CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	11/8/2012
From	Ruyi He, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 203441
Applicant	NPS Pharmaceuticals, Inc
Date of Submission	11/30/2011
PDUFA Goal Date	12/30/2012 (with 3 months extension)
Therapeutic Class	Glucagon-like peptide-2 (GLP-2) analog
Proprietary Name / Established (USAN) names	Teduglutide (rDNA origin)/ GATTEX®
Proposed Indication(s)	The treatment of adult patients with Short Bowel Syndrome (SBS). GATTEX is used to improve intestinal absorption of fluid and nutrients.
Proposed Dosage forms / Strength	GATTEX should be administered by subcutaneous (SC) injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. GATTEX should **not** be administered intravenously or intramuscularly. The recommended daily dose of GATTEX is 0.05 mg/kg body weight.
Recommended:	I recommend that NDA 203441 for Teduglutide (rDNA origin)/ GATTEX® be approved for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral nutrients/fluids to improve intestinal absorption of fluid and nutrients.

1. Introduction

GATTEX (teduglutide [rDNA origin]) (also known as ALX-0600; or [gly2]-hGLP-2) is being developed for the treatment of adult patients with Short Bowel Syndrome (SBS). It is a 33–amino acid recombinant analog of human Glucagon-like peptide-2 (GLP-2), a peptide secreted primarily from the lower gastrointestinal tract.

The product is administered by subcutaneous (SC) injection. Teduglutide appears to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth. Teduglutide may accelerate intestinal adaptation after bowel resection and enhances selective barrier function in the small intestine according to the sponsor.

Teduglutide use in humans is expected to produce an increase in intestinal absorption through increases in surface area (histological effects in crypts and villi). With increased absorption of fluids, nutrients and electrolytes it is expected that subjects will maintain their nutritional status while reducing parenteral nutrition/intravenous fluids (PN/I.V.) dependence.

2. Background

Short bowel syndrome results from surgical resection or congenital defect and is characterized by the inability to maintain protein/energy, fluid, electrolyte, and/or micronutrient balance(s) when on a conventionally accepted, normal diet. Patients with SBS are highly prone to malnutrition, diarrhea, dehydration, and an inability to maintain weight due to the reduced intestinal capacity to absorb macronutrients, water, and electrolytes.

Major small intestinal resection resulting in SBS often requires long-term PN/I.V. support due to severe malabsorption of nutrients and fluids. Although PN/I.V. support is life-saving in patients with intestinal failure, it is often associated with life-threatening complications. Therefore, therapies to treat SBS and reduce PN/I.V. dependence offer the potential to improve long-term survival and decrease complications secondary to ongoing use of PN/I.V. A reduction in the need for parenteral support may also result in clinically meaningful benefits such as an increase in the number of days off of PN/I.V. per week, decreased nocturia and less interrupted sleep, reduced infusion time per day, decreased stomal output or diarrhea, and reduced costs and resources associated with managing patients dependent on PN/I.V.

Historically, clinical care of patients with short bowel syndrome (SBS) has mainly focused on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, anti-diarrheal, and anti-secretory agents. Although surgical procedures such as bowel lengthening surgery or intestinal transplantation have been suggested as potential treatments, both options are associated with significant morbidity and mortality and are therefore considered only in selected patients.

For treating patients with SBS, the FDA approved Zorbtive [somatropin (rDNA origin) for injection, NDA 021597] in 2003. In 2004 the FDA approved NutreStore [L-glutamine for oral solution, NDA 021667] which should be administered as a cotherapy with Zorbtive together with optimal management of short bowel syndrome, such as a specialized oral diet. These are the only approved drugs for this condition; hence, there continues to exist a substantial need for additional treatment options.

Overview of Regulatory Activity
Subsequent to a pre-Investigational New Drug (IND) meeting on 20 October 1998, clinical development was initiated with the submission of IND 58,213 on 26 April 1999, supporting the development of teduglutide for the treatment of SBS. United States (US) orphan drug status was granted on 29 June 2000.

NPS and the Division of Gastroenterology and Inborn Errors Products (DGIEP) participated in 3 key face-to-face meetings to discuss the designs of the Phase 3 studies. The first of these meetings was the 06 October 2003 End-of-Phase 2 meeting wherein the Division agreed to the following key elements of the Study CL0600-004 protocol:

- acceptance of the primary endpoint (subjects achieving a reduction of 20% to 100% from baseline in weekly PN/I.V. volume at Week 24),
- selection of the SBS subject population,
- PN/I.V. volume optimization/stabilization procedure,
- use of placebo as the control,
- use of the teduglutide 0.05 mg/kg/day and 0.10 mg/kg/day dose levels to be tested
- the statistical analysis methodology to be employed.

After the results of Study 004 were known, a Type C Meeting was held on 18 January 2008. At this meeting, NPS agreed to perform a confirmatory trial (Study 020). The Division acknowledged NPS' choice of the 0.05 mg/kg/day teduglutide dose for Study 020. Lastly, a meeting was held on 14 July 2008 to further discuss the results of Study 004, the planned Phase 3 Study (020) and the acceptability of the same PN/I.V. reduction volume endpoint of the development program for filing a marketing application. The Division confirmed that only one additional confirmatory study using a 2-arm design (teduglutide 0.05 mg/kg/day vs placebo) would be necessary to support a filing.

3. CMC/Device

Dr. Yichun Sun is the CMC reviewer for this NDA and he concluded in his review that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

The applicant agreed to add a test method and acceptance criterion for (b) (4) to the drug substance specification in the amendment dated June 18, 2012. The applicant is currently developing a suitable procedure for evaluating teduglutide drug substance and plans to test representative batches, establish acceptance criteria, and add this test to the drug substance specification. The applicant proposes to implement this process as a post approval commitment. Because it is a potential safety concern, we will designate development of this specification as a post approval requirement (PMR).

Drug Substance

The active ingredient is teduglutide (rDNA origin) that is a 33 amino acid glucagon-like peptide-2 (GLP-2) analog manufactured using a strain of *Escherichia coli* (*E. coli*) modified by recombinant DNA technology. (b) (4) Teduglutide drug substance is a clear, colorless to light straw colored liquid composed of teduglutide in aqueous buffer.

Teduglutide for injection is supplied in a sterile, single-use 3-mL, USP Type I glass vial containing 5 mg of teduglutide as a white lyophilized powder. Each vial also contains 3.88 mg L-histidine, 15 mg mannitol, 0.644 mg monobasic sodium phosphate monohydrate, and 3.434 mg dibasic sodium phosphate heptahydrate. The lyophilized powder is intended to be reconstituted

with 0.5 mL of sterile Water for Injection (sWFI), USP, which is provided in a prefilled syringe, immediately before administration by subcutaneous injection.

A CMC site inspection/recommendation by the Office of Compliance is still pending as of the date of this review. It should be available soon.

Regarding Immunogenicity Assessments, we consulted Laboratory of Immunology, in the Office of Biotechnology Products, Division of Therapeutic Proteins. Faruk Sheikh, Ph.D., Staff Fellow, and Susan Kirshner, Ph.D., Associate Chief, Laboratory of Immunology found that the validation of the antibody screening assay and the neutralizing antibody assay were complete and accepteable for use in clinical sample analysis. The review team from the Laboratory of Immunology does not recommend additional studies at this time for the issue related to cross reaction to endogenous GLP; however, they do recommend that patients in on-going clinical studies continue to be tested to provide as much longitudinal immunogenicity data as possible, since this will likely be a life long therapy. In addition Dr. Sheikh recommends that the sponsor should be prepared to test samples from any patient who loses efficacy to Gattex treatment. I agree.

Most patients with SBS have part of their intestine removed and therefore may produce very low amount of endogenous GLP-2, therefore the impact of cross reactivity may not have much effect on treatment efficacy. Since, subjects with persistent antibodies to either teduglutide or GLP-2 continued to respond to treatment and did not show any evidence of clinical pathologies associated with immune-mediated reactions, the Laboratory of Immunology does not recommend additional studies at this time. See Dr. Sheikh's review for details.

4. Nonclinical Pharmacology/Toxicology

Dr. Tamal Chakraborti is the reviewer and Dr. Sushanta Chakder is the team leader for this NDA and they concluded in the review that from a nonclinical standpoint, this NDA is recommended for approval and has no recommendation for Post-Marketing Commitments, Agreements, Post-Markeeting Requirements and/or Risk Management Steps.

Based on the Dr. Chakraborti's review, the applicant has conducted adequate nonclinical studies with teduglutide which included pharmacology, safety pharmacology, pharmacokinetics, and acute toxicology studies in mice; and repeated dose toxicology studies in mice (14 days to 26 weeks duration), rats (14 day to 13 weeks duration), and Cynomolgus monkeys (14 to 1 year duration); toxicology studies in juvenile minipigs (14 days to 90 days duration); genotoxicity studies (Ames test, chromosome aberration test in Chinese hamster ovary cells, *in vivo* micronucleus test in mice), reproductive toxicology studies (fertility and early embryonic development in rats, and embryo-fetal development in rats and rabbits; pre and postnatal development studies in rats); and special toxicology studies in rabbits (antigenicity and local tolerance studies).

In toxicology studies, teduglutide was administered subcutaneously to mice (26-week treatment) up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg), rats (13-week treatment) up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg), and Cynomolgus monkeys (1-year treatment) up to 25 mg/kg/day (about 500 times the recommended daily human dose of 0.05 mg/kg).
In pivotal repeated dose toxicology studies, major treatment-related effects were related to the pharmacological activity of teduglutide and were seen in all species. In the 26-week study in mice at 2, 10 and 50 mg/kg/day, major treatment-related histopathological changes were seen at all doses in the small and large intestine (epithelial and villus hypertrophy and hyperplasia), gall bladder (epithelial hypertrophy and hyperplasia accompanied by subacute inflammation), sternal bone marrow (myeloid hyperplasia) and injection site (inflammation and necrosis). In the 13-week study in rats at 10, 25 and 50 mg/kg/day, major treatment-related histopathological changes were seen at all doses in the small and large intestine (mucosal hypertrophy and hyperplasia) and injection site (inflammation and necrosis). In the 1-year study in Cynomolgus monkeys at 1, 5 and 25 mg/kg/day, major treatment-related histopathological changes were seen at all doses in the small and large intestine (mucosal hyperplasia), stomach (mucosal hyperplasia), pancreas (hypertrophy/hyperplasia of the pancreatic duct epithelium), liver and gall bladder (epithelial hypertrophy and hyperplasia of the bile duct in the liver and mucosal hypertrophy/hyperplasia of the gall bladder) and injection site (inflammation and necrosis).

Teduglutide was negative in the Ames test, *in vitro* chromosomal aberration test in Chinese hamster ovary (CHO) cells, and *in vivo* mouse micronucleus test. In a 2-year carcinogenicity study by the subcutaneous route in Wistar Han rats at 3, 10 and 35 mg/kg/day, teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. There were no drug related tumor findings in females. A 2-year mouse carcinogenicity study is ongoing. By virtue of its mechanism of action (intestinotrophic activity or growth promoting pharmacological effect) and the findings of the carcinogenicity study in rats, teduglutide has the potential to cause hyperplastic changes including carcinogenicity in humans.

In the subcutaneous fertility and early embryonic development study in rats at 2, 10 and 50 mg/kg/day, teduglutide did not show any adverse effects on early embryonic development or fertility parameters up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). In the subcutaneous embryofetal development study in rats at 2, 10 and 50 mg/kg/day, teduglutide was not teratogenic up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). In the subcutaneous embryofetal development study in rabbits at 2, 10 and 50 mg/kg/day, teduglutide was not teratogenic up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). In the subcutaneous pre and postnatal development study in rats at 10, 25 and 50 mg/kg/day, teduglutide did not show any significant adverse effect on pre and postnatal development up to 50 mg/kg/day.

Overall, based on Dr. Chakraborti's review, nonclinical safety of teduglutide has been adequately tested in several toxicology studies. Nonclinical studies conducted with teduglutide provide adequate assurance of safety and support its proposed use at the intended therapeutic dosage and in accordance with the proposed product labeling. However, by virtue of its mechanism of action (intestinotrophic activity or growth promoting pharmacological effect) and the findings of the carcinogenicity study in rats, teduglutide has the potential to cause

hyperplastic changes including carcinogenicity in humans. For detail, please see Dr. Chakraborti's review.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Lanyan Fang is the Clinical Pharmacology reviewer for this NDA and Dr. Yow-Ming Wang, is the Team Leader. They reviewed the NDA and concluded that NDA 203441 is approvable. They recommend a post marketing requirement (PMR) as a sub-study of the long term post-marketing safety trial to assess the long-term impact of anti-drug antibodies (ADA) on safety and efficacy (to include *in vivo* determination of ADA levels). See Dr. Fang's review for details.

