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APPLICATION NUMBER:

203441Orig1s000

MEDICAL REVIEW(S)

Summary Safety Review for Regulatory Action

Date	(Stamped date)
From	Joyce Korvick, MD, MPH Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products ODE III, CDER FDA
Subject	Division Safety Director Summary Review
NDA #	203441
Applicant Name	NPS Pharmaceuticals
Date of Submission	November 30, 2011
PDUFA Goal Date	September 30, 2012, major amendment - extended to December 31, 2012
Proprietary Name / Established (USAN) Name	Gattex (teduglutide [rDNA origin])
Dosage Forms / Strength	Lyophilized Powder for Injection, 5 mg
Orphan Drug Designation	6-29-2000
Route of Administration	Subcutaneous
Review Classification	Standard
Proposed Indication(s)	GATTEX® (teduglutide [rDNA origin]) powder for subcutaneous injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS). Gattex is used to improve intestinal absorption of fluid and nutrients.
Action/Recommended Action for NME:	Approval: Indication as per approved labeling (see approval letter)

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	John Troiani
Statistical Review	Behrang Vali
Pharmacology Toxicology Review	Tamal Chakraborti
CMC Review.	Yichun Sun
Quality Microbiology Review (sterile products)	Brian Riley
Clinical Pharmacology Review	Lucy Fang
Clinical Pharmacometrics Review	Anshu Marathe
QT IRT Review	Moh Jee Ng
Immunogenicity Review	Joao Pedras-Vasconcelos
Facilities Review/Inspection	Zhong Li
DCDP of OPDP	Kendra Jones/Eunice Chung-Davies
DSI - Division of Bioequivalence and GLP Compliance	Young Moon Choi
Office of Scientific Investigations	Khairy Malek
CDTL Review	Ruyi He
OSE/DMEPA	Manizheh Siahpoushan
OSE/DRM	Carolyn Yancey

OND=Office of New Drugs
 DCDP of OPDP=Division of Consumer Drug Promotion in the Office of Prescription Drug Promotion
 Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DMPP=Division of Medical Policy Programs
 DRM=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Division Safety Deputy Director Review

1. Introduction

The purpose of this review is to highlight the risks and benefits associated with the use of Gattex (teduglutide [rDNA origin]) for injection to be used in patients with Short Bowel Syndrome (SBS), as well as, commenting on the Risk Evaluation and Mitigation Strategy (REMS), the post-marketing required studies (REMS) and the professional labeling including the Medication Guide (MG).

2. Background

Small Bowel Syndrome (SBS) results from surgical resection of some or all of the small or large intestine. If extensive, it can lead to malabsorption of protein, fluid, electrolytes and micronutrients. Following surgery, compensatory increases in bowel absorptive capacity can take up to two years to occur. If after two years the SBS patient still requires total parenteral nutritional support, it is unlikely that that patient will be completely weaned from such support¹.

Teduglutide has been shown to increase villus height and crypt depth of the intestinal epithelium resulting in enhanced absorptive capacity of the intestine.

Teduglutide is a 33 amino acid peptide that differs from its natural analog, glucagon-like peptide-2 (GLP-2) receptor agonist in the substitution of alanine (in native GLP-2) for glycine at the second position at the N-terminus. This single amino acid substitution provides resistance to in vivo degradation of teduglutide by dipeptidyl protease-IV (DPP-IV) resulting in an extended half-life. Teduglutide is manufactured using a recombinant strain of Escherichia coli.

The European Commission granted marketing authorization for “Revestive-teduglutide” on August 30, 2012. There is limited post-marketing experience in countries outside of the United States at the time of this review.

Regulatory History:

20 October 1998: Pre-IND meeting

26 April 1999: IND 58,213 submission for teduglutide in SBS

29 June 2000: US Orphan Drug designation granted

06 October 2003: End of Phase 2 meeting on clinical (Study 004) and nonclinical topics. Key items discussed were:

- Dosing: 0.05 and 0.10 mg/kg/day
- Standard outpatient care re: PN and concomitant medications
- Though study population would exclude SBS patients with unstable PN regimens, the results of the trial could potentially be extrapolated to such patients
- Proposed PN optimization/stabilization procedures, performance of colonoscopy in patients with a colon, mucosal biopsies of small intestine
- Primary efficacy endpoint is percent responders (reduction of at least 20% from baseline in weekly PN/IV volume at Week-24).

¹ Buchman AL. The clinical management of short bowel syndrome: steps to avoid parenteral nutrition. 1997. Nutrition. 13(10): 907-13.

- Conduct of two (replicative) trials was strongly recommended based on NME status
- 06 June 2006: Type C Meeting.** FDA gives PK advice for special populations of hepatic and renal impairment. No formal drug-drug interaction studies are required, unless evidence arises for interactions. (Applicant later submitted hepatic impairment and multi-dose PK studies on 30-Jun-2010; and renal impairment study on 13-Sep-2011).
- 23 January 2007: Type C Meeting.** Primary endpoint change discussed. By this time, Study 004 had randomized 84 patients and 55 patients had completed 24 weeks of treatment. Sponsor stated this change was not based on an interim analysis. FDA suggested performing a second clinical trial using the new primary endpoint. Note: Protocol amendment #4 (13-Feb-2007) incorporates primary endpoint change.
- 18 January 2008: Type C Meeting.** Results of Study 004 are known. Need for and design of confirmatory Phase 3 study (CL0600-020) for at least 24 weeks collecting safety and efficacy data. FDA notes lack of a clear dose-response relationship for efficacy in Study **004**.
- 14 July 2008: Meeting to further discuss the results of Study CL0600-004, the planned Phase 3 Study (CL0600-020) and the acceptability of the same PN/I.V. reduction volume endpoint of the development program for filing a marketing application.** “FDA notes that the study does show some clinical benefit however dose response has not been demonstrated. Study 004 has not shown which is the best dose for phase 3 studies. FDA indicates that the NPS is free to select its dose. It would accept a 0.05 mg/kg/day to support an NDA; however it is not convinced that 0.05 mg/kg/day is the best dose.” FDA confirms that “one additional study is needed” and “that a 2 arm design (0.05 mg/kg/day vs. placebo) would be acceptable to support an NDA”. FDA encourages collection of neutralizing antibody data.
- 30 November 2011: NDA submitted to the FDA
- 10 August 2012: NDA amendment submission extends review date to 30 December 2012.**
- 30 August 2012: European Commission adopted the CHMP decision granting marketing authorization for “Revestive-teduglutide”, and an orphan medicinal product for human use.**
- 3 August 2012: FDA received major amendment within 3 months of the user fee goal date, therefore the review clock was extended and a new user-fee-goal date of December 30, 2012 was established.**
- 16 October 2012: FDA held Gastrointestinal Drug Advisory Committee (GIDAC)**

Highlights of Review Issues:

- 1. New Molecular Entity:** first in its class; glucagon-like peptide-2 (GLP-2)
- 2. Efficacy:** demonstrated by two randomized controlled studies both with extensions. The primary efficacy endpoint was amended in one of these during the conduct of the study.
- 3. Primary Endpoint:** evaluation of clinical meaningfulness, advice sought from the Advisory Committee
- 4. Safety:** potential safety concerns based upon mechanism of action of Gattex.
- 5. Risk Mitigation and Evaluation Strategies (REMS):** discussion at the GIDAC Meeting.

3. CMC/Device

The Chemistry and Manufacturing review concludes that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

The Amended CMC review concludes that:

“The updated drug substance specification now includes limits for the Class I metals (b) (4), in conformance with USP <232> recommendations. NPS Pharmaceuticals also makes a Post Marketing Commitment to add limits to the drug substance specification for the remaining metals listed in the USP monograph. This will be done as soon as the method for determining the metals is appropriately validated, but no later than March 31, 2013. This approach is considered acceptable since

the primary safety concern regarding trace metals that can be present in the drug product comes from the Class I metals (b) (4). The proposed limits ensure that no unsafe levels of these metals will be present in the drug substance. Limits for the additional metals will further improve the quality of the drug substance, but these metals do not pose the same potential safety hazard as those of the Class 1 metals.”

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspection is acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The applicant has conducted adequate nonclinical studies with teduglutide which included pharmacology, safety pharmacology, pharmacokinetics, acute toxicology studies mice, repeated dose toxicology studies in mice (14 days to 26 weeks duration), rats (14 day to 13 weeks duration), 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, embryofetal development in rats and rabbits, and pre and postnatal development in rats), and special toxicology studies (antigenicity and local tolerance studies). Toxicology studies were conducted using the subcutaneous (SC) route, the intended clinical route of administration.

In pivotal repeated dose toxicology studies, major treatment-related effects were related to the pharmacological activity of teduglutide which were seen in all species. These included epithelial and villus hypertrophy and hyperplasia in the small and large intestine, gall bladder epithelial hypertrophy and hyperplasia accompanied by subacute inflammation in the gall bladder, mucosal hyperplasia of the stomach, hypertrophy/hyperplasia of the pancreatic duct epithelium, epithelial hypertrophy and hyperplasia of the bile duct in the liver, and mucosal hypertrophy/hyperplasia of the gall bladder.

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 subcutaneous route in Wistar Han rats at 3, 10 and 35mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05mg/kg, respectively), 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.

The non-clinical pharmacology review concludes:

“Overall, 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.”

In addition, Pregnancy Category B was recommended based upon animal reproduction studies.

These findings were discussed at the Advisory Committee and will be mentioned in the context of the professional labeling, Medication Guide and Risk Evaluation and Mitigation Strategies (REMS) below.

The reviewer recommended approval.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding non-clinical pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology is detailed in the approved professional labeling. I will mention clinical pharmacology studies and findings which are relevant to the safety of Gattex.

Pharmacodynamic Studies:

In Studies ALX-0600-92001 and CL0600-004, endoscopies were performed and mucosal biopsy samples were obtained for histopathological examination of absorptive epithelium including villus height, crypt depth, and mitotic index, and to evaluate biological parameters, including compositional and functional analyses. These findings agree with the mechanistic action of Gattex by stimulation of the GLP-2 receptors in the gastrointestinal tract. The studies demonstrated increased villus height, and crypt depth, as well as increased absorption of fluids.

Potential for Increased Absorption of Oral Medications:

Based upon the pharmacodynamic effect of Gattex, there is a potential for increased absorption of concomitant oral medications, which should be considered if the concomitant drugs require titration or have a narrow therapeutic index.

Renal Impairment:

Fifty percent (50%) dosage reduction was recommended in subjects with moderate to severe renal impairment and end stage renal disease (ESRD) patients based on the results from Study CL0600-018.

Through QT (TQT) interval Studies: The effect of Gattex on the QT interval was studied in the TQT study (Study C09-001)

The reviewers comment:

“The effect of single subcutaneous dose of teduglutide 5 mg and 20 mg on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 70 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia’s correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 20 mg is expected to cover the high exposure clinical scenario. No significant QTc prolongation was detected at a supra- therapeutic teduglutide dose of 20 mg in the TQT study.”

Immunogenicity:

Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of Gattex may trigger the development of antibodies. In a randomized, double-blind, placebo-controlled, parallel-group, multi-national, multi-center, clinical trial (CL0600-020) in adults with SBS, the incidence of anti-Gattex antibody was 0% (0/16) at Week 12 and 18% (6/34) at Week 24 in subjects who received subcutaneous administration of 0.05 mg/kg Gattex once daily. The anti-Gattex antibodies were cross-reactive to native glucagon-like peptide (GLP-2) in five of the six subjects (83%) who had anti-Gattex antibodies. In the extension study (CL0600-021), the immunogenicity incidence rate increased over time to 27% (14/51) at 12 months and 38% (13/34) at 18 months. Anti-Gattex antibodies appear to have no impact on short term (up to 1.5 years) efficacy and safety although the long-term impact is unknown.

A total of 40 subjects were tested for neutralizing antibodies--20 of these subjects had no neutralizing antibodies, and the remaining 20 subjects had no detectable neutralizing antibodies although, the presence of teduglutide at low levels in these study samples could have resulted in false negatives (no neutralizing antibody detected although present).

Finally, anti-teduglutide antibody has cross-reactivity to native GLP-2. The implication of this cross-reactivity with endogenous GLP-2 for the safety of long term treatment with teduglutide is unknown. The sponsor is continuing to evaluate this issue in the long-term clinical study CL0600-021.

The reviewers did not recommend PMR/PMCs (Postmarket Requirement/Postmarket commitment).

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Quality microbiology reviewer (for product sterility) has recommended approval. No issues are raised.

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Efficacy was assessed by analyzing the data from the two SBS placebo-controlled trials (Study 004 [CL0600-004] and Study 020 [CL0600-020]). Each of these trials had non-randomized open-label extensions (Study 005 [CL0600-005] and Study 021 [CL0600-020], respectively). These were multinational trials conducted in the US, Canada, and Europe.

Study 004 and Study 020 were conducted sequentially. Study 004 was a three arm placebo-controlled study: teduglutide 0.05 mg/kg/day; teduglutide 0.10 mg/kg/day. The preliminary results of Study 004 were available during discussions regarding the design of the primary endpoint and statistical analysis plan of Study 020. While these studies are similar in design there were several key differences worth noting: the fluid management algorithm, primary endpoint and statistical analysis plans.

Fluid management algorithm:

Gattex patients were to have their fluid requirements managed according to protocol algorithm during the conduct of the study. Study 004 and Study 020 had different fluid management algorithms to guide the clinicians in the selection of the PN/I.V. (parenteral nutrition/intravenous) fluid administered. Study 004 allowed only a 10% fluid reduction at key time points, while Study 020 allowed a 30% reduction in fluid. Thus, the absolute change in volume during the study period for Study 004 appears to be smaller than that of Study 020.

In Study 004 at Weeks 4, 8, 12, 16, and 20, investigators adjusted each patient's PN/I.V. volume based on percent change in urine output. In Study 020, an additional fluid adjustment occurred at Week 2.

Primary Efficacy Endpoint:

Study 004 amended the primary endpoint from a clinical response of a $\geq 20\%$ decrease in PN/I.V. fluid volume at Weeks 20 and 24 to be a 6-level categorical "graded response score" during the conduct of the study. NPS felt that this endpoint would more clearly differentiate the clinical efficacy of teduglutide.

Statistical Analysis Plan:

The analysis plan for Study 004 was a pre-specified efficacy hypothesis testing order where the graded score was first tested for the comparison of 0.10 mg/kg/day group versus placebo. Since statistical significance was not demonstrated in this comparison all subsequent reported p-values were deemed exploratory in nature. The comparison of teduglutide 0.05 mg/kg/day and placebo demonstrated an effect, but statistical significance could not be established due to the prespecified hierarchical multiplicity adjustment testing strategy. The key secondary endpoint for Study 004 had been the original endpoint prior to the amendment. Again, due to the testing procedure statistical significance could not be determined.

Efficacy of Gattex was not demonstrated for Study 004 based upon the pre-specified primary outcome variable and analysis plan. Possible reasons included the following:

1. Change in primary endpoint from a simple responder endpoint (clinical response of $\geq 20\%$ decrease in PN/I.V. fluid volume at Weeks 20 and 24) to a 6-level categorical 'graded response score'.
2. PN/I.V. fluid volume adjustment was limited to no more than 10% in Study 004
3. The first PN/I.V. fluid volume adjustment occurred at Week 4 in Study 004, as opposed to earlier in the trial.
4. The high-dose group (0.10 mg/kg/day), which also had a 32% higher baseline weekly PN/I.V. volume relative to the 0.05 mg/kg/day dose group, was tested first in the hierarchical hypothesis testing procedure and failed to demonstrate efficacy ($p=0.161$). Therefore, testing stopped after the high-dose group, so that testing was not able to proceed to the (0.05 mg/kg/day dose group.
5. Higher baseline weekly PN/I.V. fluid requirement in the 0.10 mg/kg/day group led to numerically smaller percent change results, and hence fewer patients who achieved clinically relevant response in the 0.10 mg/kg/day group relative to the 0.05 mg/kg/day dose group.

The design of Study 020 was modified based on the preceding considerations. The primary endpoint for the study was designated as the attainment of at least 20% reduction from Baseline in PN/I.V. volume at Weeks 20 and 24. This study tested the efficacy of teduglutide 0.5mg/kg/day vs. placebo.

Study 020 demonstrated a statistically significant ($p=0.002$) difference between teduglutide and placebo for the primary endpoint (percent responders in each study group who achieved at least 20% reduction in weekly PN/I.V. volume at Weeks 20 and 24): 62.8% versus 30.2% (teduglutide versus placebo). The percent volume reductions in Study 020 were 32% (teduglutide) and 21% (placebo) ($p=0.025$). Mean reduction of weekly PN/I.V. (L/week) was 4.4 L/week for teduglutide and 2.3 L/week for placebo ($p<0.001$).

Although Study 004 did not meet the protocol-specified primary endpoint (i.e., difference between teduglutide 0.10 mg/kg/day and placebo for the graded response analysis was not statistically significant), the key secondary endpoint in Study 004 did demonstrate a nominal benefit. The percent responders in the teduglutide 0.05 mg/kg/day group was greater than placebo (16/35, 45.7% vs 1/16, 6.3%). This analysis supports the efficacy findings of Study 020. Additionally, two patients 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.

The preceding data were determined to be sufficient to approve Gattex (teduglutide) for the following agreed upon indication:

“GATTEX® (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.”

8. Safety

Across all clinical studies, 566 subjects were exposed to at least one dose of Gattex (190 patient-years of exposure; mean duration of exposure was 17 weeks). Of the 566 subjects, 173 subjects were treated in Phase 3 SBS studies (134/173 [77%] at the dose of 0.05 mg/kg/day and 39/173 [23%] at the dose of 0.10 mg/kg/day).

The most commonly reported ($\geq 10\%$) adverse reactions in patients treated with Gattex across all clinical studies ($n = 566$) were: abdominal pain (30.0%); injection site reactions (22.4%); nausea (18.2%); headaches (15.9%); abdominal distension (13.8%); upper respiratory tract infection (11.8%).

The rates of adverse reactions in subjects with SBS participating in two randomized, placebo-controlled, 24-week, double-blind clinical studies (Study 1 and Study 3) are summarized in Table 1. Only those reactions with a rate of at least 5% in the Gattex group, and greater than placebo group, are summarized in Table 1. The majority of these reactions were mild or moderate. Of subjects receiving Gattex at the recommended dose of 0.05 mg/kg/day, 88.3% ($N=68/77$) experienced an adverse reaction, as compared to 83.1% (49/59) for placebo. Many of these adverse reactions have been reported in association with the underlying disease and/or parenteral nutrition.

