 (9.3%)	7 (16.3%)
5	0	0
p-value for Treatment Comparison [1]		0.004

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment group.
[1]: The treatment comparison is based on an extended Cochran-Mantel-Haenszel test with standardized mid-ranks adjusted for the randomization stratification variable Baseline PN/I.V. fluid weekly volume (≤6 L/week, >6 L/week).

Reviewer Comments:
As a reminder, this endpoint was the primary endpoint for the CL-0600-004 study as explained above in section 3.2.1.1. Albeit an exploratory result, in this analysis the 0.05 mg/kg/day teduglutide dose is significantly better than Placebo. This analysis was re-conducted utilizing the PP analysis set with no changes to the conclusions.

As stated previously in section 3.2.1.2, all patients participating in study CL-0600-020 were eligible to roll over into the long term efficacy and safety trial CL-0600-021. Figure 6 below displays the long term weekly PN volume across cumulative weeks of treatment exposure.

Figure 6
Mean (± SE) PN Weekly Volume by Treatment Group – CL-0600-020/CL-0600-021 (ITT)



Note: Subject 0109-1001 experienced catheter related sepsis at day 517 (week 74) and was treated with increased volumes of PN/IV. This subject is not included in this figure.

Source: Response to Information Request (Sequence 0021 on 20Jun2012) - Figure 2.2 on pg. 16.

Reviewer Comments:
As can be seen from Figure 6, weekly PN volume continues to decline during further teduglutide treatment exposure thereby suggesting a positive long-term efficacy profile.

Reviewer Summary Comments:
The results within this section show that the efficacy of the 0.05 mg/kg/day teduglutide dose was confirmed. Tests for all endpoints until stopping PN usage were significant. And although an exploratory result, the 0.05 mg/kg/day teduglutide dose was significantly better than Placebo in the analysis of the Graded Response endpoint as well. Consequently, regarding overall level of

evidence, the 0.05 mg/kg/day teduglutide dose results within trial CL-0600-020 are viewed positively as the formal basis for an efficacy claim to be reflected by the product's label.

3.3 Evaluation of Safety

During the CL-0600-004 and CL-0600-020 trials, there were a cumulative total of zero deaths in patients administered teduglutide. In addition, there was a cumulative total of only three malignancy related events in the 0.05 mg/kg/day teduglutide group. Based on the clinical review, a relationship between malignancy and teduglutide could not be concluded based on such few cases, especially considering that all of these patients were deemed to be already at a high risk for the type of malignancy with which they were diagnosed. Please see Section 7 of the clinical review for full details regarding the safety profile of teduglutide.

As stated previously, an Advisory Committee meeting regarding this marketing application was held on October 16, 2012. The committee members found no major safety issues which would preclude product approval while also coming to a consensus regarding the applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) to be utilized for addressing potential safety concerns post-market.

3.4 Benefit-Risk Assessment

Based on the clinical review, the risk-benefit tradeoff favors the approval of teduglutide with the Advisory Committee members concurring unanimously. Please see the clinical review for full details.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

In studies CL-0600-004 and CL-0600-020 (see above in Tables 4 and 6 respectively), the majority of enrolled and randomized patients were Caucasian and between the ages of 18 and 65. In addition, most of the patients participating in these trials were from European countries. Hence race, age, and geographic region analyses were not applicable. Due to this lack of representation, extrapolation of these study results to patients who are not Caucasian, not between 18 and 65 years old, and not from Europe should be made with caution.

Efficacy was assessed by gender, and it was found that the results were consistent across the female and male subgroups.

4.2 Other Special/Subgroup Populations

In studies CL-0600-004 and CL-0600-020 (see above in Tables 4 and 6 respectively), the majority of enrolled and randomized patients also had Baseline PN/I.V. volumes of greater than 6 Liters. The efficacy analysis results shown above in Tables 8 and 13, along with subsequent comments, indicate that the efficacy in these trials was more clearly demonstrated in this patient subgroup. However, the sample size for this subgroup is too small to support a more definitive conclusion regarding subgroup efficacy.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no statistical issues that impacted the overall conclusions of trials CL-0600-004 and CL-0600-020. Each study's design was adjudicated as being adequate, and the applicant's corresponding analysis plans were deemed appropriate. The change in primary endpoint during the conduct of trial CL-0600-004 could have possibly been an issue, however it ultimately was not. The premise behind this change in primary endpoint was understandable and acceptable. And although it would have been more ideal to have organized the meeting, which motivated said change in endpoint, prior to study enrollment, the fact that it was conducted using an independent and blinded team of consultants resulted in no regulatory review issues. As seen in section 3.2.4.1, this change in endpoint made no impact on the interpretation of this study's results/conclusions.