Based on the review provided by Dr. Fang, Clinical Pharmacology Findings are summarized as follows:

Pharmacokinetics (PK)

Absorption

Teduglutide was absorbed with a peak concentration at 3-5 hours after subcutaneous (SC) administration at the abdomen, thigh, or arm with the to-be-marketed concentration (10 mg/mL). The maximal plasma concentration and exposure (Cmax and AUC) of teduglutide was dose proportional over the dose range of 0.05 to 0.4 mg/kg. No accumulation of teduglutide was observed following repeated daily SC administration. In healthy subjects, teduglutide had an absolute bioavailability of 88% after abdominal SC administration. Following SC administration of 0.05 mg/kg/day of teduglutide to subjects with SBS, median peak teduglutide concentration (Cmax) was 36.8 ng/mL and overall median area under the curve (AUC0-τ) was 0.15 $\mu g \cdot hr/mL$.

Metabolism

The metabolic pathway of teduglutide was not investigated in humans; however, as an analog to native GLP-2, teduglutide is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous GLP-2. Teduglutide is not likely to be metabolized by common drug metabolizing enzymes such as CYP, glutathione-S-transferase, or uridine-diphosphate glucuronyltransferase.

Elimination

Following IV administration in healthy subjects, teduglutide plasma clearance was approximately 127 mL/hr/kg which is roughly equivalent to the GFR suggesting that teduglutide is primarily cleared by the kidney. Teduglutide was rapidly eliminated with a mean terminal half life (t1/2) of approximately 2 hours in healthy subjects and 1.3 hours in SBS subjects.

Special Population

Plasma concentration-time profiles of teduglutide were similar for healthy younger and elderly subjects. Except for creatinine clearance (CLcr), none of the evaluated intrinsic factors including age, gender, and hepatic impairment had a significant effect on the PK of teduglutide.

Hepatic Impairment

Following a single SC administration of 20 mg of teduglutide to subjects with moderate hepatic impairment, teduglutide Cmax and AUC were lower (10 ~15%) compared to those in healthy matched control subjects; no dose adjustment is needed when administered to individuals with moderate hepatic impairment. Teduglutide was not assessed in subjects with severe hepatic impairment.

Renal Impairment
Following a single SC administration of 10 mg teduglutide to subjects with moderate to severe renal impairment or end stage renal disease (ESRD), teduglutide Cmax and AUC0-∞ increased with increasing degree of renal impairment. The primary PK parameters of teduglutide increased up to a factor of 2.6 (AUC0-∞) and 2.1 (Cmax) in ESRD subjects compared to healthy subjects. Based on these results, SBS patients with renal impairment would be exposed to higher levels of teduglutide due to a decrease in the renal clearance of the drug. Therefore, a dose reduction of 50% is recommended in patients with moderate to severe renal impairment and ESRD.

Drug-Drug Interaction (DDI)
No *in vivo* DDI studies were conducted based on results from *in vitro* studies in which significant inhibition or induction of tested cytochrome P450 isozymes was not observed at 2000 ng/mL teduglutide, a concentration significantly greater (55-fold) than of the median Cmax at the clinical dose of 0.05 mg/kg.

The potential for teduglutide mediated drug-drug interactions exists considering teduglutide has demonstrated a PD effect of increasing intestinal absorption. This effect needs to be considered when teduglutide is co-administered with drugs requiring titration or having a narrow therapeutic index.

QTc Prolongation
No significant QTc prolongation was detected at a supra-therapeutic teduglutide dose of 20 mg in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between teduglutide (5 mg and 20 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, indicating that the magnitude of moxifloxacin can be detected in this study.

Immunogenicity
Immunogenicity incidence – anti-drug antibody (ADA)
In the pivotal Phase 3 study (CL0600-020), the incidence of anti-teduglutide IgG antibody was 0% (0/16) at Week 12 and 18% (6/34) at Week 24 in subjects who received SC administration of 0.05 mg/kg teduglutide once a day. Of the 16 subjects, who were ADA negative (ADA-) at Week 12, 2 subjects were confirmed to be ADA positive (ADA+) at Week 24. This suggests that the immunogenicity incidence rate increased with the duration of treatment.

In the Phase 3 open label extension study (021) where subjects had the option to continue taking teduglutide 0.05 mg/kg/day for up to 2 years, twenty-seven out of 85 subjects (27/85, 32%) were ADA positive at one or more time points post baseline up to the approximate

1-year data cut (study currently ongoing). Among 34 subjects who were treated with teduglutide in both the pivotal study and the extension study, 6 subjects tested ADA+ at baseline (of which 5 continued to be ADA+) in the extension study and 8 additional subjects became ADA+ post-baseline. The incidence rate was 38% (13/34) for subjects who received teduglutide treatment for the duration of 18 months. Among 51 subjects who initiated teduglutide treatment in the extension study, 14 subjects were ADA+ (14/51, 27%) during the extension study after teduglutide treatment of 12 months.

Overall, the immunogenicity incidence rate increased with the duration of treatment (18% at 6 months, 27% at 12 months and 38% at 18 months) and the majority of subjects had the first occurrence of ADA+ finding at Month 6 post-treatment.

Cross-reactivity of ADA to GLP-2
Anti-teduglutide specific antibodies showed evidence of cross reactivity against the native GLP-2 protein in five out of the six ADA positive subjects in Study CL0600-020.

Immunogenicity incidence – neutralizing antibody
No subjects in the SBS population developed neutralizing antibodies during the clinical trials. This result should be interpreted with caution as circulating drug concentration could interfere with the assay for neutralizing antibodies as the assay has a drug tolerance of 1.5 ng/mL.

Immunogenicity Impact on PK, Efficacy and Safety
The impact of ADA on PK is unknown as it has not been adequately assessed. The sponsor's population PK analysis was unsuccessful in evaluating the effect of ADA on teduglutide PK due to an inadequate design.

ADA appears to have no impact on the short term clinical efficacy up to 1.5 years; however, the long term impact is unknown. In the pivotal Phase 3 study (CL0600-020), all 6 subjects who were ADA positive ADA at Week 24 were responders. In the extension study (CL0600-021), 26 out of 27 subjects who developed positive ADA post baseline had reduced PN/IV volume at the time of last dosing visit.

ADA appears to have no impact on the short term clinical safety up to 1.5 years; however, the long term impact is unknown. None of the 6 subjects who developed positive ADA in CL0600-020 study had evidence of a hypersensitivity adverse event (AE) or immune related clinical symptoms. In the open-label extension CL0600-021 study, 3 of 27 subjects who tested positive for ADA experienced an injection site reaction without evidence of any other hypersensitivity reactions.

Young Moon Choi, Ph.D., Pharmacologist and Michael F. Skelly, Ph.D., Pharmacologist from the Bioequivalence Branch, Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations conducted audits of the pharmacokinetic bioanalytical portions of safety-efficacy study 004 and its extension Study 005. They recommend that pharmacokinetic portions of study CL0600-004 be accepted for agency review. The reviewers recommend that the immunologic assessments from Tandem Labs for studies CL0600-004 and CL0600-005 be accepted for agency review.

6. Clinical Microbiology

Bryan S. Riley, Ph.D. did a Product Quality Microbiology Review for this NDA and concluded that the drug product is sterile (b) (4) and lyophilized and recommends that the NDA be approved. For a detailed Product Quality Microbiology evaluation, please see Dr. Riley's review.

7. Clinical/Statistical- Efficacy

Evidence of efficacy of teduglutide 0.05 mg/kg/day for the treatment of SBS is provided by the two Phase 3 studies (020 and 004), the completed long-term extension study to 004 (Study 005), and the ongoing extension study to 020 (Study 021). Dr. John Troiani is the medical officer and Behrang Vali is the statistician for this NDA.

Both Phase 3 studies, 020 and 004 were prospective, randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter studies. The population enrolled in these studies was adult subjects with SBS due to intestinal resection who were dependent on parenteral support for at least 12 months (including PN/I.V. support) and for at least 3 times per week. The studies were conducted in the United States, Canada, and Europe at a total of 27 and 32 centers for Studies 020 and 004, respectively. The underlying cause and severity of SBS was comparable among centers.

Studies 020 and 004 included a screening visit, baseline treatment optimization period, and a stabilization period prior to randomization. If at screening subjects did not have a stable PN/I.V. volume as indicated by a targeted urine output of 1.0-2.0 L/day, they entered an optimization period (8 weeks maximum). The purpose of the optimization period was to establish each subject's tolerated baseline PN/I.V. fluid volume which would result in urine output between 1.0 and 2.0 L/day. Following the optimization period, all subjects entered a 4 to 8 week stabilization period during which they were maintained on the stabilized, tolerated PN/I.V. volume. Subjects who demonstrated PN/I.V. volume stability for at least 4 consecutive weeks were eligible for randomization and entry into the treatment period. If a subject failed to remain stable for at least 4 consecutive weeks immediately prior to randomization, the subject was allowed to start the optimization period again. Those subjects who failed to stabilize after 2 attempts were not randomized.

Following the optimization and stabilization period, subjects were randomized into a 24-week treatment phase. For Study 020, subjects were randomized in a 1:1 ratio into the teduglutide 0.05 mg/kg/day or placebo treatment groups. In Study 004, subjects were randomized in a 2:2:1 ratio to teduglutide 0.05 mg/kg/day, teduglutide 0.10 mg/kg/day or placebo treatment groups, respectively. The choice of dose for Study 004 was based upon the results of a phase 2 study wherein a highly significant increase in gastrointestinal fluid absorption of approximately 750 to 1000 mL/day (corresponding to a relative increase of up to 30%) was observed at the end of treatment with both doses of 0.10 and 0.15 mg/kg/day, but not with the dose of 0.03 mg/kg/day. The 0.10 mg/kg/day dose was selected as the high dose because there was no difference observed

between the 0.10 mg/kg/day and 0.15 mg/kg/day groups and 0.05 mg/kg/day was selected as the low dose to determine whether a dose lower than 0.10 mg/kg/day but greater than 0.03 mg/kg/day was effective. In Study 020, the dose of 0.05 mg/kg/day was chosen to confirm the results from Study 004 observed in the corresponding dose group. In Study 004, the 0.10 mg/kg/day dose group provided no further clinical benefit as compared with the 0.05 mg/kg/day group at the end of the treatment period; therefore, 0.05 mg/kg/day of teduglutide was selected as the dose for Study 020.

In both studies, teduglutide or matching placebo was to be administered by subcutaneous injection once daily into 1 of the 4 quadrants of the abdomen, either thigh, or in Study 020 only, into either arm. Adjustments of PN/I.V. volume were to be made at dosing Weeks 2 (Study 020 only), 4, 8, 12, 16, and 20. These adjustments were to be made by the investigator in accordance with the protocol-established guidance based on 48-hour urinary output collected just before the study visit. PN/I.V. fluid volume reductions were to be made if adequate hydration was demonstrated with an increase of at least 10% in urinary output from the baseline value. The PN/I.V. volume adjustment was maintained until the next dosing visit if the subject tolerated the reduction (i.e., was not dehydrated) at an interim safety evaluation conducted by the investigator.

The efficacy endpoints for both studies were related to the reduction from baseline in PN/I.V. volume at various subsequent study time points, however, the primary efficacy variables differed between studies. For Study 020, the primary efficacy variable was the percentage of subjects that demonstrated a relevant response (i.e., a reduction of 20% to 100% from baseline in PN/I.V. volume) at Week 20 and 24 of treatment. Subjects who met these criteria were deemed "responders" and as such, the primary efficacy analysis in Study 020 is also referred to as the "responder analysis." For patients requiring parenteral support 5 times per week, a 20% reduction could translate into a reduction of parenteral support by 1 day per week. Further, reductions in PN/I.V. volume might result in a reduction in the number of days per week of PN/I.V. support. Slower infusion rates leading to decreased frequency of nocturia and less interrupted sleep, reduced infusion time per day, decreased stomal output or diarrhea, and reduced costs and resources associated with managing patients on long-term PN/I.V. support. A reduction in the burden of parenteral support can also be translated into decreased infusion time which would have several clinical advantages, in particular the potential decrease of the risk of I.V.-catheter associated sepsis and/or other complications secondary to the chronic use of parenteral support such as liver disease. Therefore, this primary endpoint, even at the 20% reduction level, is clinically meaningful.