Adverse Reaction	Placebo (N=59) n (%)	GATTEX 0.05mg/kg/day (N=77) n (%)
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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)
Sleep Disturbances	0	4 (5.2)
Cough	0	4 (5.2)
Skin Hemorrhage	1 (1.7)	4 (5.2)
Subjects with Stoma		
Gastrointestinal Stoma Complication	3 (13.6) ^a	13 (41.9) ^a

^aPercentage based on 53 subjects with a stoma (N = 22 placebo; N = 31 GATTEX 0.05 mg/kg/day)

In placebo-controlled Studies 1 and 3, 12% of patients in each of the placebo and Gattex study groups experienced an injection site reaction.

Deaths

A total of 3 deaths were reported during the drug development. Two were enrolled in Study 021 and had a diagnosis of malignancy (cases discussed below). One died prior to treatment with teduglutide during the screening period.

Adverse Reactions of Special Interest

Malignancy. Three subjects were diagnosed with malignancy in the clinical studies, all of whom were male and had received Gattex 0.05 mg/kg/day in Study 2. One subject, who had a history of abdominal radiation for Hodgkin’s disease two decades prior to receiving Gattex and a liver lesion on CT scan prior to receiving study drug, was diagnosed with metastatic adenocarcinoma of unconfirmed origin after 11 months of exposure to Gattex. Two subjects had extensive smoking histories, and were diagnosed with lung cancers (squamous and non-small cell) after 12 months and 3 months of Gattex exposure, respectively.

Colorectal Polyps. In the clinical studies, 6 subjects were diagnosed with polyps of the G.I. tract after initiation of study treatment. In the SBS placebo-controlled studies, 1/59 (1.7%) of subjects on placebo and 1/109 (0.9%) of subjects on Gattex 0.05 mg/kg/day were diagnosed with intestinal polyps (inflammatory stomal and hyperplastic sigmoidal after 3 and 5 months, respectively). The remaining 4 polyp cases occurred in the extension studies--two colorectal villous adenomas (onset at 6 and 7 months in Gattex 0.10 and 0.05 mg/kg/day dose groups, respectively), one hyperplastic polyp (onset 6 months in Gattex 0.10 mg/kg/day dose group), and one small duodenal polyp (onset at 3 months in Gattex 0.05 mg/kg/day dose group).

Gastrointestinal Obstruction. Overall, 12 subjects experienced one or more episodes of intestinal obstruction/stenosis: 6 in SBS placebo-controlled studies and 6 in the extension studies. The 6 subjects in the placebo-controlled trials were all on Gattex: 3/77 (3.9%) on Gattex 0.05 mg/kg/day and 3/32 (9.4%) on Gattex 0.10 mg/kg/day. No cases of intestinal obstruction occurred in the placebo group. Onsets ranged from 1 day to 6 months. In the extension studies, 6 additional subjects (all on Gattex 0.05 mg/kg/day) were diagnosed with intestinal obstruction/stenosis with onsets ranging from 6 days to 7 months. Two of the 6 subjects from the placebo-controlled trials experienced recurrence of obstruction

in the extension studies. Of all 8 subjects with an episode of intestinal obstruction/stenosis in these extension studies, 1 subject required endoscopic dilation and none required surgical intervention.

Gallbladder, Biliary and Pancreatic Disease. For gallbladder and biliary disease in the placebo-controlled studies, 3 subjects were diagnosed with cholecystitis, all of whom had a prior history of gallbladder disease and were in the Gattex 0.05 mg/kg/day dose group. No cases were reported in the placebo group. One of these 3 cases had gallbladder perforation and underwent cholecystectomy the next day. The remaining 2 cases underwent elective cholecystectomy at a later date. In the extension studies, 3 subjects had an episode of acute cholecystitis; 2 subjects had new-onset cholelithiasis; and 1 subject experienced cholestasis secondary to an obstructed biliary stent. For pancreatic disease in the placebo-controlled studies, 1 subject (Gattex 0.05 mg/kg/day dose group) had a pancreatic pseudocyst diagnosed after 4 months of Gattex. In the extension studies, 1 subject was diagnosed with chronic pancreatitis; and 1 subject was diagnosed with acute pancreatitis.

Fluid Overload. In the placebo-controlled trials, fluid overload was reported in 4/59 (6.8%) of subjects on placebo and 9/77 (11.7%) subjects on Gattex 0.05 mg/kg/day. Of the 9 cases in the Gattex group, there were 2 cases of congestive heart failure (CHF), 1 of whom was reported as a serious adverse event and the other as non-serious. The serious case had onset at 6 months, and was possibly associated with previously undiagnosed hypothyroidism and/or cardiac dysfunction.

Concomitant Oral Medication. Gattex can increase the absorption of concomitant oral medications such as benzodiazepines and psychotropic agents. In the placebo-controlled trials, an analysis of episodes of cognition and attention disturbances was performed for subjects on benzodiazepines. One of the subjects in the Gattex 0.05 mg/kg/day group (on prazepam) experienced dramatic deterioration in mental status progressing to coma during her first week of Gattex therapy. She was admitted to the ICU where her benzodiazepine level was >300 mcg/L. Gattex and prazepam were discontinued, and coma resolved 5 days later.

These adverse reactions were not common among patients receiving Gattex. However, the seriousness of the potential for acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex (teduglutide [rDNA origin]) for injection is based upon the mechanism of action of Gattex, animal data (hyperplasia) and the cases listed above.

Therefore, based upon these potential serious adverse reactions, it was recommended that they be managed through labeling and a REMS (this is further discussed below). Monitoring for obstruction, colonic malignancy and biliary disorders is recommended in the labeling, and those recommendations should be communicated to all physicians prescribing Gattex.

9. Advisory Committee Meeting

The Gastrointestinal Drugs AC Committee (GIDAC) met on October 16, 2012.

The members of the committee agreed that the primary endpoint as defined was clinically meaningful and that it described a clinically meaningful benefit in adult patients with Short-Bowel Syndrome (SBS). Additionally, the committee voted unanimously that efficacy was demonstrated based upon data from Study 020 and 004 (Study C10600-004; CL0600-020).

Regarding the potential tumor promoting effects of teduglutide, the committee discussed the adequacy of the recommended safety monitoring described in the label proposed by the applicant for monitoring the development of malignancy in the colon and other gastrointestinal tract sites.

Members of the panel noted that the Applicant's recommendations for colonoscopy might be reasonable, and also useful for monitoring in a registry. With respect to small bowel cancers, currently there is not a good way to screen for them, therefore the current proposal involving clinical awareness and vigilance should be reasonable. One member mentioned that perhaps serial colonoscopy every two years with multiple biopsies looking for dysplasia is needed and would provide a better way of assessing cancer risk.

Regarding the potentially long latency period for onset and identification of intestinal and non-intestinal (gallbladder, pancreas, lung, possibly others) malignancy, many members felt that the 7-year follow-up proposed in the REMS timetable for submission of REMS assessments is probably insufficient; and that at least a decade of follow-up would be better. One member stated that longer-term data related to malignancy were needed.

Additionally, the committee discussed cases of extra-intestinal malignancies reported in the safety database, and what additional safety monitoring, if any, would be needed for patients receiving teduglutide. Members mentioned that no other monitoring besides regular health maintenance would be recommended at this time and the standard approach is appropriate. One member noted the importance of physician education. One member who was an oncologist recommended against contraindicating this drug in patients with malignancies outside of the gastrointestinal tract.

Considering the potential side effects of teduglutide that include biliary disease, pancreatic disease, gastrointestinal stenosis and obstruction, the panel discussed the adequacy of the recommended laboratory and imaging studies described in the label proposed by the applicant. Members agreed that the standard of care monitoring for these events is sufficient, consisting of liver and pancreatic enzymes every 3 to 6 months, clinical history and physical exam, and imaging as indicated by the status of the patient.

In general, the panel felt there was nothing to specifically recommend regarding immunogenicity and neutralizing antibodies at this time. One member noted that he was reassured by the Applicant's nonclinical data which did not demonstrate evidence of any phenotypic change to interfere with GLP-2 pathway. The Applicant stated they would test for antibodies for 6 months after discontinuation of teduglutide in Study 021.

The proposed REMS was discussed by the panel. Ten of the 12 voting members recommended the REMS, and felt that the Communication plan was appropriate (1 No vote; 1 abstained). The panel commented that the registry can be done as a post marketing study. One member noted some concern in terms of the registry. Another member mentioned that while the plan should not be burdensome, more than just a mass mailing to physicians should be required. Another member commented on the need for patient education as well as physician education. One member suggested that the timetable for the proposed REMS Assessments might be considered to occur more frequently, for example, every 6 months since many SBS patients are seen every two-weeks to every three-months.

The member who voted "No" commented that, although the outline for the prescriber is good, the REMS does not require evaluating the patient's level of knowledge; or informing the patient and care team as part of the evaluation. One member underscored the importance of recognizing that not all SBS patients are

cared for by a collaborative cross-disciplinary team. This member emphasized how important one-on-one patient education is from the prescriber who may be an internist working with a gastroenterologists.

Based upon the risks and benefits associated with Gattex for the treatment of patients with SBS who require PN/I.V., all members recommended approval.

Finally, the committee commented on post-approval studies. Panel members expressed the need for a registry for colorectal and other cancers that follows patients for at least 10 years in addition to the REMS and post-marketing survey oversight. It was commented that perhaps there should be a mandatory registry; however most members felt that while a mandatory registry would yield more useful information, making it mandatory would be overly burdensome on patients. Members thought that the frequency of reporting within the registry needs to be defined. One member noted the need for rigorous data collection, where compliance or participation would not be an issue. Besides safety surveillance, collection of data on quality of life and other behavioral assessments was also recommended. A few members also noted the importance of patient education, and also recommended additional data in pediatrics. One member also wanted to see studies and data, which include pre- and post treatment colonoscopy and biopsies for dysplasia to see if there are any premalignant changes.

10. Pediatrics

Gattex is a designated orphan product and so the PREA requirements do not apply. At this time there is no pediatric data regarding the safety or efficacy of Gattex.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name – I am in concurrence with the with OSE/DMEPA recommendation of sponsor's propose proprietary name: Gattex (11/19/2012).
- Physician labeling has been negotiated and agreed upon by the FDA and NPS as appended to the approval letter.
- A Medication Guide is part of the approved labeling for Gattex. It will be packaged with the medication (unit of use). It has been agreed upon by the FDA and NPS as appended to the approval letter.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Approval with REMS

- **Risk Benefit Assessment:**

Decisional factors considered in a Risk-Benefit Assessment include an analysis of the 1.) medical condition being treated, 2.) unmet medical need, 3.) clinical benefits of treatment, 4.) risks associated with treatment, and 5.) management of those risks.

1. Analysis of medical condition being treated

The number of patients in the United States requiring total parenteral nutrition (TPN) is approximately 40,000. In the Oley Foundation Home TPN Registry, 26% of TPN patients had SBS, which suggests that the number of patients with SBS requiring TPN is approximately 10,000.² FDA granted Orphan Designation (on June 29, 2000) to the recombinant human glucagon-like peptide-2 formulation for subcutaneous injection for the proposed treatment of SBS (adults).

Short Bowel Syndrome (SBS) results from surgical resection of some or all of the small or large intestine. Conditions that can result in bowel resection include Crohn's disease, malrotation, volvulus, intussusception, necrotizing enterocolitis, mesenteric vessel thrombosis, trauma, and others. Loss of the small intestine, if extensive, leads to malabsorption of protein, fluid, electrolytes, and micronutrients. According to the 2006 consensus statement:

“Short-bowel syndrome results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet.”³

The clinical presentation of SBS varies depending on the length and anatomy of the excised bowel as well as concomitant illness and medication. The loss of intestine can lead to malabsorption with consequent fluid imbalance, weight loss, anemia, and malnutrition. Depending on severity, malabsorption might be overcome by increasing oral intake. When increasing oral intake fails to provide sufficient nutrition, antimotility agents can be given to prolong nutrition-mucosa contact time to improve absorption. When both of these treatment modalities fail, patients become dependent on TPN therapy. It is this latter group of patients to whom teduglutide is targeted.

Following bowel resection in SBS, compensatory increases in bowel absorptive capacity by the remaining bowel can take up to two years to occur. In many cases it is insufficient to compensate fully for the lost intestine. If after two years the SBS patient still requires TPN support, it is unlikely the patient will be completely weaned from such support.⁴ For many patients SBS is a lifelong disease associated with significant increases in morbidity and mortality

Although TPN is lifesaving, it is associated with clinical complications. These complications can include malnutrition, diarrhea, dehydration, nutrient deficiencies, electrolyte imbalance, recurrent intestinal obstruction, intestinal polyps, intestinal obstruction, gallbladder/pancreatic/hepatic disease, sepsis, liver injury, and blood clots. Thus both SBS and TPN supplementation are associated with multiple long-term multi-organ system derangements ranging from mild to life threatening. In addition, being tethered to the infusion apparatus required for TPN is a significant quality of life issue that directly affects mobility and lifestyle. TPN therapy is typically given for 10 or more hours a day for 5-7 days a week. Consequently, weaning from TPN is a cornerstone of clinical management in SBS.

2. Unmet Medical Need:

There are limited pharmacologic therapeutic options in the United States for SBS treatment in adult patients restricted to pharmacological therapy:

² Oley Foundation. North American home parenteral and enteral nutrition patient registry annual report, 1994

³ O'Keefe SJD, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J, Short bowel syndrome and intestinal failure: Consensus definitions and overview. *Clinical Gastroenterology and Hepatology*. 2006; 4:6-10

⁴ Buchman AL. The clinical management of short bowel syndrome: steps to avoid parenteral nutrition. 1997. *Nutrition*. 13(10): 907-13.

ZORBTIVE [somatotropin (recombinant DNA origin) for subcutaneous injection] is a human growth hormone (hGH) produced by recombinant DNA technology indicated in SBS patients receiving specialized nutritional support (Orphan Drug approved by FDA on December 3, 2003). ZORBTIVE therapy should be used in conjunction with optimal management of SBS.

- WARNINGS include “Benzyl alcohol as a preservative in Bacteriostatic Water.
- CONTRAINDICATIONS include patients with active neoplastic growth (either newly diagnosed or recurrent; any anti-tumor therapy should be completed prior to starting therapy with ZORBTIVE) and in patients with a known hypersensitivity to growth hormone.

A Risk Evaluation and Mitigation Strategy (REMS) was not required for ZORBTIVE.

NUTRESTORE (L- glutamine) powder for oral solution for the treatment of SBS in patients receiving specialized nutritional support when used in conjunction with a recombinant hGH that is approved for this (SBS) indication (Orphan Drug, NME, approved by FDA June 10, 2004).

- WARNINGS AND PRECAUTIONS section of labeling includes the following: “Routine monitoring of renal and hepatic function is recommended in patients receiving IPN, particularly in those with renal or hepatic impairment.” There is no BOX WARNING in NUTRESTORE labeling.

A REMS is not required for NUTRESTORE

The approval of teduglutide would provide a new molecule which is targeted to the receptors in the gastrointestinal tract. This is a potential improvement over the systemic effect known to occur in patients treated with growth hormone.

3. Clinical Benefits of Therapy:

As mentioned above, the primary endpoint was determined to be clinically meaningful by the reviewers and the members of the GIDAC. Because PN/I.V. dependence is associated with considerable morbidity, the efficacy results described below are viewed as clinically meaningful; some patients were weaned off PN/I.V., patients required less fluid volume, and therefore less time was needed for administration of fluid freeing the patient from tethering to the infusion pump.

Study 020 Results:

- The primary efficacy endpoint was based on a clinical response, defined as a subject achieving at least 20% reduction in weekly PN/I.V. volume from Baseline (immediately before randomization) to both Weeks 20 and 24. The percentages of treatment group responders were compared in the intent-to-treat population of this study which was defined as all randomized patients.
- 63% (27/43) of Gattex-treated subjects versus 30% (13/43) of placebo-treated subjects were considered responders ($p=0.002$).
- At Week 24, the mean reduction in weekly PN/I.V. volume was 4.4 Liters for Gattex -treated subjects (from pre-treatment baseline of 12.9 Liters) versus 2.3 Liters for placebo-treated subjects (from pre-treatment baseline of 13.2 Liters/week) ($p<0.001$).
- Twenty-one subjects on Gattex (53.8%) versus 9 on placebo (23.1%) achieved at least a one-day reduction in PN/I.V. support.

Study 021 Results:

This is an ongoing two-year open-label extension of Study 020 in which 88 subjects receive Gattex 0.05 mg/kg/day. Ninety-seven percent (76/78) of subjects from Study 020 elected to enroll in Study 021. An

additional 12 subjects entered Study 2, who had been optimized and stabilized but not randomized in Study 020 because of closed enrollment.

- Of responders in Study 020 who entered Study 021, 100% (25/25) sustained their response to Gattex after one year of continuous treatment.
- A 20% or greater reduction of parenteral support was achieved in 72% (31/43) of subjects after an additional 28 weeks of continuous Gattex treatment.
- The mean reduction of weekly PN/I.V. volume was 5.2 L/week after one year of continuous Gattex treatment.
- Six subjects in Study 021 were weaned off their PN/I.V. support while on Gattex. Subjects were maintained on Gattex even if no longer requiring PN/IV support. These 6 subjects had required PN/I.V. support for 3 to 18 years, and prior to Gattex had required between 4 L/week and 13 L/week of PN/I.V. support.

Study 004 Results:

- The primary efficacy endpoint was a graded categorical score that did not achieve statistical significance for the high dose. Further evaluation of PN/I.V. volume reduction using the endpoint of response (defined as at least 20% reduction in PN/I.V. fluid from Baseline to Weeks 20 and 24) showed that 46% of subjects on Gattex 0.05 mg/kg/day responded versus 6% on placebo.
- Subjects on Gattex at both dose levels experienced a 2.5 L/week reduction in parenteral support requirements versus 0.9 L/week for placebo at 24 weeks. Two subjects in the Gattex 0.05 mg/kg/day dose group were weaned off parenteral support by Week 24.

Study 005 Results:

This is a blinded, uncontrolled extension of Study 004, in which 65 subjects from Study 004 received Gattex for up to an additional 28 weeks of treatment.

- Of responders in Study 004 who entered Study 4, 75% sustained response on Gattex after one year of treatment.
- In the Gattex 0.05 mg/kg/day dose group, a 20% or greater reduction of parenteral support was achieved in 68% (17/25) of subjects.
- The mean reduction of weekly PN/I.V. volume was 4.9 L/week (52% reduction from baseline) after one year of continuous Gattex treatment.
- The subjects who had been completely weaned off PN/I.V. support in Study 004 remained off parenteral support through Study 005. During Study 005, an additional subject from Study 004 was weaned off parenteral support.

4. Risks Associated with Therapy:

The most commonly reported ($\geq 10\%$) adverse reactions in patients treated with Gattex across all clinical studies (n = 566) were: abdominal pain (30.0%); injection site reactions (22.4%); nausea (18.2%); headaches (15.9%); abdominal distension (13.8%); upper respiratory tract infection (11.8%). In addition, in the two controlled clinical trials for SBS, fluid overload occurred (11.7%).