5.2 Collective Evidence

The efficacy of the 0.05 mg/kg/day teduglutide dose, for which the applicant is pursuing labeling, was confirmed by trial CL-0600-020. Starting with the Binary Response endpoint, tests for all endpoints until stopping PN usage were significant. And although an exploratory result, the 0.05 mg/kg/day teduglutide dose was significantly better than Placebo in the analysis of the Graded Response endpoint as well. Consequently, regarding overall level of evidence, the 0.05 mg/kg/day teduglutide dose results from trial CL-0600-020 are viewed positively as the formal basis for an efficacy claim to be reflected in the product's label.

In trial CL-0600-004, it is to be noted, albeit exploratory, that the 0.05 mg/kg/day teduglutide dose did suggest a difference with Placebo when tested for the Binary and Graded Response endpoints. Hence, regarding overall level of evidence, the 0.05 mg/kg/day teduglutide dose results from trial CL-0600-004 are viewed as supportive.

Based on a sustained efficacy profile shown during the extension studies and with the Advisory Committee's concurrence regarding the clinical meaningfulness of the Binary Response endpoint, there appears to be sufficient level of evidence to support an efficacy claim for

teduglutide. As addressed in section 4.2, there appeared to be less of an effect in the subgroup of patients who had less than 6 liters of PN/I.V. volume at baseline; however there was insufficient data to support a clearer extrapolation of these results to treatment naïve patients who are not being administered at least 6 Liters of weekly PN prior to additional medical intervention with teduglutide.

5.3 Conclusions and Recommendations

As previously mentioned, there was a sufficient level of evidence to support an efficacy claim for teduglutide, and the claims currently reflected within the applicant's submitted product label were verified during this NDA review. With further motivation under the current public health circumstances in which Short Bowel Syndrome is a rare, serious and life-threatening condition with an unmet medical need, this reviewer supports the approval of teduglutide for the treatment of adult patients with this condition.

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/s/

BEHRANG VALI
12/08/2012

MICHAEL E WELCH
12/10/2012
Concur with review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203441 **Applicant: NPS Pharmaceuticals** **Stamp Date: 11/30/2011**

Drug Name: Gattex (teduglutide [rDNA origin]) powder for subcutaneous injection **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	Yes			Would have been easier if the TOC for the main body of the study reports had included links to Appendices. Need to rely on Global Submit.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Yes			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	Yes			
4	Data sets in EDR are accessible and they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	Yes			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			NA	
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			NA	DSMB met to review safety only.
Appropriate references for novel statistical methodology (if present) are included.			NA	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	Yes			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	Provided for Study CL0600 -020 only.			Study CL0600-04: CSR describes sensitivity analyses (Section 11.4.2.2 of CSR, page 76) but I can't find the results.

Additional requests:

1. For Study CL0600-020, describe the number of subjects who were randomized after two optimization attempts, their treatment assignment, and their identification codes. Although the statistical analysis plan for Study CL0600-020 states "If a subject fails to remain stable for at least four consecutive weeks immediately prior to randomization, the subject may start the optimization period again" (Section 5.1), we were unable to find a descriptive analyses of these subjects.
2. For Study CL0600-004, provide minutes for meetings that discussed study endpoint changes, while the study was ongoing.
3. For Study CL0600-004, discuss the results of the sensitivity analyses described in Section 11.4.2.2 of the clinical study report or identify the section where the results are discussed. We are unable to locate the results of the sensitivity analyses.

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/s/

LISA A KAMMERMAN
02/09/2012

MICHAEL E WELCH
02/09/2012