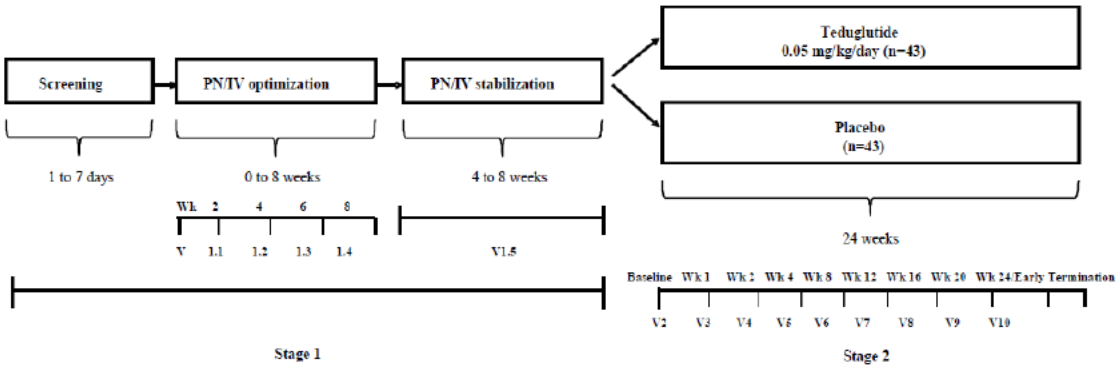
For Study 004, the original protocol stated that the primary efficacy variable was also to be a responder analysis defined as it was in Study 020. However, per Study 004 Protocol Amendments 4 and 4b (finalized prior to the blind being broken), the primary efficacy analysis was modified to incorporate both the intensity and duration of the reduction in PN/I.V. volume (i.e., graded response). Following the amendment, the responder analysis was retained as a secondary efficacy analysis in Study 004.

Study CL0600-020

Study 020 was a randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter study. The entire study was comprised of 2 stages (Figure 1).

Stage 1 included a screening visit, an optimization period of a maximum of 8 weeks, and a stabilization period that demonstrated stable administration of PN/I.V. volume for a minimum of 4 weeks up to a maximum of 8 weeks.

Figure 1: Study Design – Study CL0600-020



PN/I.V.= Parenteral nutrition/intravenous fluids; V=Visit; Wk=Week

The purpose of the optimization period was to establish each subject's tolerated baseline PN/I.V. volume which would result in urine output between 1.0 and 2.0 L/day. Subjects who demonstrated PN/I.V. volume stability for at least 4 weeks were eligible for randomization and entry into the treatment period. Baseline values were determined at the end of the stabilization period just prior to the start of the dosing period. Stage 2 was to be a dosing period of 24 weeks. Randomization was to be stratified by PN/I.V. consumption level at baseline (≤6 L/week, >6 L/week).

Efficacy Endpoints:

The primary efficacy variable was the percentage of subjects who demonstrated a response at Week 20 and at Week 24 (responder). A response was defined as the achievement of a 20% to 100% reduction from baseline in weekly PN/I.V. volume.

The secondary efficacy variables were based upon reductions in PN/I.V. volume. The variables were to include: percent change and absolute change in PN/I.V. volume between baseline and last dosing visit; duration of response; the proportion of subjects with ≥ 20% reduction or a ≥ 2 L reduction from baseline in weekly PN/I.V. volume at Week 20 and at Week 24; the number of subjects who stop (were able to wean from) PN/I.V. and the time to discontinuation of PN/IV. The reduction of the number of days with PN/I.V. infusion was an exploratory measure.

Statistical Methodology:

The primary analysis compared the response rates for the 2 treatment groups using Cochran-Mantel-Haenszel test statistics adjusted for the stratification variable (baseline PN/I.V., 6 L/week or less, or more than 6 L/week). All categorical secondary endpoints were analyzed in a similar fashion. Continuous secondary endpoints were analyzed using analysis of variance

incorporating treatment effects and continuous measures corresponding to stratification variables. Secondary efficacy parameters were hierarchically tested.

Subject Demographics and Baseline Characteristics:
The Intent-to-Treat (ITT) Population included 86 subjects who were randomized: 43 placebo and 43 teduglutide 0.05 mg/kg/day. In general, baseline demographic data were similar between treatment groups. The majority of subjects enrolled in this study were Caucasian (83/86 subjects, 96.5%), between 45 and 65 years of age (46/86 subjects, 53.5%). 15.1% (13/86 subjects) were ≥65 years of age. The population was 46.5% male (40/86 subjects) and 53.5% female (46/86 subjects). There were no statistically significant differences between treatment groups in any of the demographic and baseline characteristics.

Table 1 Demographics and Baseline Characteristics - ITT Population

Parameter	Statistic	Placebo (N=43)	Teduglutide 0.05 mg/kg/day (N=43)	All Subjects (N=86)
Age at Informed Consent (years)	**n**	**43**	**43**	**86**
	Mean (SD)	49.7 (15.6)	50.9 (12.6)	50.3 (14.1)
	Median	50.0	50.0	50.0
	Min, Max	18, 82	22, 78	18, 82
	p-value		0.694	
<45 years	n (%)	14 (32.6)	13 (30.2)	27 (31.4)
45-<65 years	n (%)	23 (53.5)	23 (53.5)	46 (53.5)
≥65 years	n (%)	6 (14.0)	7 (16.3)	13 (15.1)
Gender	**n**	**43**	**43**	**86**
Male	n (%)	19 (44.2)	21 (48.8)	40 (46.5)
Female	n (%)	24 (55.8)	22 (51.2)	46 (53.5)
	p-value		0.829	
Race	**n**	**43**	**43**	**86**
White	n (%)	41 (95.3)	42 (97.7)	83 (96.5)
Black	n (%)	1 (2.3)	0	1 (1.2)
Asian	n (%)	1 (2.3)	1 (2.3)	2 (2.3)
Ethnicity	**n**	**43**	**43**	**86**
Hispanic or Latino	n (%)	4 (9.3)	5 (11.6)	9 (10.5)
Not Hispanic or Latino	n (%)	39 (90.7)	38 (88.4)	77 (89.5)
Baseline PN/I.V. Randomization Stratification	**n**	**43**	**43**	**86**
≤6 L/week	n (%)	7 (16.3)	8 (18.6)	15 (17.4)
>6 L/week	n (%)	36 (83.7)	35 (81.4)	71 (82.6)
Height (cm)	**n**	**43**	**42**	**85**
	Mean (SD)	165.9 (9.6)	166.9 (9.7)	166.4 (9.6)
	Median	166.0	168.0	167.0
	Min, Max	142, 190	147, 190	142, 190
	p-value		0.657	
Body Weight at Baseline (kg)	**n**	**43**	**42**	**85**
	Mean (SD)	61.70 (12.61)	62.74 (11.41)	62.21 (11.97)
	Median	59.10	61.40	60.85
	Min, Max	40.9, 86.0	43.4, 87.9	40.9, 87.9
	p-value		0.691	

The reasons for major intestinal resection in this SBS population were: vascular disease (29/85 subjects, 34.1%), Crohn's Disease (18/85 subjects, 21.2%) or "other" reason (18/85 subjects, 21.2%). A stoma was present in 38/85 subjects (44.7%) with the most common type being jejunostomy/ileostomy (31/38 subjects, 81.6%). The mean length ±SD of the remaining small intestine was 77.3 ± 64.4 cm (range: 5 to 343 cm). The length of small intestine was greater for subjects in the teduglutide group (86.2 cm) compared with the placebo group (68.7 cm) and this may be a potential bias in favor of the teduglutide group. The colon was not in continuity in 37/85 subjects (43.5%). Forty-eight of 85 subjects (56.5%) had some degree of colon in continuity. For subjects with any remaining colon, a mean of 63.1% of colon was present. Subjects in the placebo group had a higher numerical percentage of mean colon remaining (70.3%) than the teduglutide group (55.6%). This may balance the potential bias in which the length of small intestine was greater for subjects in the teduglutide group (86.2 cm) compared with the placebo group (68.7 cm). Of the 24 subjects with remaining distal/terminal ileum, the ileocecal valve was present in 13 subjects (54.2%).

Mean (±SD) prescribed weekly PN/I.V. volume at baseline was 12.87 L (±7.57). Mean prescribed days/ week requiring PN/I.V. infusion was 5.73 (±1.59) days. Most of the subjects (75/85, 88.2%) had a subclavian central venous I.V. access. Ten of 85 subjects (11.8%) were treated for central I.V. line infections during the 6 months prior to screening. The most frequently reported GI medical/surgical histories were gastrointestinal disorders (teduglutide 40/42 subjects, 95.2%; placebo 41/43 subjects, 95.3%) and infections and infestations (teduglutide 25/42 subjects, 59.5%; placebo 23/43 subjects, 53.5%).

The majority of subjects reported having taken at least one concomitant medication (teduglutide 41/42 subjects, 97.6% and placebo 41/43 subjects 95.3%; Safety Population). The most frequently reported concomitant medications (≥15% in either treatment group) were proton pump inhibitors (esomeprazole, omeprazole and pantoprazole) and antipropulsives (loperamide).

Efficacy Results:
The results of the primary efficacy analysis from Study 020 are summarized in Table 2. The number and percent of subjects with a clinically relevant response at week 20 and at week 24 (responders) was greater in the teduglutide treatment group (27/43 subjects, 62.8%) compared with the placebo group (13/43 subjects, 30.2%). This difference was statistically significant (p = 0.002).

Table 2: Subjects Achieving a Clinically-Relevant Response at Week 20 and at Week 24 – Intent-to-Treat Population – Study CL0600-020

Response Status	Statistic	Placebo (N= 43) n (%)	Teduglutide 0.05 mg/kg/day (N= 43) n (%)
Non-responder	n (%)	30 (69.8)	16 (37.2)
Responder	n (%)	13 (30.2)	27 (62.8)
	p-value		0.002

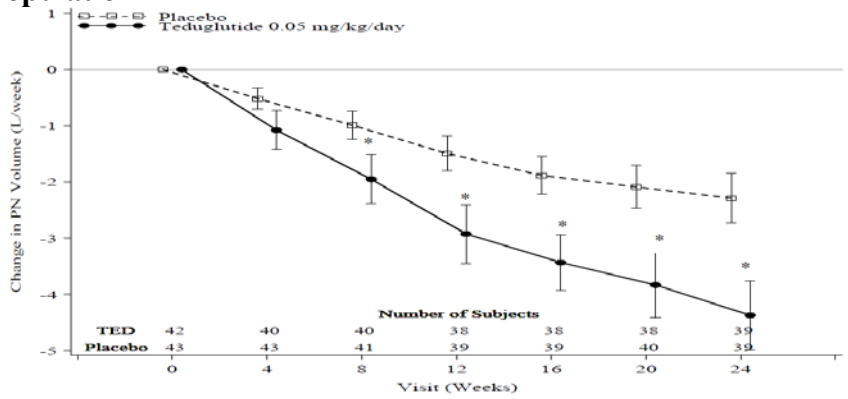
N, n = number

Note: Percentages are based on the number of subjects in the Intent-to-Treat Population.
Note: The treatment comparison is based on a Cochran-Mantel-Haenszel test adjusted for the randomization stratification variable.

The results of key secondary efficacy analyses from Study 020 are summarized below:

At all visits, subjects on teduglutide had greater absolute and percent changes from baseline in actual PN/I.V. volume compared to placebo, with statistical significance starting at Week 8 and Week 12, respectively, and continuing through Week 24 (Figure 2).

Figure 2: Absolute Change in PN Volume (L/week ± SE): Intent To Treat (ITT) Population



L=liter; SE=standard error, TED=teduglutide
* p < 0.05

The mean absolute change from Baseline in PN/I.V. volume at Week 24 was greater in the teduglutide group compared with placebo (-4.4L/week and -2.3L/week, respectively, p <0.001).

The mean percent change from Baseline in PN/I.V. volume at Week 24 was greater in the teduglutide group compared with placebo (-32% and -21%, respectively, p = 0.017).