Adverse events which occurred less frequently and were related to the mechanism of action of Gattex include possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders.

5. Management of Risks:

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Gattex (teduglutide [rDNA origin]) for injection to ensure that the benefits of the drug outweigh the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex (teduglutide [rDNA origin]) for injection.

The elements of the REMS will be: Communication Plan, elements to assure safe use (health care providers who prescribe Gattex (teduglutide [rDNA origin]) for injection will have training regarding the risks and safe use of Gattex), and a timetable for submission of assessments of the REMS.

The majority of patients treated for SBS are seen by a specific physician groups including gastroenterologists, colorectal and gastrointestinal tract surgeons. As mentioned above, with knowledge of the recommended monitoring for possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex, physicians may be able to intervene early and mitigate these risks.

The final recommendation regarding whom to treat with Gattex and the issue of malignancies is addressed in the labeling. Teduglutide exerts its effects mainly on the gastrointestinal tract and it is unknown if it would have a growth promoting effect on tissues outside of gastrointestinal tract. Based on the pharmacologic activity and findings in animals, Gattex has the potential to cause hyperplastic changes including neoplasia.

The labeling recommends that:

- In patients at increased risk for malignancy, the clinical decision to use Gattex should be considered only if the benefits outweigh the risks.
- In patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), Gattex therapy should be discontinued.
- In patients with active non-gastrointestinal malignancy, the clinical decision to continue Gattex should be made based on risk-benefit considerations.

Overall benefits exceed risks when patients are closely monitored for common side effects, as well as for potential signs of malignancy. At this time it is not certain that the risks of malignancy in the gastrointestinal tract or extra-intestinal sites are elevated. Careful monitoring and attention to patients' symptoms will be key in early diagnosis. It is felt that the professional labeling, the REMS and the Medication Guide will provide information regarding prospective monitoring of these patients to mitigate these risks.

It is well known that growth factors promote cell growth and can promote malignancy. It may be that Gattex has an effect limited to the gastrointestinal tract. Long-term safety studies will have to be conducted to determine if this is so.

This recommendation was discussed and agreed upon by all review disciplines. The additional safety information regarding these potential serious adverse reactions will be collected in the registry.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The elements of the REMS will be: Communication Plan, elements to assure safe use (training for health care providers who prescribe GATTEX (teduglutide [rDNA origin]) for injection and appropriate risk information for patient education), and a timetable for submission of assessments of the REMS.

The Goal of the REMS is:

To inform prescribers and patients 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.

Recommendation for other Postmarketing Requirements and Commitments

Since Gattex is likely to be used life-long in SBS patients, it is important to continue to follow this cohort to gain more specific information of the potential risk of the development of malignancy. The following study will be helpful to further that understanding.

PMR 1978-1: A prospective, multi-center, long-term, observational, registry study, of short bowel syndrome patients treated with teduglutide in a routine clinical setting, to assess the long-term safety of teduglutide. Design the study around a testable hypothesis to rule out a clinically meaningful increase in colorectal cancer risk above an estimated background risk in a suitable comparator. Select and justify the choice of appropriate comparator population(s) and corresponding background rate(s) relative to teduglutide-exposed patients. Provide sample sizes and effect sizes that can be ruled out under various enrollment target scenarios and loss to follow-up assumptions. The study's primary outcome should be colorectal cancer, and secondary outcomes should include other malignancies, colorectal polyps, bowel obstruction, pancreatic and biliary disease, heart failure, and long-term effectiveness. Patients should be enrolled over an initial 5-year period and then followed for a period of at least 10 years from the time of enrollment. Progress updates of registry patient accrual and a demographic summary should be provided annually. Registry safety data should be provided in periodic safety reports.

Final Protocol Submission: 09/2013

Study Completion: 12/2029

Final Report Submission: 6/2031

PMC # 1978-2: Elemental Impurities specifications will be expanded to include limits and testing for all metals, as recommended in USP <232>.

Final Report: March 31, 2013.

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/s/

JOYCE A KORVICK
12/20/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: 15-Nov-2012

FROM: John Troiani, MD, PhD *Clinical Reviewer, DGIEP*

THROUGH: Ruyi He, MD *Medical Team Leader, DGIEP*

SUBJECT: Edits to Clinical Review of NDA 203,441

TO: General

The following are updates and some minor changes to the clinical review of NDA 203,441, where strikethrough text should be deleted and underlined text should be added:

1. Site inspections resulted in no data having to be excluded
2. p. 48: Delete strikethrough phrase: “Across 15 clinical studies and ~~624~~ subjects (Table 15), 566 (safety population) were on teduglutide and 198 on placebo.”
3. p. 51, Section 7.2.1: “update (~~Apr-2012~~ Oct-2011), exposure”
4. Section 7.6.2 (p. 88): add: “Pregnancy Category B.”
5. p. 69: change date: “As of ~~April-2012~~ October 2011 in the SBS extension studies...”

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/s/

JOHN S TROIANI
11/15/2012

RUYI HE
11/15/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 203,441
Priority or Standard	Standard
Submit Date(s)	30-Nov-2011
Received Date(s)	30-Nov-2011
PDUFA Goal Date	30-Dec-2012
Division / Office	Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)
Reviewer Name(s)	John Troiani, MD, PhD
Review Completion Date	31-Oct-2012
Established Name	Teduglutide (rDNA origin)
(Proposed) Trade Name	GATTEX®
Therapeutic Class	Glucagon-like peptide-2 (GLP- 2) analog
Applicant	NPS Pharmaceuticals, Inc
Formulation(s)	Powder for subcutaneous (SC) injection
Dosing Regimen	0.05 mg/kg SC once daily
Indication(s)	Treatment of adults with short bowel syndrome (SBS) to improve intestinal absorption of fluid and nutrients
Intended Population(s)	Patients with SBS

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment.....	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	11
1.4	Recommendations for Postmarket Requirements and Commitments	12
2	INTRODUCTION AND REGULATORY BACKGROUND	13
2.1	Product Information	13
2.2	Tables of Currently Available Treatments for Proposed Indications	13
2.3	Availability of Proposed Active Ingredient in the United States	14
2.4	Important Safety Issues With Consideration to Related Drugs.....	14
2.5	Summary of Presubmission Regulatory Activity Related to Submission	14
2.6	Other Relevant Background Information	17
3	ETHICS AND GOOD CLINICAL PRACTICES.....	19
3.1	Submission Quality and Integrity	19
3.2	Compliance with Good Clinical Practices	19
3.3	Financial Disclosures.....	19
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	19
4.1	Chemistry Manufacturing and Controls	19
4.2	Clinical Microbiology.....	19
4.3	Preclinical Pharmacology/Toxicology	20
4.4	Clinical Pharmacology	22
4.4.1	Mechanism of Action.....	22
4.4.2	Pharmacodynamics.....	23
4.4.3	Pharmacokinetics.....	23
5	SOURCES OF CLINICAL DATA.....	25
5.1	Tables of Studies/Clinical Trials	25
5.2	Review Strategy	26
5.3	Discussion of Individual Studies/Clinical Trials.....	26
6	REVIEW OF EFFICACY	33
6.1	Indication	33
6.1.1	Methods	33
6.1.2	Demographics	33
6.1.3	Subject Disposition.....	36
6.1.4	Analysis of Primary Endpoint(s).....	37
6.1.5	Analysis of Secondary Endpoints(s)	41
6.1.6	Other Endpoints	43

6.1.7	Subpopulations	47
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	47
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	47
6.1.10	Additional Efficacy Issues/Analyses	47
7	REVIEW OF SAFETY.....	48
7.1	Methods.....	48
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	48
7.1.2	Categorization of Adverse Events	50
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	50
7.2	Adequacy of Safety Assessments	51
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	51
7.2.2	Explorations for Dose-Response	52
7.2.3	Special Animal and/or In Vitro Testing	53
7.2.4	Routine Clinical Testing	53
7.2.5	Metabolic, Clearance, and Interaction Workup	53
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	53
7.3	Major Safety Results	54
7.3.1	Deaths.....	54
7.3.2	Nonfatal Serious Adverse Events	55
7.3.3	Dropouts and/or Discontinuations	57
7.3.4	Significant Adverse Events	60
7.3.5	Submission Specific Primary Safety Concerns	60
7.4	Supportive Safety Results	80
7.4.1	Common Adverse Events	80
7.4.2	Laboratory Findings	80
7.4.3	Vital Signs	82
7.4.4	Electrocardiograms (ECGs)	82
7.4.5	Special Safety Studies/Clinical Trials	82
7.4.6	Immunogenicity	83
7.5	Other Safety Explorations.....	86
7.5.1	Dose Dependency for Adverse Events	86
7.5.2	Time Dependency for Adverse Events.....	86
7.5.3	Drug-Demographic Interactions	86
7.5.4	Drug-Disease Interactions.....	87
7.5.5	Drug-Drug Interactions.....	87
7.6	Additional Safety Evaluations	88
7.6.1	Human Carcinogenicity	88
7.6.2	Human Reproduction and Pregnancy Data.....	88
7.6.3	Pediatrics and Assessment of Effects on Growth	88
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	88
7.7	Additional Submissions / Safety Issues	88

8	POSTMARKET EXPERIENCE.....	88
9	APPENDICES	89
9.1	Literature Review/References	89
9.2	Labeling Recommendations	89
9.3	Advisory Committee Meeting.....	91

Table of Tables

Table 1 Table of currently available treatments.....	14
Table 2 SBS Efficacy and Safety Studies.....	25
Table 3 Other human studies	26
Table 4 Completed visits in ongoing Study 021 (as of 30-Jun-2011): Safety population	32
Table 5 Geographic distribution, ITT (020, 004).....	33
Table 6 Demographics, ITT (020, 004).....	34
Table 7 Reasons for resection leading to SBS for studies 020 and 004 (safety population)	35
Table 8 Surgical history (020, 004)	36
Table 9 Subject disposition (020, 004)	37
Table 10 Definition of primary endpoint (graded response score) in trial 004	38
Table 11 Primary endpoint (graded response score) distribution, Study 004	38
Table 12 Primary efficacy results of Study 020	40
Table 13 Secondary endpoints, ITT (020, 004).....	42
Table 14 Days reduction in PN (005, 021)	46
Table 15 Counts of safety population by study.....	49
Table 16 Overall adverse event counts for teduglutide subjects (safety population)....	50
Table 17 Exposure to teduglutide in SBS Placebo-controlled Trials (004, 020)	51
Table 18 Non-fatal SAE and AE rates, safety population, SBS studies.....	55
Table 19 SAEs with rates >1% in 0.05 (approvable) dose group and greater than placebo rate, SBS Placebo-controlled trials	56
Table 20 SAEs with marginal rate >2% in Long-Term SBS studies	57
Table 21 Patient disposition, SBS Placebo-controlled trials (004, 020).....	58
Table 22 GI Polyp-related adverse events	62
Table 23 Common AEs (in at least 5% of subjects on 0.05 mg/kg/day) and more frequent with teduglutide, SBS Placebo-controlled studies.....	80
Table 24 Selected laboratory values (studies 004, 020).....	81

Table of Figures

Figure 1 Structural formula of teduglutide	13
Figure 2 Study 004 flowchart.....	27
Figure 3 PN/I.V. adjustment decision tree	28
Figure 4 Study 020 flowchart.....	29
Figure 5 Absolute mean change (SEM) in PN volume by visit, ITT (020, 004).....	43
Figure 6 Mean percent change (SEM) in PN volume, ITT (020, 004)	44
Figure 7 Percent responders by week, ITT (020, 004)	45
Figure 8 Mean PN/I.V. volume by antidrug antibody (ADA) positivity status	75
Figure 9 Antibody positivity by months of teduglutide exposure (studies 020, 021)	84
Figure 10 ADA(+) subjects' weekly PN/I.V. volume (Studies 020, 021).....	85

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approve GATTEX® for the indication of treatment of adults with short bowel syndrome (SBS) who are dependent on parenteral fluids to improve intestinal absorption of fluid and nutrients.

1.2 Risk Benefit Assessment

The risk-benefit tradeoff favors approval of teduglutide based on the following observations:

1. Benefit. Rare and serious disease. Short-Bowel Syndrome (SBS) with parenteral nutrition (PN) dependency is a rare and very serious disease with high morbidity and mortality. SBS and PN are both associated with very serious complications involving all organ systems. The psychosocial toll of SBS with PN dependency is devastating. Patients are dependent on, and tethered to, complicated and bulky equipment, often through the night, and it takes hours a day just to plan and organize their day of PN infusions and other activities. Sleep deprivation, depression, and mood disturbance are ubiquitous in this population. Fecal and urinary incontinence are extremely common, and impose enormous social stress on the patient and his/her entire social network. GATTEX is the first effective long-term treatment for this condition.
2. Benefit. Efficacy. The data in this Application demonstrate efficacy.
 - a. The primary endpoint of 20% reduction in PN in Study 020 was clinically and statistically significant ($p=0.002$). Twice as many patients on teduglutide (63%) achieved at least 20% reduction in their PN/I.V. volume by Weeks 20 and 24, as compared to patients on placebo (30%). Efficacy data from study 004 are supportive of those from study 020. The FDA Advisory Committee (AC) convened on 16-Oct-2012 was unanimous that 20% PN/I.V. reduction is clinically significant in this population.
 - b. Two important pre-specified secondary endpoints of Study 020 – absolute change in PN/I.V. volume between baseline and Week 24 and attainment of at least a 1-day reduction in PN/I.V. – showed that the teduglutide group had twice the reduction in PN/I.V. volume and more than twice the rate as placebo on achievement of one or more days reduction of PN/I.V.

- c. As of 16-Oct-2012, complete weaning from PN/I.V. has been achieved in 15 patients in this development program, all on teduglutide 0.05 mg/kg/day:
 - i. Study 004: 2 patients were weaned off PN/I.V. by Week-24 and remained off through Study 005 for another 6 months
 - ii. Study 005: 1 patient was weaned off PN/I.V.
 - iii. Study 020: 0 patients were weaned off PN/I.V.
 - iv. Study 021: 12 patients were weaned off PN/I.V. as of Oct-2012
 - d. Long-term efficacy is supported by open-label extension studies 005 and 021. In study 021, all responders from Study 020 remained responders in study 021. In study 005, 75% of responders that were enrolled from study 004 remained responders in study 005.
3. Risks. Potential clinical safety issues. The potential clinical safety issues of teduglutide fall into 3 main categories, which stem from its mechanism of action, the underlying disease including chronic parenteral nutrition, and the nonclinical safety profile. The potential safety issues at this time include the following:
- a. Acceleration of neoplastic growth and enhanced growth of colorectal polyps
 - i. Malignancy. Three patients in the phase 3 trials were diagnosed with malignancy, and all were in the teduglutide group at a dose of 0.05 mg/kg/day. On the other hand, each of these patients was at high risk for their diagnosed malignancy. From these data, it cannot be determined whether teduglutide played any role in these malignancies. No malignancies were observed in the nonclinical studies at much higher doses but less duration of exposure.
 - ii. Intestinal polyps. Few polyps (n=2) were seen in the SBS Placebo-controlled trials—one in the placebo group and one in the teduglutide 0.05 mg/kg/day group. In the long-term studies, two patients have been diagnosed with adenomas with villous features after 6 months of exposure to teduglutide. Intestinal and other GI tract polyps (pancreatobiliary) were observed in the nonclinical studies.
 - b. Intestinal obstruction/stenosis. These events appeared to be dose-dependent in the placebo-controlled data: none in the placebo group, 4% in the teduglutide 0.05 mg/kg/day group, and 9% in the 0.10 mg/kg/day group. None of these cases required surgery. In the extension studies, 8 additional subjects were reported to have experienced obstruction/stenosis. At least half of these patients had a

- history of prior obstruction, none required surgical intervention, and one patient underwent endoscopic dilation.
- c. Cholecystitis. All 4 cases occurred in the teduglutide group and none in the placebo group. Onset was between 1 and 3 months. One patient developed gallbladder perforation and underwent semi-emergent cholecystectomy. Two patients underwent elective cholecystectomy. The remaining patient was probably actually not cholecystitis based on a history and concurrent diagnosis of renal colic and the lack of imaging to establish cholecystitis. All patients had a history of gallbladder disease, which is very common in this population. Subacute inflammation in the gallbladder was observed in the nonclinical studies.
 - d. Pancreatic disease. No cases of true pancreatitis were reported. One patient had a pancreatic pseudocyst diagnosed after 4 months of teduglutide exposure. In the extension studies, two patients had history of recurrent pancreatitis—one patient was diagnosed with an episode of chronic pancreatitis (onset at 6 months) and the other had acute pancreatitis diagnosed at 15 months. Pancreatitis was not observed in the nonclinical studies, although hyperplastic lesions of the pancreatic ducts were seen.
 - e. Fluid overload. Fluid overload AEs occurred in 7% of placebo group subjects and 12% of teduglutide group subjects (0.05 mg/kg/day). Two cases of congestive heart failure (CHF) were reported, both in the teduglutide group—one case was an SAE after 6 months of teduglutide exposure likely secondary to previously undiagnosed cardiac disease from hypothyroidism; and the other was an AE for which details are not available at this time. Fluid overload was not reported in the nonclinical studies.
 - f. Immunogenicity. These limited data at this time do not support an effect of immunogenicity on safety or efficacy beyond 18 years. The effect of immunogenicity on PK has not been studied.

In this population of patients with SBS and PN/I.V. dependency, the risk-benefit profile of GATTEX favors benefit. Not only did patients do twice as well on GATTEX than placebo in terms of response to fluid reductions in volume and days, but nearly 20% of patients on GATTEX were able to be completely weaned off PN/I.V. Because PN-dependency is associated with considerable morbidity, this represents a clear benefit in the PN-dependent population with SBS. Given this benefit, I feel that most patients would accept some additional safety monitoring for the possibility of being weaned completely from PN, or at least having some days or even hours every week off PN. The AC also favored approval, and this drug had been authorized for marketing in the EU at the end of Aug-2012 under the name REVESTIVE.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

REMS and 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, and biliary-pancreatic disease.

The goal of the REMS would be as proposed by the Applicant:

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 must include:

A. Communication Plan

- Education materials to include
 - **Dear Healthcare Provider (DHCP) letter** will be disseminated to target healthcare prescribers (b) (4)
 - Target prescribers include:
 - Gastroenterologists
 - Colorectal/Gastrointestinal Surgeons
 - **Dear Professional Society letter** will be distributed to the leadership of professional organizations for dissemination of safety risk information with GATTEX to their members
 - **Prescriber Educational Slide Deck** for face-to-face presentation by Medical Science Liaisons to prescribers
 - **Patient educational material** for prescribers to use to educate patients about the serious risks with GATTEX
 - At the AC meeting some members felt that patients should also be tested on their knowledge of GATTEX

B. Timetable for submission of assessments

- NPS Pharmaceuticals will 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.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of this review, we are requiring a patient registry that would provide long-term safety and efficacy data, ideally for decades. Safety data collection is especially important for the following potential safety issues for GATTEX®:

- Neoplasia
 - We concur with the Applicant that colonoscopy is needed within 6 months before starting teduglutide.
 - Labeling negotiations will occur after finalization of this review. Among issues to be discussed would be whether colonoscopy should be done after one year of GATTEX in all patients or only in patients with polyp/s prior to starting teduglutide. Colonoscopy is risky in this population because of the washout and the fluid/electrolyte imbalance associated with it. Another issue is that the GATTEX population might not be similar to the general population to which the polyp guidelines apply. Patients on GATTEX might be at increased risk for polyp formation especially in the long-term. The frequency of colonoscopy will be discussed in cases where the patient is and is not polyp-free after certain periods of time on GATTEX.
- Pancreatobiliary function
 - We concur with the Applicant that the relevant labs (total bilirubin, amylase, lipase, alkaline phosphatase) be obtained within 6 months before starting teduglutide and then every 6 months while on teduglutide.
- Immunogenicity
 - Per Clinical Pharmacology Review: “The sponsor should assess the long-term impact of anti-drug antibodies (ADA) on safety and efficacy to include *in vivo* determination of ADA levels.”
 - For patients who are unresponsive or worsen on teduglutide after 6 months, or who lose efficacy after being on teduglutide more than 6 months, or who develop hypersensitivity reactions that could potentially be attributed to teduglutide, anti-drug antibody levels should be drawn and recorded in the registry. These issues and others will be discussed in labeling discussions with the Applicant that will occur after finalization of this review.

2 Introduction and Regulatory Background

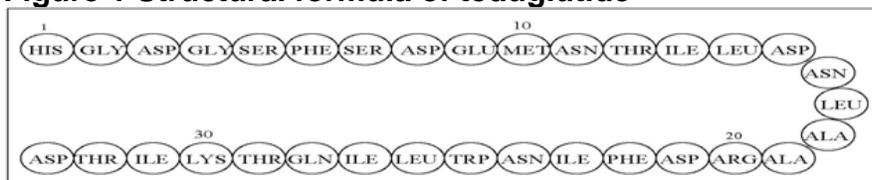
2.1 Product Information

GATTEX (teduglutide) is a human recombinant analog (E. Coli) of glucagon-like peptide-2 (GLP-2). GLP-2 is 33-amino acid proglucagon-derived peptide secreted by the endocrine L-cell primarily in the lower gastrointestinal tract in response to luminal nutrients, particularly carbohydrates and fats. GLP-2 is believed to promote growth and repair of intestinal epithelium. The chemical name for GATTEX is:

L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutamyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid

It has the following structural formula (Figure 1).

Figure 1 Structural formula of teduglutide



Proposed indication: Treatment of adults with short bowel syndrome (SBS). GATTEX is used to improve intestinal absorption of fluid and nutrients. The Applicant proposes that GATTEX results in decreased need for total parenteral nutrition in patients with SBS.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently available approved treatments for the proposed indication appear in Table 1.

Table 1 Table of currently available treatments

Treatment	Drug Class	Indication	Main Safety Issues
Specialized Nutrition—parenteral, oral, enteral, micronutrient	Multiple	Inability to obtain complete nutrition due to shortened bowel	-Sepsis -Electrolyte imbalance and associated complications -Nutritional deficiency
ZORBTIVE®	Somatropin (rDNA origin, rhGH) for subcutaneous administration	“Treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Zorbtive® therapy should be used in conjunction with optimal management of Short Bowel Syndrome.”—for 4 weeks	-Contraindicated “in patients with active neoplasia” -Death in patients with acute critical illness from heart or abdominal surgery, trauma, or acute respiratory failure. -Non-fatal: Allergic reaction, acute pancreatitis, impaired glucose tolerance, carpal tunnel syndrome, swelling, abdominal pain, nausea, vomiting; papilledema in children
NUTRESTORE®	L-glutamine powder for oral suspension	“Treatment of Short Bowel Syndrome (SBS) in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication.”—for 16 weeks	Similar to safety profile when given with growth hormone—see ZORBTIVE safety profile (above)

2.3 Availability of Proposed Active Ingredient in the United States

This is a new molecular entity (NME) that is not approved in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no other approved GLP-2 analogues in the United States. ZORBTIVE™ is a growth hormone (GH) analogue with neoplastic potential, which is contraindicated in malignancy (Table 1). GH receptors are located throughout the body, in contrast to GLP-2 which seems to be mostly confined to the gastrointestinal system. Because it is a GH analogue, ZORBTIVE™ can cause glucose intolerance. ZORBTIVE™ studies did not exceed 4 weeks in duration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following regulatory activity occurred under IND 58,213 and NDA 203,441:

20 October 1998: Pre-IND meeting.

- “The potential hyperproliferative effects of ALX-0600 on the colon should be assessed in humans in terms of intestinal absorption and histological changes in the small bowel, colon, and stomach.”

- Test for antibody production
- Endoscopy at baseline and completion

26 April 1999: IND 58,213 submission for teduglutide in SBS

29 June 2000: US orphan drug status granted

06 October 2003: EOP2 meeting on clinical (Study 004) and nonclinical topics. Agreed were:

- Dosing: 0.05 and 0.10 mg/kg/day
- Standard outpatient care re: PN and concomitant medications
- Though study population would exclude SBS patients with unstable PN regimens, the results of the trial could be extrapolated to such subjects
- Proposed PN optimization/stabilization procedures, performance of colonoscopy in patients with a colon, mucosal biopsies of small intestine
- Primary efficacy endpoint is percent responders (reduction of at least 20% from baseline in weekly PN/IV volume at Week-24).
- Conduct of two (replicative) trials was strongly recommended based on NME status
- Extent of representation of US population would be a review issue

19 December 2003: nonclinical follow-up discussion

06 June 2006: t-con. Type C Meeting. FDA gives PK advice for special populations of hepatic and renal impairment. No formal drug-drug interaction studies are required, unless evidence arises for interactions. (Applicant later submitted hepatic impairment and multi-dose PK studies on 30-Jun-2010 in SD-211; and renal impairment study on 13-Sep-2011 in SD-224).

23 January 2007 (Type C Meeting). Primary endpoint change discussed. By this time, Study 004 had randomized 84 patients and 55 patients had completed 24 weeks of treatment. Sponsor stated this change was not based on an interim analysis. FDA suggested performing a second clinical trial using the new primary endpoint. Note: Protocol amendment #4 (13-Feb-2007) incorporates primary endpoint change.

14 Feb 2007. Applicant amended primary efficacy analysis for Study 004.

18 January 2008: Type C Meeting. Results of Study 004 are known. Need for and design of confirmatory Phase 3 study (CL0600-020) for at least 24 weeks collecting safety and efficacy data (drug would be used chronically). FDA has efficacy concerns with 0.05 mg/kg/day dose due to lack of clear dose-response relationship or clear efficacy demonstration in 004, but no safety concerns. Immunogenicity would be monitored, and tQT study should be conducted (Study 001).

14 July 2008. Pre-NDA Meeting. Data available from 004 and 005. Applicant requests FDA to accept an NDA for filing. "FDA notes that the study does show some clinical benefit however dose response has not been demonstrated. 004 has not shown which is the best dose for phase 3 studies. FDA indicates that the Sponsor is free to select its dose. It would accept a 0.05 mg/kg/day to support an NDA, however it is not convinced

that 0.05 mg/kg/day is the best dose.” FDA confirms that “one additional study is needed” and “that a 2 arm design (0.05 mg/kg/day vs. placebo) would be acceptable to support an NDA”. FDA encourages collection of neutralizing antibody data.

19 Oct 2010: meeting to discuss CMC issues and to obtain agreement re: CMC data package. Two sites at two different scales for manufacturing teduglutide. FDA stated “it may also be necessary to demonstrate drug substances compatibility with animal studies and/or a PK/PD study in humans prior to NDA submission.”. Applicant agreed. See 25-Oct-2010 Clinical Pharmacology Review (submitted to IND)

22 April 2011: Advice Letter to sponsor (IND 58,213): “We do not agree that teduglutide, a 33-amino-acid peptide, is a “biological product” as defined in section 351(i)(1) of the Public Health Service Act.”

25 April 2011: Type B Pre-submission Meeting—clinical, preclinical, submission logistics. See Meeting Minutes (under IND, dated 23-May-2011). Main points addressed:

- Re: ongoing 021 long-term study: FDA recommended to delay submission until about 64 patients with at least 12 months of exposure are in the initial safety and efficacy databases
- Immunogenicity—FDA concern about cross-reactivity with endogenous GLP-2. Characterize if Ab’s are specific to endogenous GLP-2 vs teduglutide, and whether neutralizing. Characterize impact of immunogenicity on PK, efficacy, safety.
- Clinically meaningful measures of nutritional status should be included. “FDA noted that these analyses could be supportive of the primary endpoint and should be included in the ISE.”
- A pediatric waiver is not required based on Orphan Designation
- For priority review status, Applicant should submit a detailed rationale for why GATTEX offers “a *significant* improvement compared to products currently marketed.”
- Insufficient information to determine whether a REMS is necessary

16 August 2011: initial CMC presubmission

30 Nov 2011: NDA submitted to FDA

27 Jan 2012: Designated as Standard review

10-Aug-2012: NDA amendment submission extends review date to 30 Dec 2012

30-Aug-2012: European Commission adopted the CHMP decision granting marketing authorization for “Revestive-teduglutide”, and an orphan medicinal product for human use.

2.6 Other Relevant Background Information

ZORBTIVE™ (somatropin (rDNA origin) for subcutaneous Injection)

- Human Growth hormone (hGH) analog, recombinant
- NDA 021597
- Approved 12/01/03
- Label (last was 12/01/03)
 - Indication: Adults only: “Treatment of SBS in patients receiving specialized nutritional support...should be used in conjunction with optimal management of Short Bowel Syndrome.”
 - Precaution: “Zorbtive™...therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of short bowel syndrome.”
 - Dosage: “0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily.”
Volume for injection is 2 mL, max
 - Injection sites should be rotated
 - “Administration for more than 4 weeks has not been adequately studied.”
 - “Discontinue Zorbtive for up to 5 days for severe toxicities. Upon resolution of symptoms, resume at 50% of original dose. Permanently discontinue treatment if severe toxicity recurs or does not disappear within 5 days.”
 - Safety
 - Contraindications
 - “Growth Hormone therapy should not be initiated in patients with acute critical illness due to complications of open heart or abdominal surgery, multiple trauma, or acute respiratory failure.”
 - Known hypersensitivity to growth hormone
 - Active neoplasia (either newly diagnosed or recurrent). Antitumor therapy should be completed before starting ZORBTIVE.
 - Known sensitivity to Benzyl Alcohol. that neonates can have
 - All subjects (100%, 30/30) treated for 4 weeks had an AE compared to control group (89%, 8/9)

- Has been associated with acute pancreatitis, new onset impaired glucose tolerance/Type 2 diabetes mellitus
- Diabetic ketoacidosis, coma—in some cases resolved when hGH was discontinued
- No long-term animal carcinogenicity studies
- AEs in active-controlled trials (control group received only dietary manipulation + glutamine; treatment group received same + hGH) with exposure for 4 weeks:
 - AE rates (control vs hGH): 8/9 (89%) vs 16/16 (100%)
 - Most frequent AEs:
 - Peripheral edema: 1/9 (11%) vs 13/16 (81%)
 - Facial edema: 0/9 (0%) vs 7/16 (44%)
 - Arthralgia: 1/9 (11%) vs 5/16 (31%)
 - Injection site reaction/pain: 1/9 (11%) vs 4/16 (25%)
 - Efficacy
 - Parenteral fluid volume reduction of 26% (13.5 to 10.5 L/week)

NUTRESTORE®

- L-glutamine powder for oral solution
- NDA 021667
- Approved 06/10/04
- Label (03/14/11)
 - Indication: “the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication”
 - Precaution: Impaired hepatic function may result in elevated ammonia
 - Dosage: “30 g daily in divided doses (5 g taken 6 times per day orally) for up to 16 weeks. Should be taken with meals or snacks at 2- to 3-hour interval while awake.”
 - Safety: see label for ZORBTIVE
 - Efficacy: see label for ZORBTIVE

It should be noted that GH and GLP-2 are different molecules with different targets and mechanisms of action. GH has receptors throughout the body, whereas GLP-2 is more localized to the GI tract.

Medical Reviewer Comment. In the nonclinical studies, the growth promoting effects of teduglutide were confined to the GI system.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity are acceptable.

3.2 Compliance with Good Clinical Practices

The Applicant states that they are in compliance with good clinical practice (GCP).

3.3 Financial Disclosures

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.

Medical Reviewer Comment. These disclosures are acceptable. Based on the information submitted by the Applicant, there are no unacceptable conflicts of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no efficacy or safety issues from chemistry, which recommends approval.

4.2 Clinical Microbiology

The drug product is sterile [REDACTED] (b) (4) and lyophilized. Assessment of microbiologic risk is not applicable. See Product Quality Microbiologic Review (Mar-30-2012).

4.3 Preclinical Pharmacology/Toxicology

Pharmacology studies examined the intestinotrophic activity of teduglutide in several animal species. In mice, teduglutide increased weight and length of the small intestine and enhanced epithelial barrier function. Teduglutide also increased the absorptive function of the intestinal mucosa in rats and monkeys. In a rat model of SBS, teduglutide increased the rate or magnitude of the intestinal adaptive response to intestinal resection at a dose of 0.2 mg/kg/day. In neonatal piglets with jejunoileal resection, teduglutide showed significant improvements in crypt-villus architecture in the small intestine, duodenal, jejunal and ileal glucose transport and jejunal glutamine transport.

In pivotal toxicology studies, major treatment-related effects (hypertrophy/hyperplasia) were related to the pharmacological activity of teduglutide. In the 26-week toxicity study in mice at 2, 10 and 50 mg/kg/day, major treatment-related histopathological changes were seen in the small and large intestines (epithelial and villus hypertrophy and hyperplasia), gall bladder (epithelial hypertrophy and hyperplasia accompanied by subacute inflammation), and sternal bone marrow (myeloid hyperplasia). In the 1-year toxicity study in *Cynomolgus* monkeys at 1, 5 and 25 mg/kg/day, major treatment-related histopathological changes were seen in the small and large intestines (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). In juvenile minipigs, similar treatment-related histopathological changes were observed in the small intestines (minimal/slight villous hypertrophy), gall bladder (cystic mucosal hyperplasia), and extrahepatic bile duct (cystic mucosal hyperplasia).

Teduglutide was not genotoxic in the Ames test, *in vitro* chromosomal aberration test in Chinese hamster ovary (CHO) cells, or *in vivo* mouse micronucleus test. In a 2-year carcinogenicity study by the subcutaneous route in rats at 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct (0/50, 0/50, 1/50 and 4/50 at 0, 3, 10 and 35 mg/kg/day, respectively; $p=0.0037$, trend test) and jejunum (0/50, 1/50, 0/50 and 5/50 at 0, 3, 10 and 35 mg/kg/day, respectively; $p=0.0031$, trend test) of male rats. There were no drug related tumor findings in females. Due to its growth promoting pharmacological effects, teduglutide has a potential to cause hyperplastic changes, including tumor formation.

Findings in the individual studies are presented below. Major treatment-related effects were related to the pharmacological activity of teduglutide, and were seen in all species as follows:

- 26-week study in mice (2, 10, 50 mg/kg/day), seen at all doses

- Small and large intestine—epithelial and villus hypertrophy and hyperplasia
- Gallbladder—epithelial hypertrophy and hyperplasia with subacute inflammation
- 13-week study in rats (2, 10, 50 mg/kg/day), seen at all doses
 - Small and large intestine—mucosal hypertrophy and hyperplasia
 - Injection site—inflammation and necrosis
- 1-year study in Cynomolgus monkeys (1, 5, 25 mg/kg/day), seen at all doses
 - Small and large intestine—mucosal hyperplasia
 - Stomach—mucosal hyperplasia
 - Pancreas—hypertrophy/hyperplasia of the pancreatic duct epithelium
 - Liver—epithelial hypertrophy and hyperplasia of bile duct in the liver and of the gall bladder
 - Gallbladder—mucosal hypertrophy/hyperplasia
- 14-day study in juvenile minipigs (5, 25 mg/kg/day), seen at all doses
 - Small and large intestine—hyperplasia
 - Nonglandular stomach—mucosal hyperplasia associated with ulceration/erosion
 - Gallbladder and bile duct—mucosal hyperplasia
 - Injection site—inflammation and necrosis
- 90-day study in juvenile minipigs (1, 5, 25 mg/kg/day), seen at all doses
 - Small intestine—minimal/slight villous hypertrophy
 - Gallbladder—cystic mucosal hyperplasia at all doses
 - Extrahepatic bile duct—cystic mucosal hyperplasia
 - Injection site—inflammation and necrosis
 - ECG changes—small, not dose-related, seen only once (Week-13), and not significant
- Ames test—negative. Teduglutide is not genotoxic.
- 2-year carcinogenicity study in Wistar Han rats (3, 10, 35 mg/kg/day)
 - Jejunum (male rats)—statistically significant changes in incidence of adenoma
 - Bile duct (male rats)—statistically significant changes in incidence of adenoma
 - NOEL set at 3 mg/kg/day (10-fold higher AUC than 0.05 mg/kg/day dose)
- Teratogenic studies—negative
- A second 2-year carcinogenicity study in mice is not yet complete but was agreed to by FDA Carcinogenicity Assessment Committee to be completed as a post-approval commitment.

No intestinal obstruction or fluid overload was reported in the animal studies.

Medical Reviewer Comment. Hyperplastic responses and polyps in the GI system were reported in the nonclinical studies at considerably higher doses than human, and for a shorter time than in humans. No intestinal obstruction was reported in the nonclinical studies, unlike the human trials where all cases occurred in the teduglutide groups but not placebo. Subacute gallbladder inflammation was seen in the nonclinical studies, and in humans cholecystitis occurred in the teduglutide groups but not placebo. Volume overload was not seen in the nonclinical studies, but was reported in the human trials where it occurred more frequently in the teduglutide than placebo group. In the human trials, two patients were diagnosed with adenomas with villous features in the extension studies after 6 months of teduglutide exposure.

4.4 Clinical Pharmacology

The information in this section comes from the Clinical Pharmacology Review, which was based on 4 *in vitro* drug-drug interaction study reports, 6 single-dose pharmacokinetic (PK) study reports, 3 multiple-dose pharmacokinetic/pharmacodynamic (PK/PD) study reports, and PK/PD and immunogenicity data from 4 Phase 3 studies with SBS subjects.