The percentage of subjects with a duration of response for ≥3 consecutive visits was higher in the teduglutide group (24/43 subjects, 55.8%) than in the placebo group (12/43 subjects, 27.9%).

The distribution of duration of response categories was statistically significant (p=0.005) between treatment groups in favor of teduglutide.

The percent of subjects who achieved at least a 20% or 2 L reduction in PN/I.V. volume at Week 20 and at Week 24 was greater in the teduglutide treatment group compared with placebo (70% and 37%, respectively, p = 0.002).

No subjects were considered to have completely weaned off of their PN/I.V. fluid at the end of the study. One placebo subject had stopped PN/I.V. fluid during the 14 days prior to Week 24 however, this subject was not considered successful in weaning off PN/I.V. support since PN/I.V. was only temporarily interrupted due to hospitalization and catheter replacement (the implanted catheter was not working) immediately prior to Week 24. PN/I.V. support was provided to this subject both before and after the episode of catheter malfunction.

By Week 24, 30/39 (77%) of subjects on teduglutide demonstrated a response. Further analyses showed that a 1-day or more reduction in weekly actual PN/I.V. volume at Week 24 was achieved in 21/39 subjects (53.8%) in the teduglutide group compared with 9/39 subjects (23.1%) in the placebo group (p = 0.005).

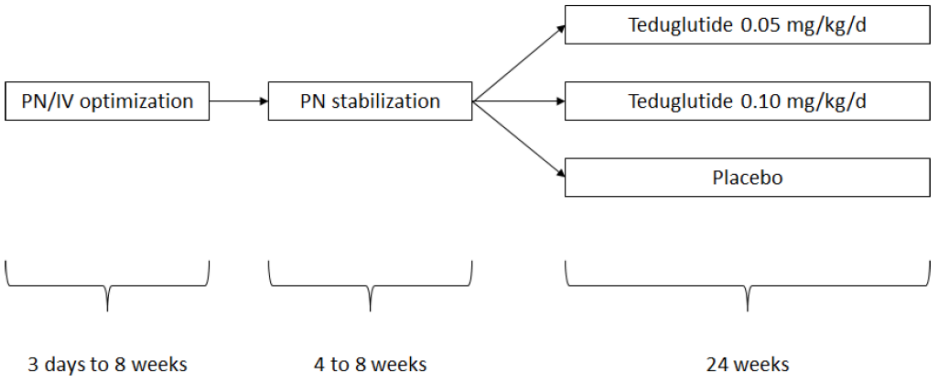
Lastly, to support the primary efficacy endpoint, an analysis of change in the fluid composite effect (PN/I.V. volume + Oral Fluid Intake volume – Urine Output volume) was performed; at all visits, greater reductions in the fluid composite effect were observed in the teduglutide group compared with the placebo group. The mean reduction in the teduglutide group was greater than that seen in the placebo group at all visits through Week 24 (- 5.38 L/week in the teduglutide group vs -1.07 L/week in the placebo group).

In summary, I concur with Dr. Troiani's assessment that based on the results of Study 020, teduglutide at a dose level of 0.05 mg/kg/day for up to 24 weeks of treatment was superior to placebo in reducing the volume of PN/I.V. in adult SBS subjects. Please see Dr. Troiani's review for a detailed efficacy evaluation.

Study CL0600-004

Study 004 was a 24-week double-blind, randomized, parallel group, placebo-controlled, multinational, multicenter study. The study consisted of a screening visit, a PN/I.V. fluid volume-optimization period, a stabilization period, a subsequent dosing period of 24 weeks (Figure 3) and a follow-up period of 4 weeks (for subjects not electing to participate in the extension study 005). Note that the Study 004 protocol and study report refer to the PN/I.V. fluid volume optimization period as the PN/I.V. optimization period and these terms should be considered synonymous.

Figure 3: Study Diagram – Study CL0600-004



After the successful completion of the stabilization period, subjects were randomized in a 1:2:2 ratio into the placebo, teduglutide 0.05 mg/kg/day, or teduglutide 0.10 mg/kg/day treatment groups.

During the 24-week treatment phase, investigators adjusted each subject's PN/I.V. volume based on guidance suggested in the protocol. Investigators increased PN/I.V. volume if urine output was less than 1.0L/day or less than at Baseline. If urine output increased by at least 10% from Baseline, investigators could decrease PN/I.V. volume by 10% of the optimized Baseline PN/I.V. volume. Attempts to reduce PN/I.V. volume were made at dosing Weeks 4, 8, 12, 16, and 20.

Efficacy Endpoints:
Based on protocol Amendments 4 and 4b which were implemented prior to completion of study enrollment and prior to the blind being broken, the primary efficacy variable was changed to be an ordered categorical (or graded) response that accounted for both intensity and duration of the response at the end of the 24-week treatment period. The original primary efficacy variable (number and percent of responders) was changed to a key secondary efficacy variable.

Statistical Methodology:
For the amended primary efficacy variable, the ordered categorical response variable was summarized for each treatment group using descriptive statistics. Overall treatment comparisons were to be made using rank analysis of covariance with strata for the baseline PN/I.V. fluid consumption level used for the stratification of the randomization and treatment group with the baseline weekly PN/I.V. volume as a covariate. A step-down procedure was to be used to adjust for multiple comparisons when testing multiple hypotheses of treatment effect. In this procedure, the high dose vs placebo comparison needed to be significant at a p=0.05 level before testing the low dose vs placebo comparison. The primary analysis was to be conducted on the protocol-defined ITT Population (including all randomized subjects who received at least 1 dose of study drug).

Overall treatment group comparisons were to be made using rank analysis of covariance with strata for the baseline PN/I.V. fluid consumption level and treatment group. The key secondary variable (response at Week 20 and at Week 24) was summarized by the number and percentage

of responders. Pairwise comparisons between treatment groups were made using Fisher's Exact Test.

The additional secondary efficacy variables were summarized using descriptive statistics at each time point for each treatment group. For change from baseline variables, pairwise differences between treatment groups utilized estimates from a 2-way repeated measures analysis of covariance (ANCOVA). The model included effects for treatment group, visits, baseline weekly PN/I.V. volume, and baseline PN/I.V. fluid stratification of the randomization as covariates.

Subject Demographics and Baseline Characteristics:
The protocol-defined ITT Population included 83 subjects who were randomized and received at least 1 dose of study medication: 16 placebo, 35 teduglutide 0.05 mg/kg/day, and 32 teduglutide 0.10 mg/kg/day. One subject randomized to receive teduglutide 0.10 mg/kg/day was not treated with study drug and was excluded from the ITT Population. The majority of subjects in the ITT Population were Caucasian (77/83, 92.8%). The age range was 19 to 79 years (mean age 48.8 years) and 32/83 subjects (38.6%) were ≥ 55 years of age. There were more female (46/83, 55.4%) than male (37/83, 44.6%) subjects. The high-dose group had a larger number of subjects (11/32, 34.4%) dependent on PN/I.V. support 6 to 7 times a week and fewer subjects receiving only I.V. fluids (3/32, 9.4%) compared with the low-dose and placebo groups, but the differences were not statistically significant among any of the treatment groups for any of the PN/I.V. fluid consumption levels. There were no significant differences across treatment groups in any of the demographic characteristics at baseline.

The primary reasons for intestinal resection in this SBS population were: Crohn's Disease (30/83, 36.1%) and vascular disease (25/83, 30.1%). A Stoma was present in 29/83 subjects (34.9%). The mean length ± SD of the remaining small intestine was 65.8 ± 45.4 cm (range: 6 to 200 cm). The colon was included in the resection in 27/83 (32.5%) subjects. Of the 56/83 (67.5%) subjects with some degree of colon in continuity, 20 subjects (35.7%) had 75% to 100% of colon remaining and 19 subjects (33.9%) had >25% to 50% of colon remaining.

The remaining 17 (30.4%) subjects had between >50% and 75% of the colon present. Of the 17/83 (20.5%) subjects with a distal/terminal ileum, the ileocecal valve was present in 9/17 (52.9%) subjects and absent in 8/17 (47.1%) subjects. The mean actual weekly PN/I.V. volume for the ITT Population was 11.1 L (± 6.03) at baseline. Subjects receiving teduglutide 0.10 mg/kg/day had a higher mean actual PN/I.V. volume at baseline (12.7 L) compared with subjects receiving teduglutide 0.05mg/kg/day (9.6 L) or placebo (10.7 L). Most subjects (71/83, 85.5%) had central venous I.V. access. Approximately one-fourth of the subjects (23/83, 27.7%) had been treated for I.V. line infections, thromboses, or occlusions during the prior 6 months. The most frequently reported GI related medical /surgical past medical history diagnoses/events were small intestinal resection (37/83, 44.6%), Crohn's Disease (30/83, 36.1%), intestinal anastomosis (27/83, 32.5%), cholecystectomy (23/83, 27.7%), short-bowel syndrome (21/83. 25.3%), partial colectomy (20/83, 24.1%), and intestinal resection (20/83, 24.1%). Percentages were comparable across treatment groups for all categories.

Efficacy Results:

The number and percent of subjects within each graded response category are summarized in Table 3. Although the number and percent of subjects with reduction of 20% to 100% from baseline in PN/I.V. volume (ie, categories 1 to 4) was higher in the teduglutide 0.10 mg/kg/day group compared with placebo, the total graded score was not statistically significantly different from placebo (p =0.161). The step down procedure stated that no further testing should be conducted if there was no statistically significant difference between teduglutide 0.10 mg/kg/day and placebo. The results of an additional exploratory analysis yielded a p-value (rank-ANCOVA) for the difference in the total graded score between the teduglutide 0.05 mg/kg/day and placebo treatment group of 0.007.

Table 3: Summary of the Results for the Graded Score - ITT Population -Study 004

	Response Category, n(%)				
	0 **No Response**	**1**	**2**	**4**	**5** **Off PN/I.V.**
Placebo	15 (93.8)	0	1 (6.3)	0	0
Teduglutide 0.05 mg/kg/day	19 (54.3)	6 (17.1)	6 (17.1)	2 (5.7)	2 (5.7)
Teduglutide 0.10 mg/kg/day	24 (75.0)	2 (6.3)	4 (12.5)	2 (6.3)	0
Total: (0.05 + 0.10 mg/kg/day)	43 (64.2)	8 (11.9)	10 (14.9)	4 (6.0)	2 (3.0)

PN/I.V. = parenteral nutrition/intravenous fluids
Note: Subject # 0126-0001 was missing the baseline value and could not be ranked.

The number and percent of responders (i.e., subjects who achieved a response at Week 20 and Week 24) was higher in the teduglutide 0.05 mg/kg/day (16/35, 45.7%) and 0.10 mg/kg/day (8/32, 25.0%) treatment groups compared with placebo (1/16, 6.3%). The p-values for the teduglutide and placebo comparisons were 0.005 and 0.172 for the teduglutide 0.05 mg/kg/day and 0.10 mg/kg/day treatment groups, respectively. A greater proportion of subjects in the teduglutide 0.05 mg/kg/day treatment group achieved at least a 1-day reduction in weekly PN/I.V. volume compared with the teduglutide 0.10 mg/kg/day or placebo treatment groups. There was no statistically significant difference for a 1-day reduction in PN/I.V. volume between either teduglutide treatment group and placebo. The Week 24 mean weekly reduction from baseline in PN/I.V. volume was similar in both teduglutide groups (~2.5L) and higher than the placebo group (0.90L); however, there were no statistically significant differences between groups. The number of subjects completely weaned off of PN/I.V. support in the teduglutide 0.05 mg/kg/day, teduglutide 0.10 mg/kg/day, and placebo groups by Week 24 was 2, 1, and 0, respectively.

Additional analyses were performed to further explore the observed lack of dose response on the primary efficacy variable and on the percent responders. The sponsor hypothesized that the observed differences between treatment groups could be explained by limitations imposed by the protocol design with respect to PN/I.V. reductions and a larger baseline PN/I.V. volume requirement in the teduglutide 0.10 mg/kg/day group than in the other 2 groups.

As noted in the design of the study, investigators were to decrease PN/I.V. volume as urine output increased. Subjects were also encouraged to keep oral fluid intake constant relative to their oral intake at baseline so that changes in urine output could be taken as a surrogate for improved intestinal absorption. To prevent investigators from reducing PN/I.V. volume to such an extent that they inadvertently caused dehydration, the protocol limited the maximum amount by which PN/I.V. volume could be reduced (no more than 10% reduction from baseline unless a subject's urine output was greater than 2 L/day and had increased at least 10% from baseline during the 48-hour measurement prior to a scheduled dosing visit). Furthermore, the protocol did not allow for PN/I.V. volume reductions until 4 weeks after beginning treatment. The sponsor further hypothesized that the results observed in the primary efficacy analysis (which only measured reductions in PN/I.V. volume) might underestimate the true clinical benefit of teduglutide (i.e., improvements in intestinal fluid absorption) because PN/I.V. volume reductions were artificially constrained and changes in oral fluid intake were not factored into the analysis.

Exploratory analyses were therefore performed to determine whether changes in oral fluid intake or changes in the composite of PN/I.V. volume, oral fluid intake volume, and urine output volume (i.e., "fluid composite effect") could provide a further possible explanation for the unexpected results observed from the primary efficacy analysis for the teduglutide 0.10 mg/kg/day treatment group. These exploratory analyses revealed that subjects in the teduglutide 0.10 mg/kg/day group reduced their 48-hour oral fluid intake substantially before Week 4 (-684.5mL) and maintained the reduction throughout Week 24 (-784.6 mL). The reduction in oral fluid intake observed in the teduglutide 0.10 mg/kg/day group was greater compared with the teduglutide 0.05 mg/kg/day and placebo groups. The mean weekly reduction in the fluid composite effect at Week 24 was significantly greater in the teduglutide 0.10 mg/kg/day treatment group (-4.83L) compared with placebo (-0.84L) ($p=0.029$). Taken together, these results were consistent with the hypothesis that teduglutide improved intestinal fluid absorption, yet protocol restrictions on PN/I.V. volume reductions resulted in decreases in oral fluid intake.

Lastly, the statistically significant difference between teduglutide 0.10 mg/kg/day and placebo for the fluid composite effect suggested that the true effect on intestinal fluid absorption is better than the effect of placebo and similar to the 0.05 mg/kg/day dose.

Analyses of oral fluid intake and the fluid composite effect were also conducted for the teduglutide 0.05 mg/kg/day treatment group. For subjects in this treatment group, oral fluid intake values varied slightly between visits, yet there was no obvious trend towards a reduction. However, similar to the results of the teduglutide 0.10 mg/kg/day treatment group, the mean weekly reduction in the fluid composite effect at Week 24 was significantly greater for the teduglutide 0.05 mg/kg/day treatment group (-5.22 L/week) compared with placebo (-1.00 L/week) ($p=0.017$).

In summary, Study 004 did not meet its primary endpoint (i.e., the difference between teduglutide 0.10 mg/kg/day and placebo for the graded response analysis was not statistically significant). The exploratory analysis indicated that the proportion of teduglutide 0.05 mg/kg/day subjects achieving a response at Week 20 and 24 (responders) was greater than placebo (16/35, 45.7% vs 1/16, 6.3%; $p<0.005$). This comparison was the primary endpoint for Study 020. Two subjects who received the teduglutide 0.05 mg/kg/day regimen were able to be

totally weaned off parenteral support by Week 24. Treatment with this teduglutide regimen resulted in a 2.5 L/week reduction in parenteral support requirements versus 0.9 L/week for placebo at 24 weeks.

Results of secondary and exploratory analyses provide a reasonable explanation for the non-significant difference between the placebo and teduglutide 0.10 mg/kg/day treatment groups which resulted in the study not meeting its primary endpoint. These additional analyses indicate that teduglutide 0.05 mg/kg/day is effective at improving intestinal absorption and treating adults with SBS. I concur that Study 004 supports the conclusion of Study 020 that teduglutide at a dose level of 0.05 mg/kg/day for up to 24 weeks of treatment was superior to placebo in reducing the volume of PN/I.V. in adult SBS subjects. Please see Dr. Troiani's review for a detailed efficacy evaluation.

Efficacy Results in Open-label Extension Studies (005, 021)
The main efficacy results for study 005 were as follows:

- Response Maintainers: 75% (18/24) of subjects in the 1-Year Active Group maintained 'response' from study 004 through 005 in each subgroup (12/16 in 0. 05 group and 6/8 in 0.10 group).
- Mean reduction of PN/I.V. volume from baseline to Week-28:
  0.05/0.05 group: 4.9 L/wk reduction (57%)
  0.10/0.10 group: 3.3 L/wk reduction (27%)
- In the 1-Year Active Group, 48% (12/25) of subjects in the 0.05 group and 37% (10/27) in the 0.10 group reduced their need for I.V. catheter access.
- In the 1-Year Active Group, 68% (17/25) subjects in the 0.05 group and 37% (10/27) in the 0.10 group achieved at least a 1-day reduction in PN/I.V. fluid use.
- Complete weaning off PN/IV: The 2 subjects completely weaned off of PN/IV in Study 004 remained PN/I.V.-free through Study 005.An additional subject was weaned completely off PN/I.V. in Study 005

The main efficacy results (interim) for ongoing trial 021 are as follows (efficacy results were available only through Month-6):

- 12 subjects have been completely weaned off PN/I.V. as of Oct-2012
- Teduglutide/teduglutide: Month-6: 91% response rate (at least 20% reduction in baseline PN/I.V.)
- Placebo/teduglutide: Month-6: reduction of PN/I.V. by 2.2+/-3.0 L/wk and 40% responders

In summary, I concur with Dr. Troiani that those data from long term extension studies support efficacy conclusions from Study 004 and Study 020.

8. Safety

The safety information in this NDA comes from 15 clinical studies conducted with teduglutide: 9 clinical pharmacology studies; four Phase 3 studies in subjects with short bowel syndrome (SBS); and two Phase 2 studies in subjects with Crohn's Disease. As of 31 October 2011, the

cut-off date for inclusion in this 4 month safety update, all studies had been completed with the exception of a Phase 3 two-year extension study in adult subjects with parenteral nutrition (PN) dependent SBS. Data from these 15 studies were included in an integrated safety analysis.

A total of 566 subjects were treated with teduglutide, and 198 subjects were treated with placebo. Of the 566 subjects treated with teduglutide, 299 subjects were treated in the Clinical Pharmacology Studies, 173 subjects were treated in the SBS Efficacy and Safety Studies, and 94 subjects were treated in Other Studies (Crohn's Disease). The 2 placebo-controlled studies are the largest controlled studies conducted in subjects with SBS.

Across all studies, 566 subjects were exposed to teduglutide: 368 (65.0%) for less than three months; and 198 (35.0%) for 3 months or longer with a maximum of 132 weeks. Of the 566 teduglutide-treated subjects, 140 (24.7%) were exposed to teduglutide for at least 6 months, and 97 subjects (17.1%) were exposed for at least 12 months.

The mean duration of exposure to teduglutide was 17.4 weeks, and the total number of person-years of exposure was 189.8 years. Most subjects were exposed to teduglutide in the clinical pharmacology studies (299/566 subjects; 52.8%); however, the greatest duration of exposure to teduglutide defined by person-years occurred in the SBS Efficacy and Safety Studies (163.2 years).

Over all studies, 198 subjects (34.9%) were exposed to placebo**:** 1 subject was exposed to placebo for 6 months or longer, and none for 12 months or longer. The mean duration of exposure to placebo was 8.2 weeks, and the number of person-years was 31.1 years. The maximum exposure for placebo-treated subjects was 28 weeks.

More males (322/566, 56.9%) than females (244/566, 43.1%) were treated with the teduglutide; however, the distribution differed by study group. There were more males (199/299, 66.6%) than females (100/299, 33.4%) treated with teduglutide in the Clinical Pharmacology Studies, but in the SBS Efficacy and Safety Studies and in the Other Studies (Crohn's Disease), there were more females (144) than males (123).

The mean age of all teduglutide-treated subjects was 41.8 years (range of 18 to 82 years).
Of the 566 subjects treated with teduglutide, 523 (92.4%) were younger than 65 years, 43 (7.6%) were ≥ 65 years, and 6 (1.1%) were aged 75 years or older.

Most subjects treated with teduglutide were white (88.7%, 502/566). Blacks accounted for 8.0% of teduglutide-treated subjects (45/566) and 3.4% were of other races (19/566). The distribution among white, black, and other races was generally consistent across study groups.

Overall, 49.6% (281/566) of subjects were treated at US sites. The mean body weight at baseline for all teduglutide-treated subjects was 70.6 kg, and ranged from 61.2 kg for subjects in the SBS Efficacy and Safety Studies to 76.4 kg for subjects in the Clinical Pharmacology Studies. The proportion of subjects who identified themselves as Hispanic or Latino was 38.1% (45/118) in the Clinical Pharmacology Studies, 9.7% (9/93) in the SBS Efficacy Studies, and 25.6% (54/211) for the combined groups.

Table 4 Enumeration of Subjects by Study Group—Safety Population—All Studies

Study Group	Statistic	Placebo	Teduglutide	Total
Clinical Pharmacology Studies	n	114	299	344
Single-dose Studies	n	77	188	196
Healthy	n	77	158	166
Hepatic Impaired	n	0	12	12
Renal Impaired	n	0	18	18
Multiple-dose Studies	n	37	111	148
Healthy	n	37	94	131
SBS	n	0	17	17
Efficacy and Safety Studies (SBS)	n	59	173	180
Placebo-controlled	n	59	109	168
Uncontrolled	n (m)	0	153 (89)	153 (141)
Other Studies (Crohn's disease)	n	25	94	100
Placebo-controlled	n	25	75	100
Uncontrolled	n (m)	0	65 (46)	65 (65)
Grand Total Subjects	n	198	566[a]	624

n = number; SBS = short bowel syndrome

Note: The value of m corresponds to the count of subjects in the cell total who have already been counted in the same column and primary study group by virtue of having participated in the placebo-controlled study. Subjects who received both teduglutide and placebo in a crossover study are counted once in the Placebo column, once in the teduglutide column, and once in the Total column.

[a]The total number of unique subjects treated with teduglutide was actually 565, as one subject who was treated with teduglutide in 2 separate studies.

Demographic characteristics of the subjects treated with placebo were generally similar to those of the subjects treated with teduglutide in the corresponding study groups with the exception of those identifying themselves as Hispanic or Latino were 17.5% (14/80) of placebo-treated subjects compared to the 25.6% (54/211) of teduglutide-treated subjects. Overall, the teduglutide and placebo groups were well balanced with respect to demographic characteristics.

Adverse Events

Since teduglutide-treated subjects come from both controlled and uncontrolled studies, any comparison to placebo should be made only within the presentation of placebo-controlled studies.

Treatment Emergent SAEs (TESAEs) were reported in 20.3% (115/566) of teduglutide-treated subjects. There were 2 reports of a TESAE with a fatal outcome in teduglutide-treated subjects (See Section below). TESAEs were reported in 9.1% (18/198) of placebo-treated subjects. There were no TEAEs leading to death in placebo-treated subjects.

Common Adverse Events - SBS Efficacy and Safety Studies

The most frequently reported TEAEs among 173 teduglutide-treated subjects were abdominal pain (39.3%, 68/173), upper respiratory tract infection (26.6%, 46/173), nausea (25.4%, 44/173), catheter sepsis (22.5%; 39/173), headaches (19.1%, 33/173), asthenic conditions (18.5%; 32/173); abdominal distension and injection site reactions (both 17.9%, 31/173), gastrointestinal stoma complication (16.2%, 28/173), urinary tract infections (15.6%, 27/173), and febrile disorders (15.0%, 20/173).