4.4.1 Mechanism of Action

Teduglutide is a human recombinant GLP-2 analog of native GLP-2, an endocrine hormone secreted by endocrine L-cells of the lower GI tract in response to luminal nutrients. The relationship between GLP-2 and small bowel epithelial growth was first documented by Gleeson et al in 1970, where a patient with an enteroglucagon-producing tumor developed small bowel hyperplasia.¹

In animal studies GLP-2 has been observed to:

- regulate proliferation and apoptosis of intestinal epithelium (crypts and villi)
- improve absolute and relative absorption of fat, nitrogen, sodium, potassium, calories, and GI fluids
- decrease fecal and stomal output of the same substances

¹ Gleeson MH, Bloom SR, Polak JM, Henry K, Dowling RH. An endocrine tumour in kidney affecting small bowel structure, motility, and function. *Gut*. 1970 Dec; 11(12): 1060.

4.4.2 Pharmacodynamics

Teduglutide administration induced structural changes in the intestinal mucosa of adult subjects with SBS, which included increased jejunal villus height and crypt depth (21 days of teduglutide in patients with SBS in study 92001). Also seen were enhanced gastrointestinal fluid absorption (at 0.10 and 0.15 mg/kg/day dose levels), improved nutrient and electrolyte absorption, and decreased stomal/fecal nutrient content. These changes reverted to baseline after discontinuation of teduglutide.

After 24 weeks of teduglutide in SBS subjects (Study 004), increases in plasma citrulline (a measure of functional enterocyte mass) were observed that were nearly an order of magnitude greater than placebo.

4.4.3 Pharmacokinetics

Absorption. With the to-be-marketed concentration (10 mg/mL), teduglutide reached peak concentration 3-5 hours after subcutaneous (SC) administration at sites in the abdomen, thigh, and arm. The maximal plasma concentration and exposure (C_{max} and AUC) of teduglutide was dose proportional over the dose range of 0.05 to 0.40 mg/kg. No accumulation of teduglutide was observed following repeated daily SC administration.

Following SC administration of 0.05 mg/kg/day dose of teduglutide to subjects with SBS, median peak teduglutide concentration (C_{max}) was 36.8 ng/mL and overall mean area under the curve (AUC_{0-T}) was 0.15 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (Study 004).

Relative Bioavailability – alternative injection sites. The relative bioavailability of teduglutide was 89% and 92% for SC injection at the thigh and the arm, respectively, relative to SC injection at the abdomen (based on ANCOVA analysis of $AUC_{0-\infty}$). The 90% confidence interval (CI) for the AUC_{0-t} or $AUC_{0-\infty}$ was within the 80% to 125% range, indicating that exposure was similar after SC injection at these three sites (Study 015).

Distribution. Following I.V. administration in healthy subjects, teduglutide had a mean (\pm SD) volume of distribution at steady state (V_{ss}) of about 103 (\pm 23) mL/kg (Study 006), similar to blood volume.

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 the endogenous GLP-2. It 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, 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 (CL0600-006). Teduglutide was rapidly eliminated with a mean terminal half life ($t_{1/2}$) of approximately 2 hours.

Special Populations

Renal Impairment (Study 018). Dosage reduction by 50% is recommended in subjects with moderate to severe renal impairment because of decreased renal clearance of teduglutide in these cases. Following a single SC administration of 10 mg teduglutide to subjects with moderate to severe renal impairment or end stage renal disease (ESRD), teduglutide C_{max} and $AUC_{0-\infty}$ increased with increasing degree of renal impairment. The primary PK parameters of teduglutide increased up to a factor of 2.6 ($AUC_{0-\infty}$) and 2.1 (C_{max}) in ESRD subjects compared to healthy subjects. Half-life is approximately 1.7 hours in renal impairment in renal-impaired volunteers.

Hepatic Impairment (Study 017). No dose adjustment is necessary in moderate hepatic impairment. Following a single SC dose of 20 mg teduglutide to subjects with moderate hepatic impairment, teduglutide C_{max} and AUC were lower (~10% to 15%) compared to healthy matched control subjects. Teduglutide PK was not assessed in severe hepatic impairment.

Elderly Population (Study 018). Plasma concentration-time profiles of teduglutide were similar for healthy non-elderly and elderly subjects. Except for creatinine clearance (CL_{cr}), none of the evaluated intrinsic factors (including age, gender, and hepatic impairment) had a significant effect on the PK of teduglutide.

Gender. No clinically relevant gender differences were observed in clinical studies.

Population PK. Only weight and dose were found to have any relationship with PK. Gender, age, body weight, BMI, creatinine clearance, and dose were tested.

Drug-Drug Interactions (DDI). Based on the results of *in vitro* studies, where no significant inhibition or induction of P450 isozymes was observed at 2000 ng/mL (55-fold median C_{max} at dose level of 0.05 mg/kg/day), no *in vivo* DDI studies were conducted. Teduglutide had no effect on gastric emptying, and can be administered with or without food.

Considering the increased intestinal absorption mechanism of teduglutide, the potential for PD effect-mediated DDI exists, and needs to be considered when co-administered with drugs requiring titration or with a narrow therapeutic index.

5 Sources of Clinical Data

Sources for clinical data used in this review come from the SBS Efficacy and Safety Studies (004, 005, 020, 021). Specifically, the SBS Placebo-controlled studies (004, 020) are used for efficacy assessment and identification of safety signals. Some results from the SBS extension studies are also reported in regards to long-term efficacy and safety.

5.1 Tables of Studies/Clinical Trials

Table 2 SBS Efficacy and Safety Studies

Clinical Trial	Dates	Design	Study Groups (number randomized)	Treatment Duration	Study population	Primary Endpoint
020 (27 sites)	11/25/08 to 01/04/11	Randomized, double-blind placebo-controlled	A. Ted 0.05 mg/kg/day (43) B. Placebo (43)	24 weeks	male and female adults with SBS and require PN at least 3 times/week	% of subjects who had a reduction of 20% to 100% in PN volume at Weeks 20 and 24 compared to baseline
004 (32 sites)	05/25/04 to 07/06/07	Randomized, double-blind placebo-controlled	A. Ted 0.05 mg/kg/day (35) B. Ted 0.10 mg/kg/day (33) C. Placebo (16)	24 weeks	male and female adults with SBS and require PN at least 3 times/week	Ordered categorical response (graded response score) related to PN volume reduction and duration at Weeks 16, 20, and 24
021 (25 sites) Open-label extension of 020	09/21/09 to ongoing	Open-label, no control group	A. Ted 0.05 mg/kg/day (88)	2 years	Subjects who completed or stopped dosing (due to ADR) in 020	Long-term safety
005 (23 sites) Open-label extension of 004	01/10/05 to 01/24/08	Randomized, double-blind, no control group	A,C. Ted 0.05 mg/kg/day (6+25=31) B,D. Ted 0.10 mg/kg/day (7+27=34)	28 weeks	Subjects who completed or stopped dosing (due to ADR) in 020	Long-term safety

[Ref: Adopted from Applicant's ISE, Table 3.1, p 24/124]

Table 3 Other human studies

Clinical Trial	Objective	Number of Subjects	Study Population	Duration of Treatment
001 (tQT) 006 (BA) 015 (BA/BE) 113 (PK/tol)	tQT Clinical pharmacology in healthy	001: Ted: 72 Plac: 69 006: 14 (all ted) 015: 18 (all ted) 113: Ted: 24 Plac: 8	Healthy	Single-dose
017 (Intrinsic Factor PK- hepatic)	Clinical pharmacology in <u>liver</u> impairment	Hepatic impair: 12 Healthy: 12	Hepatic impairment	Single-dose
018(Intrinsic Factor PK- renal)	Clinical pharmacology in <u>renal</u> impairment	Renal impair: 18 Healthy: 18	Renal impairment	Single-dose
003 (PD) 022 (PK)	Clinical pharmacology in healthy including PD for gastric emptying (003)	003: Ted: 23 Plac: 13 022: Ted: 71 Plac: 24	Healthy	Multiple-dose
92001 (SBS- PD)	Clinical pharmacology in SBS		SBS	Once daily x 21 days

5.2 Review Strategy

For the review of efficacy and identification of safety signals, the “SBS placebo-controlled studies” (004, 020) are used. Data from the open-label trials 005 and 021 (“Uncontrolled long-term studies”) are also presented.

5.3 Discussion of Individual Studies/Clinical Trials

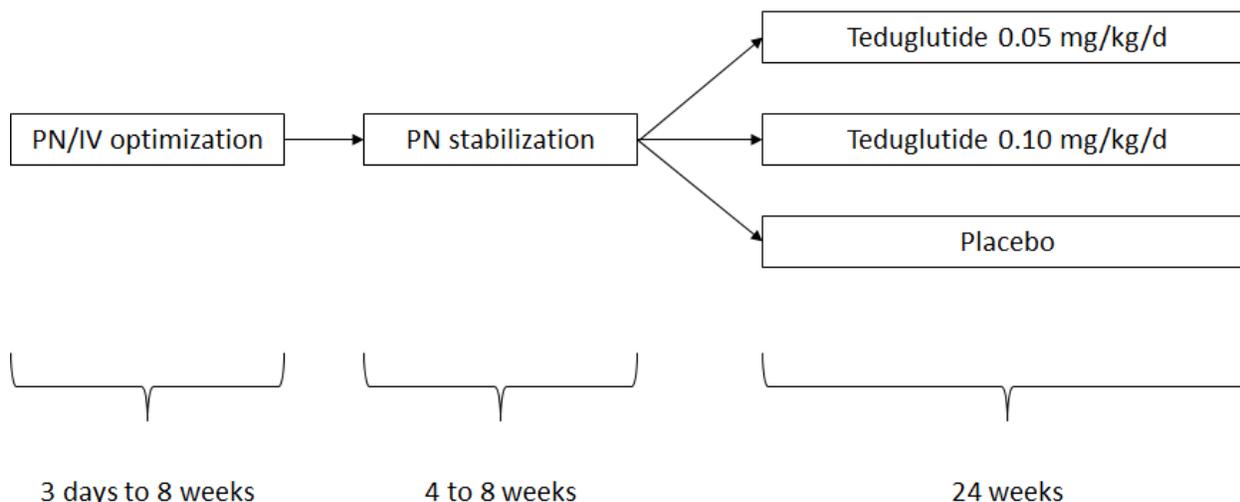
See Table 2 for list of individual studies.

Study 004. This is the first phase-3 efficacy and safety trial the Applicant conducted to support efficacy. It was a 24-week randomized, double-blind, placebo-controlled, three parallel group, multicenter trial (Figure 2) in 84 adults meeting the following major criteria as follows:

- Have SBS secondary to surgically removed intestine
- Require PN/I.V. at least 3 times weekly
- Stable for at least 4 consecutive weeks immediately before randomization based on multiple criteria for PN/I.V. usage and volume, urinary output, renal function, hematocrit, motility-altering medications, BMI, and hepatic function
- No hospital admission within 1 month before screening visit

- Failure to adhere to required washout periods

Figure 2 Study 004 flowchart



[ref: ISE, Fig 5, p.36]

In order to establish the same relative PN baseline for all patients, the protocol specified a period of fluid optimization followed by stabilization prior to randomization.

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

During stabilization, PN/I.V. volume was assessed for "stability" (urine output 1-2 L/day under constant oral intake). PN/I.V. volume at the end of stabilization was taken as 'Baseline' for all subsequent efficacy assessments.

After stabilization and baseline fluid volume assessment, subjects were randomized in a 1:2:2 ratio to placebo, subcutaneous (SC) teduglutide 0.05 mg/kg/day, or SC teduglutide 0.10 mg/kg/day. Randomization was stratified into three groups according to PN/I.V. consumption level at Baseline:

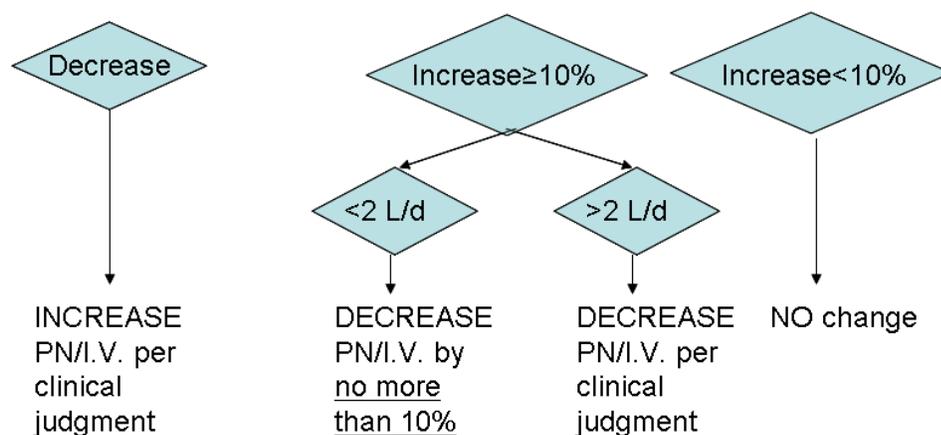
- Level 1: I.V. fluids 3 to 7 times weekly
- Level 2: PN fluids 3 to 5 times weekly
- Level 3: PN fluids 6 to 7 times weekly

The following concomitant medications were allowed, as long as they were used at a stable dose for at least 4 weeks prior to Baseline visit:

- Antimotility drugs (e.g., loperamide, diphenoxylate, codeine or other opiates)
- H2 antagonists
- Anti-diarrheal agents
- Bile acid sequestering agents
- Oral glutamine
- Proton pump inhibitors
- Diuretics
- Rehydration fluids

Commencing with initiation of treatment, each subject was followed for 24 weeks. At Weeks 4, 8, 12, 16, and 20, investigators adjusted each subject's PN/I.V. volume (Figure 3).

Figure 3 PN/I.V. adjustment decision tree
Based on URINE OUTPUT



The protocol also stipulated that oral fluid intake during the 48-hour urine output measurement period should be the same as the oral fluid intake at baseline. At Baseline and the last visit, GI endoscopy and biopsy were performed.

Demographics were similar at baseline between groups. The primary reason for the original intestinal resection was Crohn's disease (36%) followed by vascular disease (30%). Stoma was present in 35% of subjects. Mean bowel length was 66cm+/-45cm (SD). Some segment of the colon had been resected in 33% of subjects. Of subjects with any remaining colon (n=56/83), 36% had 75%-100% of their native colon remaining, whereas 34% of subjects had 25%-50% of their native colon remaining.

Study 020. This phase-3 efficacy and safety trial was initiated after completion of study 004, and its design was based on lessons learned from study 004. Trial 020 was a 24-week randomized, double-blind, placebo-controlled, two parallel group, multicenter trial

in 86 adults. The designs and populations of studies 004 and 020 were similar. However, the procedures in study 020 were changed as follows:

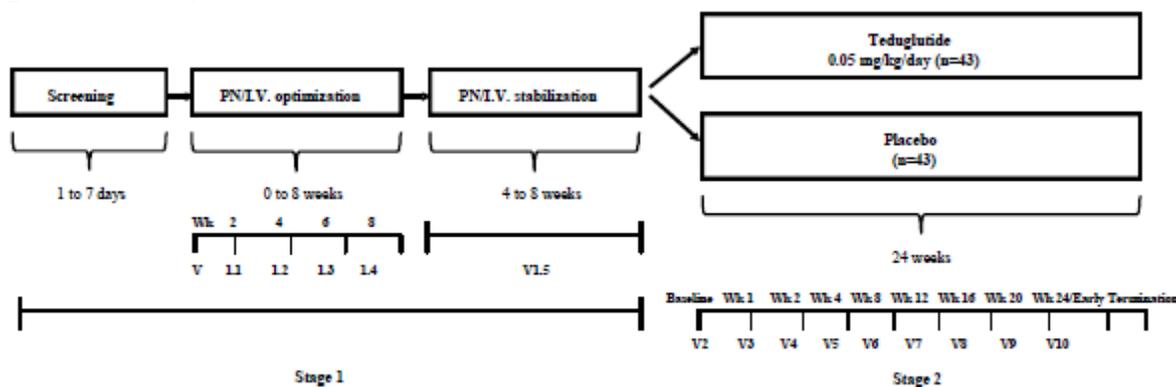
- 30% (rather than 10% in 004) reduction in PN/I.V. volume was permitted in study 020
- The first PN/I.V. adjustment occurred at Week-2 in study 020 (versus Week-4 in 004)

Additionally, study 020 has the following features not shared with study 004:

- Randomization was stratified into 2 levels of Baseline PN/I.V.: ≤ 6 L/week or >6 L/week
- Two study groups: placebo versus 0.05 mg/kg/day dose group. However, FDA (meeting minutes of 14-July-2008) was “not convinced that 0.05 mg/kg/day is the best dose.”
- Different primary endpoint: at least 20% reduction in PN/I.V. volume from baseline to both Weeks 20 and 24 (in study 004, primary endpoint was a 6-level graded categorical score based on percent reduction from Baseline to weeks 16, 20, and 24)

The design of study 020 consisted of two stages (Figure 4).

Figure 4 Study 020 flowchart



PN/I.V. = Parenteral nutrition/intravenous fluids; V=Visit; Wk=Week.
 [ref: ISE, p. 26]

In order to establish the same relative PN baseline for all patients, an important part of the study was to establish consistency in PN/I.V. fluid management among all investigators at entry and throughout the trial. To this end, the study protocol specified a period of fluid optimization followed by a period of stabilization and the criteria to manage fluids.

During optimization, a subject's PN/I.V. fluid volume was adjusted over one or more 48-hour periods. PN/I.V. was adjusted to keep urine output between 1.0 and 2.0 L/day (see Figure 3 for study 004) while the patient was asked to maintain their oral fluid intake at the same volume as during their previous 48-hour adjustment (or baseline in the case of the first adjustment). In study 020, unlike study 004 (Figure 3), up to 30% fluid reduction was allowed.

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

Once stabilized, subjects were randomized using stratified randomization with two levels of PN/I.V. fluid volume stratification: ≤ 6.0 L/week versus > 6.0 L/week. Shortly after randomization, study treatment was initiated. Commencing with initiation of study treatment, each subject was followed for 24 weeks. In trial 020, the first fluid adjustment occurred at Week-2 rather than Week-4 as in trial 004.

During the 24-week treatment period (Stage 2) at Weeks 2, 4, 8, 12, 16, and 20, investigators adjusted each subject's PN/I.V. volume as described in the protocol as follows:

- Increase PN/I.V. volume if urine output was < 1.0 L/day
- Decrease PN/I.V. volume by 10%, but no more than 30% of stabilized baseline PN/I.V. level, if urine output had increased by at least 10% from baseline:
 - If deemed medically necessary by investigator, volume could be altered as necessary

The protocol of study 020 also stipulated that oral fluid intake during the 48-hour urine output measurement period should be consistent with oral fluid intake at baseline (pre-optimization).