Table 5 Summary of Treatment Emergent AE by Preferred Term (Reported in ≥ 5% of Subjects in all Teduglutide)- SBS Efficacy and Safety Studies

		Teduglutide (mg/kg/day)		
Preferred Term	**Placebo (N= 59) n (%)**	**0.05 (N=134) n (%)**	**0.10 (N= 39) n (%)**	**ALL (N=173) n (%)**
Abdominal pain *	16 (27.1)	53 (39.6)	15 (38.5)	68 (39.3)
Upper respiratory tract infection *	8 (13.6)	34 (25.4)	12 (30.8)	46 (26.6)
Nausea *	12 (20.3)	32 (23.9)	12 (30.8)	44 (25.4)
Catheter sepsis *	10 (16.9)	31 (23.1)	8 (20.5)	39 (22.5)
Headaches *	9 (15.3)	19 (14.2)	14 (35.9)	33 (19.1)
Asthenic conditions *	7 (11.9)	23 (17.2)	9 (23.1)	32 (18.5)
Abdominal distension	1 (1.7)	26 (19.4)	5 (12.8)	31 (17.9)
Injection site reactions *	7 (11.9)	16 (11.9)	15 (38.5)	31 (17.9)
Gastrointestinal stoma complication	3 (5.1)	22 (16.4)	6 (15.4)	28 (16.2)
Urinary tract infections *	10 (16.9)	20 (14.9)	7 (17.9)	27 (15.6)
Febrile disorders *	7 (11.9)	22 (16.4)	4 (10.3)	26 (15.0)
Catheter site related reaction *	8 (13.6)	22 (16.4)	2 (5.1)	24 (13.9)
Vomiting	6 (10.2)	16 (11.9)	8 (20.5)	24 (13.9)
Fluid overload *	4 (6.8)	17 (12.7)	5 (12.8)	22 (12.7)
Musculoskeletal pain *	6 (10.2)	16 (11.9)	5 (12.8)	21 (12.1)
Weight decreased *	6 (10.2)	19 (14.2)	2 (5.1)	21 (12.1)
Diarrhoea *	7 (11.9)	14 (10.4)	5 (12.8)	19 (11.0)
Hypersensitivity *	3 (5.1)	12 (9.0)	6 (15.4)	18 (10.4)
Flatulence	4 (6.8)	13 (9.7)	4 (10.3)	17 (9.8)
Appetite disorders *	2 (3.4)	11 (8.2)	3 (7.7)	14 (8.1)
Arthralgia	3 (5.1)	9 (6.7)	4 (10.3)	13 (7.5)
Lower respiratory tract infection *	3 (5.1)	9 (6.7)	4 (10.3)	13 (7.5)
Cognition and attention disorders and disturbances *	4 (6.8)	8 (6.0)	4 (10.3)	12 (6.9)
Dehydration	5 (8.5)	10 (7.5)	2 (5.1)	12 (6.9)
Biliary tract disorder *	1 (1.7)	9 (6.7)	2 (5.1)	11 (6.4)
Gastrointestinal stenosis and obstruction *	0	8 (6.0)	3 (7.7)	11 (6.4)
Muscle spasms	4 (6.8)	8 (6.0)	3 (7.7)	11 (6.4)
Skin haemorrhage *	1 (1.7)	9 (6.7)	2 (5.1)	11 (6.4)
Hepatic enzyme increased *	2 (3.4)	4 (3.0)	5 (12.8)	9 (5.2)
Hot flush	0	9 (6.7)	0	9 (5.2)

MedDRA = Medical Dictionary for Regulatory Activities; N, n = number; SBS = short bowel syndrome; TEAE = treatment-emergent adverse event
Note: Percentages are based upon the number of subjects in the Safety Population.
Note: TEAEts are defined as any adverse event with a start date on or after the date of first dose and within thirty days after discontinuation of study drug.
Note: Subjects are counted no more than once for incidence of Preferred Term.
Note: All adverse events were coded using MedDRA version 12.0.
Note: * shows special interest in Body System or Organ Class. The preferred terms in the AE groupings represent medically similar terms

Possible Adverse Reactions

The incidence of TEAEs in subjects with SBS participating in 2 placebo-controlled, double-blind clinical studies (Studies 020 and 004) is reflected in Table 6, where 77 subjects were treated with teduglutide given at the indicated dose of 0.05 mg/kg/d. The majority of these reactions were mild or moderate. Only those reactions in which the incidence was at least 5% and in which the

incidence was greater for teduglutide than for placebo are summarized in Table 6. Of the subjects receiving teduglutide at the indicated dose of 0.05 mg/kg/day, 88.3% (N=68/77) experienced an adverse reaction as compared to 83.1% (49/59) in subjects receiving placebo. The overall high rate of TEAE reactions in this population across both the teduglutide-treated and placebo-treated subjects reflects both the underlying disease and parenteral support complications.

Table 6: Treatment Emergent Adverse Reactions Reported in ≥ 5% of Teduglutide-Treated SBS Subjects and Occurring more frequently with Teduglutide- Compared to Placebo: Studies 020 and 004 (0.05 mg/kg/day)

Adverse Drug Reaction[a]	Placebo (N=59) n (%)	Teduglutide 0.05mg/kg/d (N=77) n (%)
Abdominal Pain	16 (27.1)	29 (37.7)
Upper Respiratory Tract Infection	8 (13.6)	20 (26.0)
Nausea	12 (20.3)	19 (24.7)
Abdominal Distension	1 (1.7)	15 (19.5)
Vomiting	6 (10.2)	9 (11.7)
Fluid Overload	4 (6.8)	9 (11.7)
Flatulence	4 (6.8)	7 (9.1)
Hypersensitivity	3 (5.1)	6 (7.8)
Appetite Disorders	2 (3.4)	5 (6.5)
Arthralgia	3 (5.1)	4 (5.2)
Weight Increased	3 (5.1)	4 (5.2)
Lower Respiratory Tract Infection	3 (5.1)	4 (5.2)
Sleep Disturbances	0	4 (5.2)
Coughing and Associated Symptoms	0	4 (5.2)
Skin Hemorrhage	1 (1.7)	4 (5.2)
Subjects with Stoma Gastrointestinal Stoma Complication[b]	3 (13.6)[b]	13 (41.9)[b]

AE = adverse event; PT = preferred term; HLT = high level term; HGLT = high group level term; N, n = number

[a] Adverse reactions classified using meaningful and specific terms (PT/HLT or HGLT). Preferred terms in the AE groupings represent medically similar terms.

[b] Percentage based on 53 subjects who had a stoma (n = 22 placebo; n = 31 teduglutide 0.05 mg/kg/d)

Dose Response

The dose response analysis was based on the 2 SBS Placebo-controlled studies 004 and 020. TEAEs from these trials were reviewed and were considered to be dose related if the TEAE was reported more frequently in the teduglutide 0.10 mg/kg/d group compared to the 0.05 mg/kg/d group. Injection site reaction was the only meaningful TEAE that was reported at a notably higher frequency in the 0.10 mg/kg/d teduglutide group vs. 0.05 mg/kg/d teduglutide. In the SBS Placebo-controlled trial, injection site reaction was reported in 40.6% (13/32) of subjects in the 0.10 teduglutide group and 11.7% (9/77) in the 0.05 group (placebo 11.9% (7/59)).

Deaths
A total of 3 patients died during the drug development.

One death was reported in the ongoing Study 021. Subject 021-0155-1009, a 48-year-old man with a history of Hodgkin's disease (diagnosed in 1988 and treated with chemotherapy and radiotherapy), cecal necrosis caused by radiation, and primary liver disease, was diagnosed with a metastatic adenocarcinoma (b) (6) months after the start of treatment (treatment start date (b) (6) ; onset date of TESAE 19 June 2011). The subject's last dose of study drug was 16 June 2011 and his last study visit (discontinuation) was on 19 June 2011. The subject entered the study directly (i.e., was not treated in Study 020). Six months prior to starting teduglutide therapy, the subject had computed tomography (CT) of the abdomen, which revealed an enlarged liver with no focal lesions, an edematous gallbladder with dense bile and 2 soft tissue foci of 10 and 15 mm diameter in the splenic field suspected to be accessory spleen. A subsequent review of a pre-teduglutide CT scan by 2 independent radiologists revealed a focal liver lesion of unclear significance. The primary tumor was considered to be most likely of gastrointestinal tract origin, but its precise location was unknown. A biopsy revealed metastatic adenocarcinoma. The subject died (b) (6) days after diagnosis of adenocarcinoma (stop date of TESAE (b) (6)). An autopsy performed on (b) (6) was inconclusive as to the primary site of the cancer, and the primary cause of death was generalized intestinal malignancy. The event was considered by the investigator to be severe and related to treatment. I agree that this event may relate to treatment and patients should be monitored closely per colonoscopy at 1 year post initiation of therapy.

Another death was reported in ongoing Study 021. Subject 021-0138-1011 was diagnosed with non-small cell lung cancer and died on (b) (6). This subject was a 64-year-old white male with a history of smoking (i.e., approximately 30 cigarettes/day for approximately 30 years). He was diagnosed with non-small cell lung cancer after (b) (6) days of teduglutide treatment. The subject permanently discontinued teduglutide due to the lung cancer. The investigator reported that the stage of the cancer was T2BN2M0. The subject received chemotherapy treatment with vinorelbine and carboplatin. The investigator did not attribute the SAE to teduglutide treatment and I agree. After the cut-off date of 30 June 2011, the sponsor learned that the subject died.

Further, 1 subject (004-0139-0003) died during the screening period of study 004, prior to randomization and receipt of study drug. In the opinion of the Investigator, the subject's death was due to a massive upper gastrointestinal tract hemorrhage.

Other Significant Adverse Events

Adverse Events Leading to Discontinuation
In the combined SBS Efficacy and Safety Studies, 16.2% (28/173) of teduglutide-treated subjects experienced at least 1 TEAE that led to discontinuation; these subjects had a total of 45 TEAEs. In these studies, the rate of discontinuation TEAEs in the teduglutide 0.05 mg/kg/d treatment group (15.7%, 21/134) and the 0.10 mg/kg/d treatment group (17.9%, 7/39) were similar.

Abdominal pain was the TEAE most frequently causing discontinuation (4.6%, 8/173). Other TEAEs leading to discontinuation that were reported by more than 2 subjects treated with teduglutide in this group of studies were nausea (3 subjects), vomiting (3 subjects), abdominal distension (2 subjects), asthenia (2 subjects), constipation (2 subjects), and gastrointestinal stoma complication (2 subjects).

In the extension Study 005, 7 of the 8 subjects who discontinued due to TEAEs had been previously treated with teduglutide in Study 004, 3 with teduglutide 0.05 mg/kg/d and 4 with teduglutide 0.10 mg/kg/d. The discontinuation TEAEs in the 3 subjects in the teduglutide 0.05/0.05 mg/kg/d cohort included abdominal pain, gastrointestinal tract adenoma (later reclassified to hyperplastic colon polyp), and irritable bowel disease. The discontinuation TEAEs in the 4 subjects in the teduglutide 0.10/0.10 mg/kg/d cohort included abdominal pain, vomiting, nausea, cerebrovascular accident, and cough. In 4 of these 7 subjects, the TEAEs leading to discontinuation (inflammatory bowel disease, abdominal pain, vomiting, and nausea) were considered related to study drug by the investigator.

Adverse Events of Special Interest

Adverse Events of special interest were selected for further evaluation of the safety of teduglutide based on mechanism of action, preclinical safety data, adverse events in clinical studies, clinical laboratory data and literature review. The following areas were selected: malignancy, GI polyps, biliary, pancreas, liver-related conditions, GI stenosis and obstruction, fluid overload, and immunogenicity.

Malignancy Related Treatment Emergent Adverse Events
No treatment-emergent malignancies were reported in teduglutide placebo-controlled studies. Three subjects in the ongoing extension Study 021 were reported with neoplasms of the GI tract and lung.

Subject 021-0155-1009, a 48-year-old male was enrolled in study 021 in the teduglutide 0.05 mg/kg/day treatment group. The subject was in the stabilization/optimization phase in study 020 but the study was closed when he was eligible for randomization. A SAE of "Hepatic neoplasm" was reported on study day (b) (6)). Medical history included Crohn's Disease, intestinal resection, Hodgkin's Disease in 1988 treated with chemotherapy and radiation therapy, elevations in ALP and GGT since December 2009 and right hemicolectomy for cecal necrosis due to radiation.

An ultrasound and CT scan performed on (b) (6) to determine the cause of the elevations in biliary enzymes revealed an enlarged liver with no focal lesions, an edematous gallbladder with dense bile and 2 soft tissue foci of 10 and 15 mm diameter in the splenic field suspected to be accessory spleen. Teduglutide treatment started on 29 July 2010. On (b) (6) days on teduglutide, the subject reported back pain. On (b) (6), MRI was performed because of an increase in biliary enzymes and showed an extensive heterogenous solid tumor with a diameter of up to 114 mm; the remaining liver parenchyma revealed solid tumors of varying size. Numerous lesions consistent with metastases were seen in the bodies of

the visualized vertebrae and numerous enlarged retroperitoneal lymph nodes were noted. MRI of the lumbar spine revealed a compression fracture of L3. On (b) (6), a chest CT scan revealed numerous enlarged lymph nodes in the posterior mediastinum measuring up to 20 mm in their long axis, intralobular emphysema and enlarged lymph nodes around the gastric cardia and abdominal aorta. Study drug was discontinued on 16 June 2011. Additional biochemistry revealed a normal alpha fetal protein and a markedly elevated carcinoembryonic antigen of >100 ng/mL (normal range 0-2.5 ng/mL). On (b) (6), a fine needle aspiration biopsy and core needle biopsy of the hepatic mass were performed and revealed metastatic adenocarcinoma, probably of gastrointestinal origin.