The demographics in study 020 were similar between groups. Overall, the primary cause for intestinal resection was vascular disease (34%) followed by Crohn's disease (21%) and "other" (21%). Stoma was present in 45% of subjects, the most common type being jejunostomy/ileostomy (82%). Median small bowel length in the placebo group was 48 cm (5 cm to 343 cm); and in the teduglutide group was 70 cm (15 cm to 250 cm). The colon was not in continuity in 44% of subjects. For subjects with any colon (n=56/83), a mean of 63% of it remained. More placebo subjects than teduglutide subjects had any colon (70% versus 56%). The most frequent reported GI medical/surgical histories were GI disorders (95% in each group) and infections/infestations (59% of teduglutide subjects and 54% of placebo subjects).

Most subjects (88%) had a subclavian line; and 12% of subjects had been treated for central line infection during the 6 months prior to screening. About 96% of subjects in each group reported at least one concomitant medication. The most frequent

concomitant medications were PPIs (esomeprazole, omeprazole, pantoprazole) and loperamide (antipropulsive).

Study 005. Open-label extension of study 004. Study 005 was a 28-week randomized, double-blind, non-placebo-controlled multicenter trial in subjects who had completed 24 weeks in study 004. Of 71 subjects who completed study 004, 64 elected to enroll in 005. Each subject received the same dose in blinded fashion in study 005 as in 004. However, if placebo was received in 004, the subject was randomized to teduglutide 0.05 mg/kg/day or 0.10 mg/kg/day. The blind was maintained from the beginning of 004 through the end of 005. The study groups in 005 were denoted by the Applicant as follows:

- 1-year Active Group (continued same teduglutide dose as in study 004)
 - 0.05/0.05 (n=25)
 - 0.10/0.10 (n=27)
- 6-Month Active Group (all received placebo in study 004)
 - placebo/0.05 (n=6)
 - placebo/0.10 (n=7)

Every 4 to 6 weeks, subjects were assessed for PN/I.V. use, safety, and tolerability. For efficacy evaluations, baseline data from study 004 served as baseline data for the 1-Year Active Group, whereas Week-24 data from 004 served as baseline data for the 6-Month Active Group. Demographics and baseline characteristics in study 005 were similar to 004.

For efficacy, there was no primary efficacy endpoint or hypothesis testing. Descriptive statistics were used to summarize efficacy data. Study 005 had multiple efficacy endpoints, including the percentage of subjects who remained responders through the Week-28 visit in 005; percentage of subjects who were responders at Week-28; and volume of PN/I.V. fluid reduction at Week-28 compared to baseline. Of the 65 subjects enrolled in 005, 11 (17%) discontinued. Baseline PN/I.V. fluid requirement was 13.1 L/week (L/wk) in the 0.10/0.10 group and 9.8 L/wk in the 0.05/0.05 group.

Study 021. Open-label extension of study 020. Study 021 is an ongoing 2-year open-label, uncontrolled, multicenter trial of teduglutide 0.05 mg/kg/day in 88 subjects who either completed study 020 or qualified for randomization in 020 but were not treated because the enrollment target in study 020 had already been reached. In study 021, all subjects were treated with 0.05 mg/kg/day regardless of their dose in 020.

Efficacy and safety assessments were scheduled to occur 2 weeks after teduglutide initiation, then monthly for 3 months, then every 3 months until end-of-study. For efficacy, there was no primary efficacy endpoint or hypothesis test. Efficacy endpoints included change in PN/I.V. volume by visit, percentage responders at each visit, and others. For efficacy summary statistics, Baseline data were those from just before

randomization in study 020. For subjects who had been on placebo in 020, their baseline was taken as their last visit in 020.

Of the 86 subjects in study 020, 78 (91%) completed and were eligible to enroll in study 021. Two of the 78 subjects declined to enroll in study 021. In study 020 there were 12 additional subjects who had qualified for randomization in 020 but were not randomized because of closed randomization in 020. This brought the total enrollment pool in 021 to 88 (=78-2+12). The study groups in 021 were denoted by the Applicant as follows:

- “NT, PBO/TED” (n=51): “Not Treated, PlaceBO/TEDuglutide”: did not receive teduglutide until initiation of 021
 - 12 screened but unenrolled subjects from 020
 - 39 enrolled placebo subjects in 020
- “TED/TED” (n=37): “TEDuglutide/TEDuglutide”: all had received teduglutide in 020

The demographics in ongoing Study 021 are Caucasian (84/88, 96%), age distribution: 45-65 years (83% of subjects) and ≥65 years (17%), and baseline PN/I.V. (13.7 +/- 7.3 L/wk). The disposition of subjects in ongoing study 021 is shown in Table 4.

Table 4 Completed visits in ongoing Study 021 (as of 30-Jun-2011): Safety population

	Statistic	NT, PBO/TED	TED/TED	All Teduglutide
Completed Visit 1 (Baseline)	n (%)	51 (100.0)	37 (100.0)	88 (100.0)
Completed Visit 2 (Week 2)	n (%)	51 (100.0)	37 (100.0)	88 (100.0)
Completed Visit 3 (Month 1)	n (%)	49 (96.1)	37 (100.0)	86 (97.7)
Completed Visit 4 (Month 2)	n (%)	48 (94.1)	37 (100.0)	85 (96.6)
Completed Visit 5 (Month 3)	n (%)	45 (88.2)	36 (97.3)	81 (92.0)
Completed Visit 6 (Month 6)	n (%)	43 (84.3)	34 (91.9)	77 (87.5)
Completed Visit 7 (Month 9)	n (%)	26 (51.0)	21 (56.8)	47 (53.4)
Completed Visit 8 (Month 12)	n (%)	16 (31.4)	16 (43.2)	32 (36.4)
Completed Visit 9 (Month 15)	n (%)	6 (11.8)	5 (13.5)	11 (12.5)
Completed Visit 10 (Month 18)	n (%)	1 (2.0)	1 (2.7)	2 (2.3)
Completed Visit 11 (Month 21)	n (%)	0	1 (2.7)	1 (1.1)
Completed Visit 12 (Month 24)	n (%)	0	0	0
Total Active as of Data Cutoff	n (%)	38 (74.5)	35 (94.6)	73 (83.0)
Total Discontinued	n (%)	13 (25.5)	2 (5.4)	15 (17.0)

[ref: ISE, p. 54]

6 Review of Efficacy

6.1 Indication

Treatment of adults with short bowel syndrome (SBS). GATTEX is used to improve intestinal absorption of fluid and nutrients.

Medical Reviewer Comment. This indication should be more specific as follows: “Treatment of adults with short-bowel syndrome (SBS) who are dependent on parenteral fluids...”.

Without this additional qualification, it is conceivable that teduglutide could be prescribed for SBS patients who are not PN-dependent (PN-dependency is not necessary for a diagnosis of SBS), where efficacy of teduglutide has not been established. In the non-PN-dependent SBS population, the risks potentially outweigh the benefits. Other off-label uses can be envisioned for teduglutide including pediatrics, diarrhea, malabsorption syndromes (CF, gluten enteropathy, and a host of other conditions with malabsorption), malnutrition, recovery from bowel surgery, and weaning patients back to oral intake as in ICU and other settings.

6.1.1 Methods

Efficacy is assessed using data from the SBS Placebo-controlled trials (004 and 020). The data from these two trials are presented in juxtaposition to facilitate comparison. Efficacy data are also presented from extension studies 005 and 021.

6.1.2 Demographics

Demographics are summarized in Table 5 through Table 8.

Table 5 Geographic distribution, ITT (020, 004)

Parameter	Study CL0600-020		Study CL0600-004	
	Placebo (N=43) n (%)	Teduglutide 0.05 mg/kg/day (N=43) n (%)	Placebo (N=16) n (%)	Teduglutide 0.05 mg/kg/day (N=35) n (%)
Geographic region				
Ex-US	35 (81.4)	36 (83.7)	9 (56.3)	24 (68.6)
US	8 (18.6)	7 (16.3)	7 (43.8)	11 (31.4)

[ref: ISS, Table 8, p. 61]

Table 6 Demographics, ITT (020, 004)

Parameter	Study CL0600-020		Study CL0600-004	
	Placebo (N=43)	Teduglutide 0.05 mg/kg/day (N=43)	Placebo (N=16)	Teduglutide 0.05 mg/kg/day (N=35)
Gender n (%)				
Male	19 (44.2)	21 (48.8)	7 (43.8)	17 (48.6)
Female	24 (55.8)	22 (51.2)	9 (56.3)	18 (51.4)
Age (years)				
Mean (±SD)	49.7 (15.6)	50.9 (12.6)	49.4 (15.1)	47.1 (14.2)
Median	50.0	50.0	53.5	51.0
Min / Max	18 / 82	22 / 78	20 / 72	20 / 68
Age distribution n (%)				
< 65	37 (86.0)	36 (83.7)	14 (87.5)	31 (88.6)
≥ 65	6 (14.0)	7 (16.3)	2 (12.5)	4 (11.4)
≥ 75	3 (7.0)	1 (2.3)	0	0
Race n (%)				
Black	1 (2.3)	0	1 (6.3)	3 (8.6)
White	41 (95.3)	42 (97.7)	15 (93.8)	32 (91.4)
Other	1 (2.3)	1 (2.3)	0	0
Ethnicity n (%)				
Hispanic or Latino	4 (9.3)	5 (11.6)	n/a	n/a
Not Hispanic or Latino	39 (90.7)	38 (88.4)	n/a	n/a
Weight at baseline (kg)				
n	43	42	16	35
Mean (±SD)	61.7 (12.6)	62.7 (11.4)	61.3 (9.7)	59.0 (8.4)
Median	59.1	61.4	59.9	58.6
Min / Max	41 / 86	43 / 88	43 / 85	42 / 81
Distribution of weight at baseline (kg) n (%)				
n	43	42	16	35
<55	17 (39.5)	12 (28.6)	3 (18.8)	8 (22.9)
55 to 65	12 (27.9)	13 (31.0)	9 (56.3)	20 (57.1)
>65	14 (32.6)	17 (40.5)	4 (25.0)	7 (20.0)

[ref: Applicant ISE, Table 8, p. 60]

Table 7 Reasons for resection leading to SBS for studies 020 and 004 (safety population)

Characteristic n (%)	Study 020		Study 004	
	placebo n=43	0.05 mg/kg/day n=42	placebo n=16	0.05 mg/kg/day n=35
Reason for Resection				
Vascular	16 (37%)	13 (31%)	3 (19%)	14 (40%)
Crohn's	8 (19%)	10 (24%)	7 (44%)	10 (29%)
Injury	4 (9%)	4 (10%)	1 (6%)	3 (9%)
Volvulus	6 (14%)	3 (6%)	2 (13%)	5 (14%)
Cancer	2 (5%)	1 (2%)	0	0
Other	7 (16%)	11 (26%)	3 (18%)	3 (8%)
Stoma	17 (40%)	21 (49%)	5 (31%)	10 (29%)
Jejunostomy	5 (29%)	11 (52%)	4 (80%)	6 (60%)
Ileostomy	9 (53%)	6 (29%)	1 (20%)	2 (20%)
Colostomy	1 (6%)	4 (19%)	0	2 (20%)
Other	2 (12%)	0	0	0
Colon in continuity	23 (54%)	26 (61%)	11 (69%)	26 (74%)
Remaining small intestine [cm]: median (range)	48 (5, 343)	70 (15, 250)	60 (15, 200)	50 (6, 200)

[Adapted from ISS, Table 29]

Table 8 Surgical history (020, 004)

Preferred Term	Study CL0600-020		Study CL0600-004	
	Placebo (N=43)	Teduglutide 0.05 mg/kg/day (N=43)	Placebo (N=16)	Teduglutide 0.05 mg/kg/day (N=35)
	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least 1 medical and surgical history	43 (100.0)	43 (100.0)	16 (100.0)	35 (100.0)
Small intestinal resection	18 (41.9)	21 (48.8)	7 (43.8)	16 (45.7)
Colectomy	11 (25.6)	18 (41.9)	8 (50.0)	10 (28.6)
Short-bowel syndrome	9 (20.9)	13 (30.2)	3 (18.8)	8 (22.9)
Crohn's disease	9 (20.9)	12 (27.9)	7 (43.8)	10 (28.6)
Osteoporosis	15 (34.9)	10 (23.3)	2 (12.5)	8 (22.9)
Cholecystectomy	14 (32.6)	10 (23.3)	6 (37.5)	15 (42.9)
Intestinal anastomosis	11 (25.6)	9 (20.9)	5 (31.3)	15 (42.9)
Intestinal resection	8 (18.6)	9 (20.9)	4 (25.0)	11 (31.4)
Appendectomy	4 (9.3)	4 (9.3)	5 (31.3)	5 (14.3)
Central venous catheterization	5 (11.6)	4 (9.3)	5 (31.3)	12 (34.3)

N,n = number

Note: Subjects are counted no more than once for incidence of Preferred Term.

Note: Medical and surgical histories were coded to Preferred Term using the MedDRA dictionary, Version 12.0

Source: [Table 14.1.7.1](#) (Study CL0600-020) and [Table 14.1.2.19](#) (Study CL0600-004)

[ref: ISE, Table 11, p. 66]

Medical Reviewer Comment. Given the small sample size, the demographics were approximately balanced between teduglutide and placebo groups.

6.1.3 Subject Disposition

Subject disposition in the SBS Placebo-controlled studies appears in Table 9.

Table 9 Subject disposition (020, 004)

Category	Study CL0600-020		Study CL0600-004	
	Placebo (N=43) n (%)	Teduglutide 0.05 mg/kg/day (N=43) n (%)	Placebo (N=16) n (%)	Teduglutide 0.05 mg/kg/day (N=35) n (%)
Completed Study	39 (90.7)	39 (90.7)	15 (93.8)	27 (77.1)
Discontinued Study	4 (9.3)	4 (9.3)	1 (6.3)	8 (22.9)
Adverse Event	3 (7.0)	2 (4.7)	1 (6.3)	6 (17.1)
Death	0	0	0	0
Lost to Follow-up	0	0	0	0
Noncompliance with Study Protocol	0	0	0	0
Subject Decision/ Withdrawal of Consent	1 (2.3)	0	0	2 (5.7)
Investigator Decision	0	1 (2.3)	0	0
Other	0	1 (2.3)	0	0

N, n = number

Source: [Table 14.1.1.1](#) (Study CL0600-020) and [Table 14.1.1.7](#) (Study CL0600-004)

[ref: Applicant Table 7, ISE, p.58]

One subject (020-0208-1002) was randomized in error, and never received teduglutide. This subject was included in the primary efficacy (responder) analysis imputed as a failure and not included in other analyses.

Medical Reviewer Comment. There was a relatively low dropout rate in the placebo-controlled studies.

6.1.4 Analysis of Primary Endpoint(s)

TRIAL 004. The primary efficacy endpoint hypothesis test result of trial 004 was not statistically significant ($p=0.161$).

Before completion (06-Jul-2007) of study 004, the Applicant amended (Amendment 4, 13-Feb-2007) the protocol with a change in the primary efficacy endpoint. The original primary efficacy endpoint had been “clinically relevant response” defined on a per-subject basis (“responder”) as attainment of at least 20% reduction from Baseline in weekly PN/I.V. volume at Weeks 20 and 24. The original primary efficacy analysis had been planned to be a between-groups comparison of percent responders.

The revised primary efficacy endpoint (“graded response”) was a categorical variate (“graded response score”) with six levels (0, 1, 2, 3, 4, 5), as shown in Table 10, which allows an integer score to be calculated for each subject based on response at Weeks 16 in addition to Weeks 20 and 24. With this amendment, the original “clinically relevant response” primary endpoint was moved to the key secondary efficacy endpoint in the hypothesis testing order.

Table 10 Definition of primary endpoint (graded response score) in trial 004
Table 9-5 Criterion Values for Response in Study CL0600-004

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

[ref: CSR Study 004, Table 9-5]

To use Table 10, first note that the column headings would be more accurately denoted “Weeks 20 **and** 24” and “Weeks 16 **and** 20” rather than “Weeks 20 **to** 24” and “Weeks 16 **to** 20”, respectively. To calculate the graded response score for an individual subject, go to the applicable row in the column “Weeks 16 to 20” (based on % reduction) and the applicable column in the column entitled “Weeks 20 to 24” and read the integer at the intersection of this row and column. The integer is the graded response score.

For the primary efficacy hypothesis test, a hierarchical testing procedure was used, wherein the 0.10 mg/kg/day dose versus placebo was tested first, followed by 0.05 mg/kg/day dose versus placebo. If the 0.10 dose versus placebo p-value was not statistically significant, the primary efficacy result would be declared not statistically significant and testing would stop. In 004, testing did not proceed to the 0.05 mg/kg/day versus placebo test.

Table 11 shows the distribution of graded response scores in 004.

Table 11 Primary endpoint (graded response score) distribution, Study 004

Treatment Group (n, %)	Response Category				
	ITT Population				
	0 No Response	1	2	4	5 Off-PN
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)

[ref: CSR, 004, Table 11-6, p. 61]

Based on these data, the primary endpoint statistical results in 004 were as follows:

- No statistically significant difference between placebo and the 0.10 mg/kg/day dose group (adj-p =0.161 for the 0.10 mg/kg/day dose group versus placebo). Therefore the primary efficacy hypothesis test was not statistically significant.
- The post-hoc unadjusted p-value for the graded response score for the 0.05 mg/kg/day dose group versus placebo was p=0.007 (rank-ANCOVA).

- Post-hoc statistical calculation was performed on the key secondary endpoint (the original primary efficacy endpoint of clinically relevant response). The following statistics were reported in the ISE [ref: ISE, Table 14]:
 - o Teduglutide 0.05 mg/kg/day group: 15/35 (42.9%)
 - o Placebo group: 1/16 (6.3%)
 - o p=0.010 by CMH test

The results reported in the ISE differ from those reported in the clinical study report (CSR) for study 004. In the CSR (p. 6) the result was a teduglutide response rate of 16/35 (45.7%) versus placebo response rate of 1/16 (6.3%) for a p-value of 0.005.

The following possible reasons for the lack of statistical significance of the primary efficacy endpoint were discussed by the Applicant and FDA at the conclusion of study 004 and before designing study 020:

- In trial 004, the higher baseline PN/I.V. requirement in the 0.10 mg/kg/day dose group (12.7 L/week), which was tested first, made it more difficult to achieve 20% percent reduction in PN for a given volume reduction. In trial 004, the mean PN/I.V. volumes at Baseline and Week 24 were as follows:
 - o 0.10 mg/kg/day group (14% decrease in PN/I.V. volume from Baseline)
 - Baseline (n=29 completers): 13.2 L/week (n=32 randomized and dosed once: 12.7 L/week)
 - Week 24 (n=29 completers): 10.8 L/week
 - o 0.05 mg/kg/day group (25% decrease in PN/I.V. volume from Baseline)
 - Baseline (n=27 completers): 9.4 L/week (n=34 randomized and dosed once: 9.6 L/week)
 - Week 24 (n=27 completers): 6.9 L/week
 - o Placebo group (8% decrease in PN/I.V. volume from Baseline)
 - Baseline (n=15 completers): 9.6 L/week (n=16 randomized and dosed once: 10.7 L/week)
 - Week 24 (n=15 completers): 8.7 L/week
- Protocol-specified 10% limitation on PN/I.V. volume reduction in study 004
- Protocol-specified volume reductions not allowed until Week-4 of treatment in study 004

An important secondary endpoint result in Table 10 is that 2 patients were completely weaned off PN/I.V. by Week-24.