Primary therapy for the metastatic adenocarcinoma was not administered. The subject developed hepatic and renal failure and died on (b) (6). Autopsy on (b) (6) was inconclusive as to the primary site of the malignancy, but suggested it was intestinal.

In addition, chronic myelogenous leukemia or acute myelogenous leukemia was suspected by blood counts, but was not mentioned in the autopsy findings. Two expert radiologist consultants reviewed the subject's CT scans on (b) (6) respectively. Both radiologists agreed that the CT of (b) (6), performed prior to teduglutide therapy, showed a small, approximately 2 cm low attenuation lesion in the left lobe of the liver seen only on the contrast images. Both agreed that the lesion could not be further characterized as benign or malignant based on the CT findings.

This subject developed a gastrointestinal malignancy 22 years after receiving radiation therapy and chemotherapy for Hodgkin's disease. A high incidence of secondary malignancies after treatment for Hodgkin's disease has been increasingly encountered for decades. The risk of secondary malignancy increases with duration of follow-up and is highest among those who have received combination treatment consisting of radiation therapy and chemotherapy, as did this subject. The risk of developing a subsequent gastrointestinal cancer is increased and is highest among those treated at age 25 or younger, as was the case for this subject.

Subject 021-0138-1002, a 74-year-old male was enrolled in study 021 in the teduglutide 0.05 mg/kg/day treatment group (study 020 teduglutide 0.05 mg/kg/day group). A SAE "Lung squamous cell carcinoma stage unspecified" was reported initially as "Haemoptysis" on treatment day (b) (6). Medical history included embolectomy of the superior mesenteric artery, intestinal anastomosis, small intestinal resection, coronary artery disease and MI, GGT increased and viral hepatitis. The subject had a history of cigarette smoking. A chest X ray on (b) (6) reported as being suspicious for an abscess. Chest CT scan performed on (b) (6) was reported as having findings consistent with mycosis. Bronchoscopy was performed on (b) (6) and an acid fast bacilli test was reported to be negative for bacilli. The subject was started on INH, rifampin and pyrazinamide on 4/14/11. On (b) (6), a bronchoscopy was performed from which histopathology revealed planoepithelial (squamous cell) carcinoma of the right lung. Teduglutide was discontinued on 8/26/11 and the subject discontinued study participation on 9/6/11.

Subject 021-0138-1011, a 64-year-old male was enrolled in study 021 in the teduglutide

0.05 mg/kg/day treatment group (study 020 placebo group). "Non-small cell lung carcinoma" was reported as a SAE on day (b) (6) and "Lung neoplasm" reported on (b) (6) . End dates for these AEs were not reported. Medical history included mesenteric artery thrombosis, intestinal resection, colectomy, MI, pulmonary embolism, atrial fibrillation and tricuspid valve repair. The subject had smoked approximately 30 cigarettes per day for approximately 30 years. He was hospitalized on (b) (6) for a 2-week history of hemoptysis. Chest CT revealed a tumor of the left lung and enlarged lymph nodes of the left pulmonary hilum, mediastinum and peritracheal region. Teduglutide was discontinued on 31 March 2011. Endobronchial biopsy revealed non-microcellular carcinoma, which the investigator assessed as squamous cell carcinoma, stage T2BN2M0. On (b) (6), the subject received chemotherapy including vinorelbine and carboplatin. Early study discontinuation occurred on 25 May 2011. The subject expired on (b) (6) (post cut off date).

Both patients had histories of cigarette smoking and were from the same site in Poland where the lung cancer incidence among male PN/IV patients is over 60 times that of the general male population in Poland. Given their smoking history, age and geographical location, these subjects were at relatively high risk of developing a lung malignancy.

The possibility that Gattex may accelerate the growth of neoplasms can not be ruled out. Patients on Gattex should be monitored closely including regularly colonoscopy.

Gastrointestinal Polyp Related Treatment Emergent Adverse Events
GI polyp related TEAEs were reported in 6 teduglutide-treated subjects who were enrolled in one or more teduglutide efficacy and safety studies. No subjects with GI polyp related TEAE preferred terms were identified in clinical pharmacology studies; nor in the study of teduglutide in Crohn's Disease (Study 008) and its extension study (study 009).

Two subjects with GI polyp related TEAEs were in placebo-controlled SBS studies. One subject was treated with 0.05 mg/kg/day teduglutide and the other subject with placebo. The frequency of GI polyp related TEAEs in SBS placebo-controlled trials was 1 of 109 subjects (0.9%) for teduglutide treated subjects, and 1 of 59 subjects (1.7%) for placebo treated subjects.

In summary, a total of 7 gastrointestinal polyp related TEAEs were reported in the safety population of all teduglutide studies. Of the cases which occurred during the SBS placebo controlled studies, one occurred in a placebo group subject and two in subjects treated with teduglutide 0.05 mg/kg/day. Four other cases occurred in Studies 005 and 021, the long-term extension studies in SBS patients.

Colonic polyps are common in the western world. The prevalence of colonic polyps in Europe and North America is high, increases with age and can be as high as 25% at age 50 years. It is, therefore, not unexpected that GI polyp-related TEAEs were reported during the teduglutide clinical program. However, based on the Gattex mechanism of action and nonclinical data, Gattex has a potential to enhance growth of polyps. Therefore, patients on Gattex should be monitored closely including regularly colonoscopy.

Biliary Disease and Abnormality Related Treatment Emergent Adverse Events
A total of 4 (3.7%) subjects treated with teduglutide and 1 (1.7%) in the placebo group were reported to have treatment-emergent biliary tract-related adverse events in SBS Placebo-controlled Studies. All 4 of the teduglutide and none of the placebo subjects were reported to have cholecystitis; 2 of the 4 subjects had a prior history of cholelithiasis and 1 subject had no objective evidence of cholecystitis reported.

One subject in the placebo treated group was reported with "Gamma glutamyl transferase increased". However, this subject was found to have an abnormally high GGT at screening; therefore this subject is not counted. No subject with biliary tract-related AEs discontinued from the SBS Placebo-controlled Studies early because of such AEs.

In the Crohn's Disease placebo-controlled study, 1 subject treated with teduglutide was reported with an isolated, solitary, mild elevation of "blood alkaline phosphatase" and another teduglutide treated subject was reported with "cholecystitis," but no objective evidence of this condition was documented. Moreover, the subject discontinued study participation early due to the concurrent AE of "Crohn's Disease" exacerbation.

There were 3 subjects with reported "cholecystitis" in Studies 005 and 021. "Cholangitis", which was not reported in the SBS and Crohn's disease double-blind studies, was reported in 1 subject in extension Study 009. The subject with cholangitis also was reported to have cholecystitis; however, surgical pathology did not confirm this.

The frequency of treatment-emergent biliary tract-related categorical elevations in laboratory parameters in the SBS and Crohn's Disease placebo-controlled studies for the teduglutide groups was comparable to or lower than that for the placebo groups. No trends in the alkaline phosphatase (ALP), GGT, and total bilirubin treatment-emergent categorical changes could be identified.

All of the subjects enrolled in these studies had multiple risk factors for biliary tract disease; thus, the occurrence of biliary tract-related AEs is not unexpected in the teduglutide treated patient population. However, a somewhat higher number and frequency of subjects with cholecystitis was reported in teduglutide treatment groups in SBS Placebo-controlled Studies (4 cases [3.7%] versus none in the placebo groups). Of these 4 cases, 3 of 77 subjects (3.9%) were treated with teduglutide 0.05 mg/kg/d and 1 of 32 subjects (3.1%) was treated with teduglutide 0.10 mg/kg/d; thus, no dose response relationship is evident. Three of these cases had a documented prior history of biliary tract disease including cholelithiasis and cholestasis and one had no objective findings of cholecystitis reported. Given the small number of biliary tract events occurring in teduglutide placebo-controlled studies, the high background rate of biliary tract disease in the SBS and Crohn's Disease patient populations and the lack of trends in the biliary tract related laboratory parameter categorical analyses, an association of teduglutide with the occurrence of biliary tract disease or abnormality is uncertain at this time.

Pancreatic Disease and Abnormality Related Treatment Emergent Adverse Events
In the SBS placebo-controlled studies 004 and 020, 8 pancreas related events were reported in 4 subjects. Of these subjects, one subject was reported with "Pancreatitis"; one with "Pancreas

infection," "Ampulla of Vater stenosis," "Pancreatic duct stenosis" and "Pancreatitis chronic;" one with "Blood amylase increased" and "Lipase increased" and one with "Blood amylase" increased. Three of the 4 subjects were in teduglutide treatment groups and one subject, with "Blood amylase increased" was in a placebo group. Of the 3 teduglutide-treated subjects, one subject's pancreas related enzyme elevations were consistent with the reported SAE of small bowel obstruction rather than intrinsic pancreatic pathology. Another teduglutide-treated subject had a history of chronic pancreatitis and the third subject had amylase elevations prior to baseline. The subject in the placebo group had amylase elevations prior to the treatment phase of the study.

A total of 3 (2.8%) subjects treated with teduglutide and 1 (1.7%) in the placebo group were reported to have treatment-emergent pancreas-related adverse events in SBS Placebo-controlled Studies. However, when considering additional information such as medical history, other adverse events, clinical laboratory values and SAE narratives, the evidence shows that these 4 subjects had such events or signs of the events prior to treatment, due to non-pancreatic illness or abnormality or had contributing underlying medical conditions. In the Crohn's Disease placebo-controlled study, 2 subjects treated with teduglutide had mild amylase and lipase elevations. One of these subjects received only 3 doses of study drug and the enzyme elevations were noted 29 days after the last dose. Asymptomatic and episodic elevations of amylase and lipase occur with increased frequency in subjects with Crohn's Disease. No new pancreas-related terms were identified in long-term extension studies of teduglutide. The frequency of treatment-emergent amylase or lipase elevations in SBS Placebo-controlled Studies for teduglutide groups was comparable to or lower than that for placebo groups. In the Crohn's Disease placebo-controlled study, the incidence of amylase elevations was somewhat higher for the teduglutide groups; lipase elevations were comparable between teduglutide and placebo groups. Given the adverse event reporting and laboratory data to date, no association of teduglutide treatment and pancreatic disease or abnormality can be clearly identified.

Liver Disease and Abnormality Related Treatment Emergent Adverse Events
In the SBS Placebo-controlled Studies, liver-related AEs were reported in 5 subjects treated with teduglutide and in 1 subject on placebo with the following preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hepatic cirrhosis, and liver function test abnormal. None of the teduglutide cases were SAEs; the placebo case was reported as an SAE. All subjects completed participation in their respective studies. A review of subject data including laboratory values at screening and baseline indicate that 4 of the teduglutide-treated subjects with liver-related AEs had pre-treatment elevations of liver enzymes. Considering these data, the number and frequency of subjects with liver-related AEs in the SBS Placebo-controlled Studies was 1 (0.9%) for teduglutide and 1 (1.7%) for placebo.

In the Crohn's Disease placebo-controlled study, liver-related AEs were reported in 5 subjects (6.7%) treated with teduglutide; no cases were reported in placebo subjects. None of the cases were SAEs. Each of these subjects completed the study except for one subject who discontinued participation due to an unrelated AE. All of these subjects had mild, isolated elevations of ALT and/or AST.

In the SBS extension studies, two liver-related AE, "Hepatic cyst infection" and portal hypertension occurred which was not previously reported in the placebo-controlled studies. In this case of suspected hepatic cyst infection, CT and operative findings confirmed that the lesions were not intrahepatic. The case of portal hypertension occurred in a subject with known chronic liver disease and fibrosis. In the Crohn's Disease extension study, no new liver-related AE terms nor serious liver-related AEs were reported.

The frequency of subjects with treatment-emergent liver-related laboratory categories for teduglutide was similar that for placebo overall in both the SBS and Crohn's Disease placebo controlled study populations with no difference by dosing group.

The frequency of liver-related AEs when considering screening and baseline values was similar for teduglutide- and placebo-treated subjects in the SBS Placebo-controlled Studies but was higher for teduglutide in the Crohn's Disease study. The liver-related abnormalities in the Crohn's Disease study were isolated and mild elevations of ALT and AST. This finding is not confirmed by the objective laboratory analyses, in which the frequency of teduglutide –treated subjects with treatment emergent liver related categories was similar to or lower than that for the placebo groups for both the SBS and Crohn's Disease study populations. No association of liver disease or abnormality with teduglutide treatment can be identified in the SBS study population. In the Crohn's Disease study population, when considering the AE and laboratory data together, no definite trends associating liver-related disease or abnormality with teduglutide treatment can be identified.

Table 7: Frequency of Subjects with Treatment Emergent Liver Related Categories in SBS Placebo-Controlled Studies 004 and 020

		Teduglutide (mg/kg/day)		
	Placebo (N=59)	0.05 (N=77)	0.10 (N=32)	All (N=109)
ALT				
>3X ULN and ≥ 1.5X Baseline	1 (1.7%)	1 (1.3%)	2 (6.3%)	3 (2.8%)
>5X ULN and ≥ 1.5X Baseline	1 (1.7%)	1 (1.3%)	0	1 (0.9%)
>10X ULN	0	0	0	0
>20X ULN	0	0	0	0
AST				
>3X ULN and ≥ 1.5X Baseline	0	1 (1.3%)	1 (3.1%)	2 (1.8%)
>5X ULN and ≥ 1.5X Baseline	0	0	0	0
>10X ULN	0	0	0	0
>20X ULN	0	0	0	0
Tbili >2X ULN	2 (3.4%)	3 (3.9%)	1 (3.1%)	4 (3.7%)
Tbili >2X ULN and ALT/AST >3X ULN	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbili = total bilirubin; ULN = upper limit of normal

Gastrointestinal Stenosis and Obstruction Related Treatment Emergent Adverse Events
Patients who have had multiple abdominal surgeries, such as those in the teduglutide clinical studies are at higher risk for GI stenosis and obstruction. In the SBS Placebo-controlled Studies, a higher incidence of GI stenosis- or obstruction-related AEs was observed compared with placebo with frequencies of 0% (0/59), 3.9% (3/77) and 9.4% (3/32) for the placebo, teduglutide

0.05 and 0.10 mg/kg/day treatment groups, respectively. The highest frequency was noted in the teduglutide 0.10 mg/kg/day group. However, in both SBS placebo-controlled studies and the extension studies, none of the subjects with GI stenosis- or obstruction-related AEs required surgical intervention and 4 of 14 (29%) required an endoscopic procedural treatment.

In the Crohn's Disease placebo-controlled study, 1 of 75 subjects (1.3%) treated with teduglutide had a GI stenosis- or obstruction-related AE. This subject underwent surgical intervention. An additional 2 cases were reported in the Crohn's Disease extension study, one of which required surgical intervention. Given the higher risk for GI stenosis and obstruction in the Crohn's Disease population and the low incidence of such cases in the teduglutide Crohn's Disease studies, no firm conclusions regarding any possible association between teduglutide treatment for Crohn's Disease and GI stenosis or obstruction can be made. Please see Dr. Troiani's review for details of the GI stenosis and obstruction related AEs.

Volume Expansion Related Treatment Emergent Adverse Events
In the SBS and Crohn's Disease double-blind, placebo-controlled studies, the frequency of subjects with volume expansion-related AEs was similar in both the teduglutide and placebo treatment groups. With the exception of a case of cardiac failure congestive, none of the cases were SAEs or causes of early termination from trial participation. In the SBS and Crohn's Disease extension studies and the clinical pharmacology studies, no new volume-related AE preferred terms were reported which had not been reported in the placebo-controlled trials. At present, no association between volume expansion-related AEs and teduglutide treatment can be established.

The SAE cases of cardiac failure, congestive represent a cautionary tale. Subjects with underlying conditions predisposing to fluid retention with currently stable volumes of PN may become hypervolemic when responding to teduglutide therapy due to increased GI fluid and sodium absorption. Subjects with these conditions or circumstances may require even greater attention to their fluid balance during teduglutide induction, when the intestinal mucosa is undergoing hyperplasia.

Safety and Tolerability Summary and Conclusions
In conclusion, teduglutide administered once daily by SC injection at a dose of 0.05 mg/kg body weight is safe for use in accordance with the modified label for the treatment of adult patients with SBS.

In the assessment of safety in the teduglutide development program the majority of adverse events were GI in origin. This is not unexpected considering these are the same complications often seen in study populations of SBS subjects and Crohn's Disease. In addition, considering the direct intenstinotrophic actions of teduglutide, these GI adverse events most likely represent the mechanism of action and pharmacologic/treatment effect of teduglutide. The potential risk of carcinogenesis in regard to teduglutide as an intestinal growth factor needs to be considered and close monitoring of this potential risk is required. Nonclinical models have suggested that when pre-existing conditions and/or malignancies are present, GLP-2 analogs such as teduglutide may promote tumor growth. These potential risks may need to be considered in relation to the 1 subject who died of metastatic adenocarcinoma of unknown GI origin. These risks may be

minimized with mandatory colonoscopy at screening and follow up colonoscopy at a short interval post initiation of therapy (such as 1 year) especially for the patients with polyps at baseline. A 5 year interval for subsequent colonoscopy may be too long, especially for patients with polyps at baseline. If no polyp is identified after 1 year on therapy, the interval of 5 years for subsequent colonoscopy may be acceptable.

These potential risks of teduglutide are considered acceptable and manageable considering the high unmet need in the orphan condition of SBS with intestinal failure and if approved would offer patients an important therapeutic option that currently does not exist.

9. Advisory Committee Meeting

An FDA Advisory Committee Meeting was held on 16-Oct-2012. All members concurred that a 20% reduction in PN/I.V. was clinically meaningful. The favorable results of the secondary endpoints involving complete weaning and reduction in days on PN/I.V. support the meaningfulness of the 20% reduction. All 12 members agreed that clinically meaningful benefit has been demonstrated in adult patients with SBS treated with teduglutide and that the benefits outweigh the risks associated with teduglutide therapy in the study population. For details of the AC meeting discussion, please see Dr. Troiani's review.

10. Pediatrics

This drug has not yet been studied in children. The sponsor has requested a waiver based on orphan drug designation, for which there is no obligation under PREA and I agree.

11. Other Relevant Regulatory Issues

According to Dr. Khairy Malek from the Division of Good Clinical Practice Compliance, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

A total of 4 clinical sites were selected for inspection mainly due to high enrollment and efficacy results. All selected sites were inspected by the Division of Good Clinical Practice Compliance. Dr. Khairy Malek from FDA DSI stated that the inspectional observations made at those clinical sites would not appear to have a substantive effect on safety and/or efficacy evaluations. The inspection of the sponsor indicated that its procedures for collecting, handling, and archiving the large amounts of data generated by these studies appear to be adequate. Other observations noted during the inspection of the sponsor would not appear to have a substantive effect on safety and/or efficacy evaluations.

Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the indication. The final review of Dr. Khairy Malek is pending at this time.

Three investigators in the development program had financial arrangements to disclose to the Applicant. These included consulting fees and accepting grants for ongoing research. There were no conflicts of interest related to proprietary interest in the product or significant equity interest with the Applicant. These disclosures are acceptable.

Postmarket Risk Evaluation and Mitigation Strategies
A REMS was discussed at the Advisory Committee meeting of Oct 16, 2012. The potential safety risks of teduglutide that need to be addressed in a REMS include:

- acceleration of neoplastic growth and enhanced growth of colorectal polyps,
- intestinal obstruction,
- biliary-pancreatic disease.

The goal of the REMS would be to inform prescribers about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with GATTEX.

The elements of the REMS should include:
A Communication Plan with educational materials to include:

1. **Dear Healthcare Provider (DHCP) letter** disseminated to target healthcare prescribers *twice-a-year* for *three years*
   Target prescribers include:
   Gastroenterologists
   Colorectal/Gastrointestinal Surgeons
2. **Dear Professional Society letter** to be distributed to the leadership of professional organizations for dissemination of safety risk information with GATTEX to their members
3. **Prescriber Educational Slide Deck** for face-to-face presentation by Medical Science Liaisons to prescribers
4. **Patient educational material** for prescribers to use to educate patients about the serious risks with GATTEX

Timetable for submission of assessments:
The sponsor should submit REMS assessments to FDA according to a specified timetable: 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. For detail REMS assessment and requirement, please see Dr. Carlyn Yancey's review.

12. Labeling

DMEPA concludes that the proposed labels and labeling are unacceptable because they may introduce vulnerability that can lead to medication errors. I concur with the recommendations provided by Manizheh Siahpoushan, PharmD from DMEPA. For detail recommendations from DMEPA, please see Dr. Manizheh Siahpoushan's review.

DMEPA concludes that the re-evaluation of the proposed proprietary name, Gattex, did not identify any vulnerability that would result in medication errors with any additional names. Thus,

DMEPA has no objection to the proprietary name, Gattex, for this product at this time and I concur.

I concur that the Medguide should be a component of labeling to inform patients the serious risks associated with GATTEX.

I concur with labeling recommendations provided by Dr. Troiani listed in his review and concur with labeling recommendations provided by the review team.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend that NDA 203441 for Teduglutide (rDNA origin)/ GATTEX® be approved for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral nutrients or fluids to improve intestinal absorption of fluid and nutrients. GATTEX should be administered by subcutaneous (SC) injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. GATTEX should **not** be administered intravenously or intramuscularly. The recommended daily dose of GATTEX is 0.05 mg/kg body weight.

- Risk Benefit Assessment

Gattex (teduglutide [rDNA origin]) is a 33–amino acid recombinant analog of human Glucagon-like peptide-2 (GLP-2), that is intended for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral fluids to improve intestinal absorption of fluid and nutrients.

I concur with Dr. Troiani's risk-benefit assessment that benefits outweigh potential risk for adult patients with SBS. The risk-benefit balance is in favor of approval of Gattex (teduglutide) for the SBS indication.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  Includes restricted distribution, components of REMS

I concur with OSE reviewer, Dr. Carlyn Yancey's recommendations that the elements of the REMS should include communication Plan and the educational materials should include:

1. **Dear Healthcare Provider (DHCP) letter**
2. **Dear Professional Society letter**
3. **Prescriber Educational Slide Deck**
4. **Patient educational material**

Post-marketing surveillance should monitor for events of acceleration of neoplastic growth and enhanced growth of colorectal polyps, intestinal obstruction, and biliary-pancreatic disease.

- Recommendation for other Postmarketing Requirements and Commitments

As a PMR, the sponsor needs to conduct a patient registry that would provide long term safety and efficacy data. This registry should be at least 10 years long and include available patients with SBS who will be treated with Gattex as well as patients who will not be treated with Gattex. Safety data collection is especially important for the following potential safety issues for GATTEX®:

- Neoplasia

We recommend that a colonoscopy is needed within 6 months prior to starting teduglutide therapy and that a colonoscopy be done after one year on GATTEX in all patients. If a polyp is identified, that patient should be monitored annually. If no polyp is identified, patients may be monitored with subsequent colonoscopy at no more than 5 years intervals as proposed by the sponsor. Patients on Gattex might be at increased risk for polyp formation, especially in the long-term.

- Pancreatobiliary function

I concur with the sponsor that the relevant laboratory tests (total bilirubin, amylase, lipase, alkaline phosphatase) shoulod be obtained within 6 months prior to starting teduglutide therapy and then every 6 months while on teduglutide.

- Immunogenicity

The sponsor should assess the long term safety impact of ADA in this registry, as immunogenicity incidence rate increased with treatment duration during clinical trials. The implication of the cross-reactivity with endogenous GLP-2 for the safety of long term treatment with teduglutide is unknown. The sponsor should measure ADA in patients who show loss of efficacy.

In addition, as a PMR the sponsor should add a test method and acceptance criterion for (b) (4) to the drug substance specification. The sponsor is currently developing a suitable procedure for teduglutide drug substance evaluation and plans to test representative batches, establish acceptance criteria, and will subsequently add this test to the drug substance specification. The sponsor agreed to implement this as a post approval commitment in the amendment dated June 18, 2012. Because it is a potential safety concern, I will recommend adding it as a PMR.

- Recommended Comments to Applicant

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUYI HE
11/13/2012