Medical Reviewer Comment. The primary efficacy endpoint in study 004 was not statistically significant. I concur with the reasons previously discussed by the Applicant and FDA. Moreover, the graded categorical score was actually not ordinal though analyzed as such with ranks ANCOVA. As an illustration, consider that a score of 3 from complete weaning of PN at Weeks 20 and 24 is actually considered worse in this scoring system than a 4 achieved from only a 40% reduction. Similar examples of the

violation of ordinality can be found in Table 10. However, it is notable that 2 patients were completely weaned off PN, and this will be discussed later in this review.

TRIAL 020. The primary efficacy endpoint result in trial 020 was statistically significant. Learnings from study 004 had been used to inform the design of study 020.

The primary efficacy endpoint was the percentage of subjects with response (“clinically relevant response”) at Week 20 and Week 24. Response was defined as the achievement of at least 20% reduction in weekly PN/I.V. volume from Baseline to Week-20 and from Baseline to Week-24. Secondary efficacy endpoints included percent and absolute changes in PN/I.V. volume, duration of response, complete weaning from PN/I.V., and others.

The primary efficacy endpoint hypothesis test was the CMH test stratified by baseline PN/I.V. level (≤ 6.0 L/week versus > 6.0 L/week). The analysis population was ITT, defined as all randomized subjects who received at least one dose of study drug. There were 86 ITT subjects (43 teduglutide and 43 placebo). One subject was mistakenly randomized when testing the IVRS system, and was included in the ITT population but discontinued from the study prior to receipt of study medication because of failure to achieve stable PN/I.V. level in Stage 1.

The efficacy results were statistically significant ($p=0.002$) as shown in Table 12.

Table 12 Primary efficacy results of Study 020

Response Status	Statistic	Placebo	Teduglutide
		(N= 43) n (%)	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.

[ref: ISE, p. 32]

Medical Reviewer Comment. The primary efficacy results from trial 020 were statistically significant. In contrast to its predecessor study 004, study 020 had a straightforward primary endpoint. Study 020 also permitted larger (up to 30%) and

earlier (at 2 weeks) reductions in PN/I.V. volume. Additionally, there was no imbalance between groups in Baseline PN volume.

It is interesting that the placebo group in study 020 had a considerably higher responder rate (30%) than the placebo group in study 004 (6%). This is likely attributable to the larger and earlier allowable PN reduction in study 020 compared to that in study 004. It is also interesting that the placebo groups of both studies experienced mean reductions in PN/I.V. by the end of the trial. This is probably because there was more attention toward weaning these patients in the clinical trial setting than outside of that setting.

6.1.5 Analysis of Secondary Endpoints(s)

In studies 004 and 020, the analysis populations used to calculate continuous variables were not the same at Baseline and Week-24 within each study because of dropouts. At Week-24, the analysis population was the completers population (had data at Week-24). No imputation was done for continuous variables. To compute change in weekly PN/I.V. volume between Baseline and Week-24, only Week-24 completers could be used as this is the only analysis population with values at both Baseline and Week-24.

The prespecified secondary endpoints in trials 020 and 004 were tested hierarchically following the primary endpoint in the following order:

Prespecified hypothesis testing order in Trial 020. Testing of the secondary endpoints was prespecified as a step-down procedure to proceed only if the primary endpoint was statistically significant. The prespecified testing order of the secondary endpoints was:

1. Percent change in PN volume between baseline and last dosing visit
2. Actual change in PN volume between baseline and last dosing visit
3. Duration of response
4. Maintenance of either a 20% reduction or a 2 L reduction
5. Complete weaning of PN
6. Graded response (PRIMARY ENDPOINT IN 004 STUDY)

Prespecified hypothesis testing order in Trial 004. Trial 004 had 3 arms, and there were two dose comparisons to placebo for each endpoint. The high dose test preceded the low dose test within each endpoint. Testing of the secondary endpoints was prespecified to proceed only if the primary endpoint was statistically significant. The prespecified testing order of the secondary endpoints was:

1. Key secondary endpoint. Number and percentage of subjects who demonstrate a response at both Weeks 20 and 24 (“clinically relevant response” endpoint).

Response was defined as the achievement of at least a 20% reduction from baseline in weekly PN/I.V. volume.

2. Number and percentage of subjects with at least a 1-day reduction in weekly PN/I.V.
3. Absolute reduction from baseline in weekly PN kilocalories
4. Absolute reduction from baseline in weekly volume of PN
5. Change from baseline in plasma citrulline at dosing Week 24

Results for secondary endpoints for the approvable dose (0.05 mg/kg/day) appear in Table 13.

Table 13 Secondary endpoints, ITT (020, 004)

Parameter	Study CL0600-020			Study CL0600-004		
	Placebo (N=43)	Teduglutide 0.05 mg/kg/day (N=43)	p-value	Placebo (N=16)	Teduglutide 0.05 mg/kg/day (N=35)	p-value
Percent change from baseline in PN/I.V. volume at Week 24, Mean (±SD)	-21.0 (24.35)	-32.1(18.71)	0.025 ^a	-7.6 (11.8307)	-17.2 (48.03)	0.414
Actual change from baseline in PN/I.V. volume at Week 24, Mean (±SD)	-2.4 (2.79)	-4.3 (3.81)	<0.001 ^a	-0.80 (1.38)	-1.9 (3.00)	0.126
Subjects achieving ≥ 20% reduction in PN/I.V. volume by duration (days), n (%)			0.005 ^b			0.120
0	25 (58.1)	13 (30.2)		12 (75.0)	20 (57.1)	
1	5 (11.6)	3 (7.0)		3 (18.8)	0	
2	1 (2.3)	3 (7.0)		0	6 (17.1)	
3+	12 (27.9)	24 (55.8)		1 (6.3)	9 (25.7)	
Subjects with ≥ 20% or 2 L reduction from baseline in PN/I.V. volume at Week 20 and Week 24, n (%)	16 (37.2)	30 (69.8)	0.002 ^c	1 (6.3)	15 (42.9) ^f	0.010
Subjects Who Stopped PN/I.V. as of Week 24, n (%)	1 (2.3)	0	1.000 ^d	0	2 (5.7)	0.522
Subjects achieving at least a 1-day reduction in weekly PN/I.V. at Week 24, n (%)	9 (23.1) ^e	21 (53.8) ^e	0.005 ^c	2 (12.5)	8 (22.9)	0.277

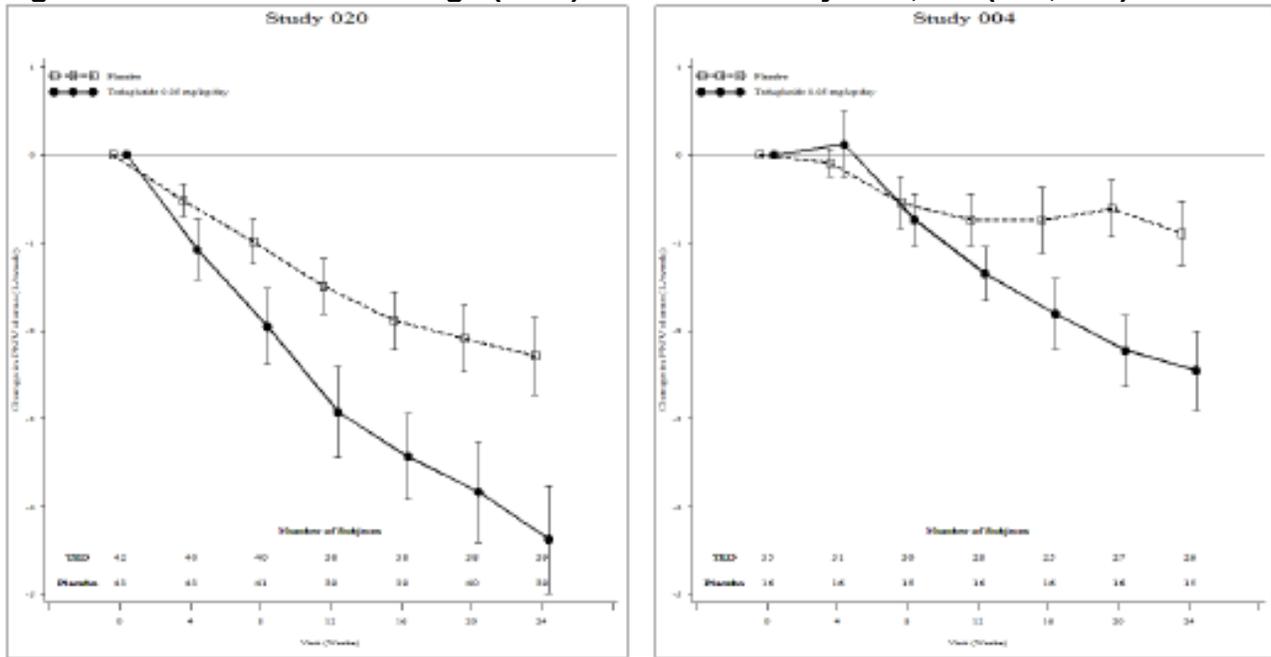
[ref: Applicant ISE, Table 16, p. 79]

Medical Reviewer Comment. The efficacy data of study 004 are supportive of the results of study 020, and are consistent with efficacy. The directions of between-groups differences favored teduglutide.

6.1.6 Other Endpoints

The following figures (Figure 5, Figure 6, Figure 7) show changes in PN/I.V. volume and response by visit. All suggest a temporal trend favoring teduglutide (dotted line is placebo).

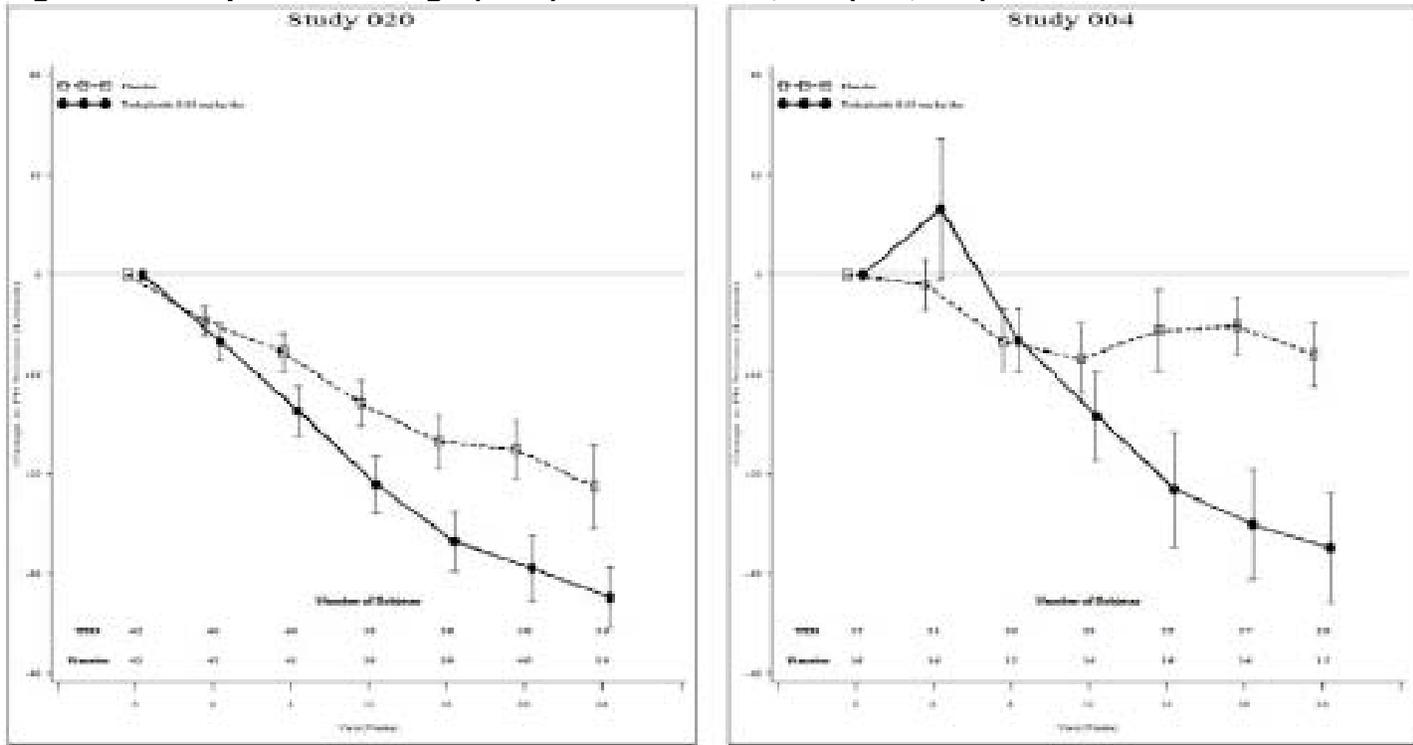
Figure 5 Absolute mean change (SEM) in PN volume by visit, ITT (020, 004)



SEM = standard error of the mean
 [ref: Applicant ISE, Figure 7, p.83]

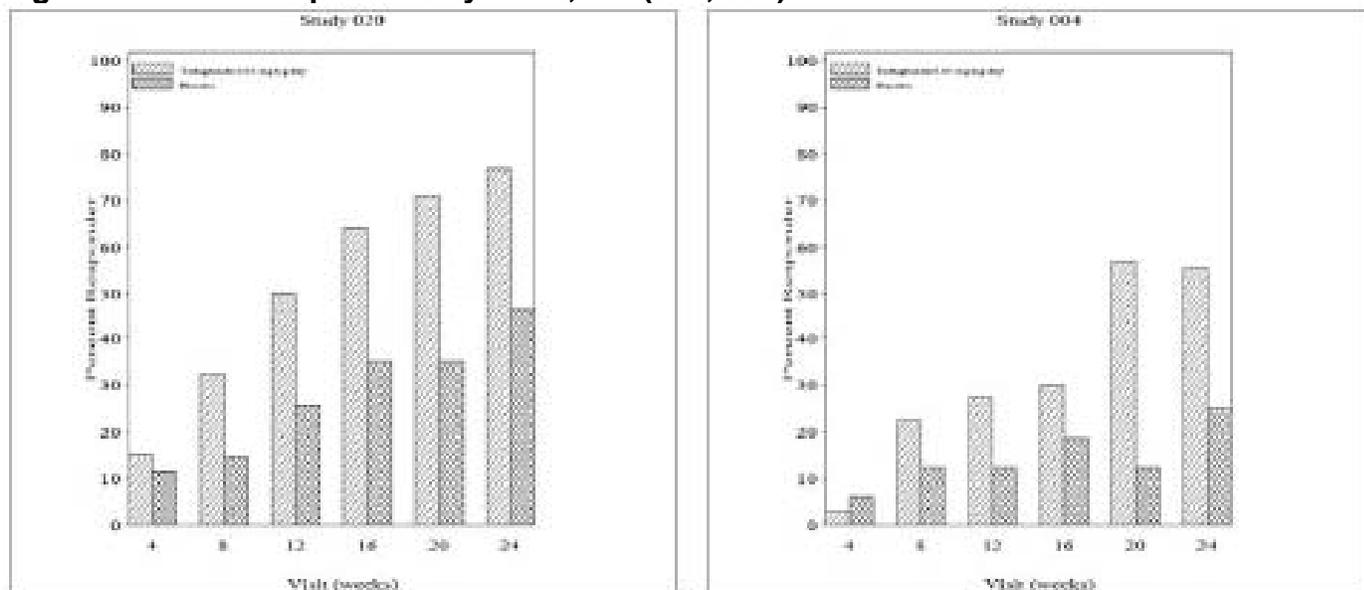
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Figure 6 Mean percent change (SEM) in PN volume, ITT (020, 004)



SEM = standard error of the mean
 [ref: Applicant ISE, Figure 8, p. 84]

Figure 7 Percent responders by week, ITT (020, 004)



Source: [Table 14.2.3.2](#) (Study CL0600-020) and [Table 14.2.2.17](#) (Study CL0600-004)

Ref: *Applicant ISE, Figure 9, p.86*

Medical Reviewer Comment. *The temporal trends in the secondary endpoints favor teduglutide.*

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 reduced their need for I.V. catheter access. In the 0.10 group it was 37% (10/27).
- 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:
 - The 2 subjects completely weaned off in 004 remained PN/I.V.-free through 005

- An additional subject was weaned completely off PN/I.V. in 005

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

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

For 005 and 021, days reduction of PN/I.V. as of Sep-2011 are summarized in Table 14.

Table 14 Days reduction in PN (005, 021)

Study Week on Teduglutide	CL0600-020/021 n (%)	N	CL0600-004/005 n (%)	N
24 Weeks (End of 004 / 020)				
At Least a 1-Day reduction	21 (53.8)	39	8 (29.6)	27
At Least a 2-Day Reduction	8 (20.5)	39	5 (18.5)	27
At Least a 3-Day Reduction	4 (10.3)	39	3 (11.1)	27
52 Weeks (28 weeks 005 / 021)				
At Least a 1-Day Reduction	18 (52.9)	34	12 (60.0)	20
At Least a 2-Day Reduction	13 (38.2)	34	6 (30.0)	20
At Least a 3-Day Reduction	8 (23.5)	34	4 (20.0)	20

N, n = number

Source: 14.2.1.13 (Study CL0600-021) and ISEPN ISEDM
 [ref: ISE, Table 30]

Medical Reviewer Comment. The extension study results are consistent with long-term efficacy, especially the number of patients who were completely weaned off PN/I.V., which represents a considerable benefit in quality of life for these patients.

6.1.7 Subpopulations

Dose Adjustment. Was not found to be required in any demographic subpopulation (age, race, gender), based on population PK analyses (see Clinical Pharmacology Review).

In patients with renal failure, the dose needs to be reduced 50% (Study 018). In moderate hepatic impairment, no dosage adjustment is necessary (Study 017).

Efficacy by Subgroup. Exploratory subgroup analyses revealed no trends favoring efficacy in any subgroup.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Relative to the teduglutide approvable dose of 0.05 mg/kg/day, trial 004 did not demonstrate a clear benefit of the 0.10 mg/kg/day dose over the 0.05 mg/kg/day dose in absolute PN/I.V. volume reduction (Liters/week)—2.5 L in both groups.

Medical Reviewer Comment. Because the 0.10 mg/kg/day dose seemed to offer no additional efficacy advantage, the dose of 0.05 mg/kg/day was selected as the approvable dose and was used in Study 020.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Trials 021 and 005 were long-term extensions of studies 020 and 004, respectively, in which all subjects received teduglutide. In study 005, 1 patient was weaned off PN/I.V.. The 2 patients off PN/I.V. in study 004 remained off in study 005. The Applicant has also reported that, of 88 patients in study 021 as of Oct-2012, 12 (14%) patients have been completely weaned off PN/I.V.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses other than those presented in other sections of this report.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The SBS Placebo-controlled studies (004, 020) are used to identify potential safety signals. Safety findings in the long-term SBS extension trials (005, 021) are also presented.

Across 15 clinical studies and 624 subjects (Table 15), 566 (safety population) were on teduglutide and 198 on placebo. For general safety evaluation, the Crohn's studies (008, 009) are not used to identify a safety signal because they represent a different population than the SBS trials. However, some subjects in the SBS studies had underlying Crohn's disease that led to the initial bowel resection.

Table 15 Counts of safety population by study

Study Group	Statistic	Placebo	Teduglutide	Total
Clinical Pharmacology Studies	n	114	299	344
Single Dose Studies	n	77	188	196
CL0600-006 (Healthy: BA)	n	0	14	14
CL0600-015 (Healthy: BA/BE)	n	0	18	18
1621/13 (Healthy: PK and Tolerability)	n	8	24	32
CL0600-017 (Intrinsic Factor PK - Hepatic)	n	0	24	24
(Hepatic Impaired)	n	0	12	12
(Healthy)	n	0	12	12
CL0600-018 (Intrinsic Factor PK - Renal)	n	0	36	36
(Renal Impaired)	n	0	18	18
(Healthy)	n	0	18	18
C09-001 (Healthy: PD Cardiac Repolarization)	n	69	72	72
Multiple Dose Studies	n	37	111	148
CL0600-022 (Healthy: PK and Tolerability)	n	24	71	95
C10-003 (Healthy: PD Gastric Emptying)	n	13	23	36
ALX-0600-92001 (SBS: Patient PD)	n	0	17	17
Efficacy and Safety Studies (SBS)	n	59	173	180
Placebo-controlled	n	59	109	168
CL0600-020	n	43	42	85
CL0600-004	n	16	67	83
Uncontrolled	n (m)	0	153 (89)	153 (141)
CL0600-021	n (m)	0	88 (37)	88 (76)
CL0600-005	n (m)	0	65 (52)	65 (65)
Other Studies (Crohn's Disease)	n	25	94	100
Placebo-controlled (CL0600-008)	n	25	75	100
Uncontrolled (CL0600-009)	n (m)	0	65 (46)	65 (65)
Grand Total Subjects	n	198	566 ^a	624

BA = bioavailability; BE = bioequivalence; n = number, PD = pharmacodynamic; PK = pharmacokinetics; 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.

Note: Seventy (70) of the 72 subjects in C09-001 received a single oral dose of 400 mg moxifloxacin, a positive control in this crossover study.

^aThe total number of unique subjects treated with teduglutide was actually 565, as one subject who was treated with teduglutide in 2 separate studies.

Source: ISS End-of-Text Table 1.1.2

[ref: Applicant Table 3, ISS, p. 48 (updated version 21-Dec-2012)]

7.1.2 Categorization of Adverse Events

Adverse events were characterized using the MedDRA system of adverse event classification.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The highest prevalence of adverse events occurred in the SBS Efficacy and Safety studies, which also had the greatest teduglutide exposure (142 person-years) (Table 16).

Table 16 Overall adverse event counts for teduglutide subjects (safety population)

	Clinical Pharmacology Studies (N = 299)			SBS Efficacy and Safety Studies (N = 173)			Other Studies - Crohn's (N = 94)			All Studies (N = 566)		
	n	(%)	Events	N	(%)	Events	n	(%)	Events	n	(%)	Events
Any TEAE												
No	125	(41.8%)	0	9	(5.2%)		9	(9.6%)	0	143	(25.3%)	
Yes	174	(58.2%)	621	164	(94.8%)	1819	85	(90.4%)	603	423	(74.7%)	3043
TEAE Severity												
Mild	169	(56.5%)	579	146	(84.4%)	972	72	(76.6%)	261	387	(68.4%)	1812
Moderate	24	(8.0%)	39	135	(78.0%)	680	66	(70.2%)	251	225	(39.8%)	970
Severe	2	(0.7%)	3	74	(42.8%)	167	35	(37.2%)	91	111	(19.6%)	261
Any TESAE												
	4	(1.3%)	6	92	(53.2%)	218	19	(20.2%)	24	115	(20.3%)	248
TESAE Severity												
Mild	1	(0.3%)	1	27	(15.6%)	41	1	(1.1%)	1	29	(5.1%)	43
Moderate	1	(0.3%)	2	49	(28.3%)	93	4	(4.3%)	5	54	(9.5%)	100
Severe	2	(0.7%)	3	47	(27.2%)	84	14	(14.9%)	18	63	(11.1%)	105
TEAE Leading to Premature Discontinuation												
	3	(1.0%)	5	28	(16.2%)	45	25	(26.6%)	51	56	(9.9%)	101
Death												
	0			1*	(0.6%)	1	0			1	(0.2%)	1

[ref: Applicant Clinical Overview, Table 5, p.32]

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

To date, 566 subjects have been exposed to teduglutide. As of the 4-month safety update (Apr-2012), exposure statistics for subjects exposed to teduglutide are as follows:

- Mean duration of exposure to teduglutide: 17 weeks
- Person-years of exposure: 190 person-years
- Exposure in SBS Efficacy and Safety studies : 163 person-years

Exposure in the 566 teduglutide-treated subjects was distributed as follows:

- 299 subjects in the clinical pharmacology studies had less than 3 months of exposure
- 173 subjects in the SBS Efficacy and Safety trials had 163 person-years of exposure
 - 33 subjects for less than 6 months
 - 43 subjects at least 6 months but no more than 12 months
 - 97 subjects for at least 12 months
- 94 subjects in other studies (Crohn's Disease) had 22 person-years of exposure
 - 94 subjects for less than 6 months
 - No subjects for 6 months or more

In the SBS Placebo-controlled trials (004, 020), exposure to teduglutide appears in Table 17.

Table 17 Exposure to teduglutide in SBS Placebo-controlled Trials (004, 020)

Statistic		Placebo-controlled Trials (004, 020)		
		Placebo n=59	0.05 mg/kg/day n=77	0.10 mg/kg/day n=32
Duration (weeks)	Mean (SD)	23 (4.5)	22 (7.0)	23 (5.6)
	Median	24	24	24
	Range	2.9 to 28	0.6 to 29	0.9 to 30
Person-years		26.2	32.3	14.3
Distribution	<6 months	19 (32%)	22 (31%)	4 (12%)
	at least 6 months	40 (68%)	53 (69%)	28 (88%)

7.2.2 Explorations for Dose-Response

Explorations for safety dose-response were undertaken using data from the SBS Placebo-controlled studies (004, 020). These data are reported in another section of this report (7.3.5 Submission Specific Primary Safety Concerns), but are summarized below for easy reference:

1. Malignancy-related events
 - a. Placebo: None
 - b. 0.05 mg/kg/day: 3/77 (3.9%): all at high risk for malignancy
 - c. 0.10 mg/kg/day: 0/32 (0.0%)
2. Bowel obstruction
 - a. Placebo: 0/59 (0.0%)
 - b. 0.05 mg/kg/day: 3/77 (3.9%): none required surgery
 - c. 0.10 mg/kg/day: 3/32 (9.4%): none required surgery
3. Cholecystitis
 - a. Placebo: None
 - b. 0.05 mg/kg/day: 3/77 (3.9%): 1 gallbladder perforation and 2 elective cholecystectomies
 - c. 0.10 mg/kg/day: 1/32 (3.3%): likely renal colic and not cholecystitis
4. Fluid overload
 - a. Placebo: None
 - b. 0.05 mg/kg/day: 4/39 (6.8%): 1 SAE of CHF
 - c. 0.10 mg/kg/day: 9/77 (11.7%)
5. Upper respiratory tract infection
 - a. Placebo: 8/ 59 (13.6%)
 - b. Teduglutide: 30/109 (27.5%)
 1. 0.05 mg/kg/day: 20/ 77 (26.0%)
 2. 0.10 mg/kg/day: 10/ 32 (31.3%)

***Medical Reviewer Comment.** These cases are presented in greater detail (7.3.5 Submission Specific Primary Safety Concerns). Of all of these events, upper respiratory infection is the least concerning except in the immune-deficient patient.*

7.2.3 Special Animal and/or In Vitro Testing

No special testing. See nonclinical studies.

7.2.4 Routine Clinical Testing

Routine clinical testing included scheduled and as-needed testing. Scheduled testing included colonoscopy at baseline and at study discontinuation, physical exam with vital signs, and laboratory tests (general chemistry, nutritional, hematology, hepatic, pancreatic, biliary).

7.2.5 Metabolic, Clearance, and Interaction Workup

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 the endogenous GLP-2. It is not likely to be metabolized by common drug metabolizing enzymes such as CYP, glutathione-S-transferase, or uridine-diphosphate glucuronyltransferase.

Clearance. Following I.V. 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 (study 006). Teduglutide was rapidly eliminated with a mean terminal half-life of approximately 2 hours in healthy subjects and 1.3 hours in SBS subjects.

Interactions. No *in vivo* drug-drug interaction (DDI) studies were conducted, based on negative results from *in vitro* studies of inhibition and induction of P450 isozymes at much higher teduglutide levels (2000 ng/mL) than expected for the approvable dose of 0.05 mg/kg/day. This is acceptable given teduglutide is not a pro-inflammatory cytokine or cytokine modulator. However, the potential for PD effect-mediated drug-drug interactions exists via teduglutide's effect of increased intestinal absorption.

Medical Reviewer Comment. *The effect of teduglutide on intestinal absorption of concomitant oral medications needs to be considered, especially those medications with a narrow therapeutic index.*

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no similar drugs in this class (GLP-2 analog).

7.3 Major Safety Results

7.3.1 Deaths

There were 2 treatment-emergent deaths reported in this development program, and both had received teduglutide:

1. Study 021

- Subject 021-0155-1009 (also see 7.3.5. Malignancy-Related Events). The patient was a 47 year-old man with a history of Hodgkin's disease, cecal necrosis secondary to abdominal radiation, and primary liver disease. He was diagnosed with metastatic adenocarcinoma after 11 months of treatment with teduglutide, and expired 10 days after diagnosis. Six months prior to starting teduglutide therapy, CT scan had shown liver enlargement without focal lesions. Subsequent review of this past CT scan by two independent radiologists revealed a focal liver lesion. Autopsy report (translation from Polish):
 - Intestines with extensive adhesions. "No malignancy was found in their sections"
 - Liver: massive metastases of adenocarcinoma with necrosis, suppuration, and multiple emboli in almost all vascular spaces (blood and lymphatic). Multifocal liver necrosis with bile stasis. "Tumor morphology (including results of immunochemical staining) indicated intestinal cancer despite atypical liver changes."
 - Pancreas: marked autolysis. "Small emboli of cancer cells in the blood vessels"
 - Lungs: "numerous emboli of cancer cells in blood vessels", emphysema, tuberculous infiltrate with caseation necrosis.
 - Multiple other sites of massive metastasis of adenocarcinoma (pubic bone, vertebrae, lymph nodes)
 - Diagnosis: "Natural death caused by the disease. Generalized malignancy (intestinal cancer with primary site difficult to localize – small intestine in the stomy region?) with massive metastases to the liver and regional abdominal lymph nodes and emboli in the vascular spaces, mainly in the lungs, was considered the primary cause of death."
- Subject 021-0138-1011 (also see 7.3.5. Malignancy-Related Events). Patient expired (b) (6) months after the data cutoff date. The patient was a 64 year-old white male with a 30-year history of smoking. He was diagnosed with non-small cell lung cancer after (b) (6) days of teduglutide therapy.

Teduglutide was permanently discontinued by the Investigator and the patient subsequently received chemotherapy. An autopsy report is not available at this time.

Medical Reviewer Comment. These 2 treatment-emergent deaths occurred after having received teduglutide in study 021, and were in patients at high risk of their respective malignancies.

7.3.2 Nonfatal Serious Adverse Events

In these studies, 20% (115/566) of teduglutide subjects experienced at least one nonfatal SAE, compared to 9% (18/198) of placebo subjects. For the SBS studies (Clinical Pharmacology, SBS Efficacy and Safety) there were higher SAE rates in the teduglutide than placebo group (Table 18).

Table 18 Non-fatal SAE and AE rates, safety population, SBS studies

	Clinical Pharmacology Studies		SBS Efficacy and Safety Studies		
	placebo (n=114)	teduglutide (n=299)	placebo (n=59)	0.05 dose (n=77)	0.10 dose (n=32)
Any AE n (%) [*]	43 (37.7%)	125 (58.2%)	49 (83.1%)	68 (88.3%)	31 (96.9%)
Any SAE n (%) [*]	0 (0%)	4 (1.3%)	17 (28.8%)	28 (36.4%)	11 (34.4%)

^{*} n (%)=number of subjects (% of subjects)

The most frequent non-fatal SAE in the teduglutide groups was catheter-related sepsis, which occurred in 6.7% (38/566) of teduglutide subjects. The second most common SAE in the teduglutide groups over all studies was “GI stenosis and obstruction”, which occurred in 1.8% (10/566) of teduglutide subjects.

At the approvable dose level (0.05 mg/kg/day), nonfatal SAEs that occurred in at least 1% of subjects in the teduglutide group and at a higher rate than placebo are shown in Table 19.

Table 19 SAEs with rates >1% in 0.05 (approvable) dose group and greater than placebo rate, SBS Placebo-controlled trials

Serious Adverse Event (SAE)	Placebo (n=59) n (%)	Teduglutide, mg/kg/day	
		0.05 (n=77) n(%)	0.10 (n=32) n(%)
G.I. stenosis/obstruction	0	3 (3.9)	2 (6.2)
Biliary tract disorder	0	3 (3.9)	0
Urinary tract infection	1 (1.7)	3 (3.9)	0
Febrile disorders	0	2 (2.6)	0
Lower respiratory tract infection	1 (1.7)	2 (2.6)	1 (3.1)
Abdominal pain	0	1 (1.3)	0
Adenovirus infection	0	1 (1.3)	0
CHF	0	1 (1.3)	0
Dehydration	0	1 (1.3)	0
Device occlusion	0	1 (1.3)	0
Drug level increased	0	1 (1.3)	0
Heart rate increased	0	1 (1.3)	0
Intestinal hemorrhage	0	1 (1.3)	0
Meningitis	0	1 (1.3)	0
Mononucleosis syndrome	0	1 (1.3)	0
Pancreatic disorders NEC	0	1 (1.3)	0
Peripheral embolus/thrombosis	0	1 (1.3)	0
Rectal abscess	0	1 (1.3)	0
SBS	0	1 (1.3)	0
Sleep disturbance	0	1 (1.3)	0
Upper respiratory tract infection	0	1 (1.3)	0
Viral infection	0	1 (1.3)	0

[adopted from ISS-4mo update, Table 48, p. 170]

In the SBS extension studies (005, 021), the following SAEs occurred with a marginal rate of at least 2% (Table 20).

Table 20 SAEs with marginal rate >2% in Long-Term SBS studies

SAE	Teduglutide, mg/kg/day		Marginal (n=139) n (%)
	0.05 (n=107) n (%)	0.10 (n=32) n (%)	
Catheter sepsis	27 (24.8)	5 (15.6)	32 (22.7)
G.I. stenosis/obstruction	5 (4.6)	1 (3.1)	6 (4.3)
Catheter site related reaction	5 (4.6)	1 (3.1)	6 (4.3)
Biliary tract disorder	5 (4.7)	1 (3.1)	6 (4.3)
Febrile disorders	6 (5.5)	0	6 (4.3)
Lower respiratory tract infection	4 (3.7)	2 (6.3)	6 (4.3)
Peripheral embolism/thrombosis	5 (4.6)	0	5 (3.5)
Cholestasis and jaundice	3 (2.8)	0	3 (2.1)
Pancreatic disorders NEC	2 (1.8)	1 (3.1)	3 (2.1)
Urinary tract infection	2 (1.8)	1 (3.1)	3 (2.1)
Abdominal pain	3 (2.8)	0	3 (2.1)
Device dislocation	1 (0.9)	2 (6.3)	3 (2.1)

[adopted from ISS-4mo update, Table 50, p. 187]

Medical Reviewer Comment. The most common SAEs in the SBS extension studies (Table 20) were also the most common in the SBS Placebo-controlled trials (top 5 rows of Table 19) with the addition of abdominal pain and device dislocation.

7.3.3 Dropouts and/or Discontinuations

In this section between-group discontinuation rates are summarized in the SBS placebo-controlled studies.

SBS Placebo-controlled trials (004, 020). In the SBS Placebo-controlled trials, subject discontinuation rates were similar in placebo and teduglutide groups (Table 21).

Table 21 Patient disposition, SBS Placebo-controlled trials (004, 020)

Subject Disposition	Placebo (n=59) n (%)	Teduglutide in mg/kg/day	
		0.05 (n=77) n (%)	0.10 (n=32) n (%)
Completed Study	54 (91.5)	66 (85.7)	29 (90.6)
Discontinued Study	5 (8.5)	11 (14.3)	3 (9.4)
Adverse event	4 (6.8)	8 (10.4)	2 (6.3)
Death	0	0	0
Lost-to-Followup	0	0	0
Noncompliance	0	0	0
W/D consent	1 (1.7)	2 (2.6)	1 (3.1)
Other	0	1 (1.3)	0

In the pooled teduglutide group in the SBS Placebo-controlled studies, the most common reasons for discontinuation were constipation and abdominal distension, for which there were no discontinuations in the placebo group. In the pooled placebo group, reasons for discontinuation included catheter sepsis, increased stool (frequency, volume), intestinal polyp, and transplantation, none of which, except for catheter sepsis, occurred in the teduglutide group.

Medical Reviewer Comment. These discontinuation rates are balanced between groups and did not affect efficacy or safety determinations in this Application.

In Table 21 in the approvable dose group (0.05 mg/kg/day), 8 (10.4%) subjects discontinued for an AE, and in the 0.10 mg/kg/day group 2 (6.3%) subjects discontinued. In the placebo group in Table 21 there were 4 (6.8%) subjects discontinued. Of these discontinuation AEs, some were not considered related to study drug—1 subject in the placebo group and 1 subject in the 0.10 mg/kg/day group.

Narratives were provided by the Applicant only for discontinuation AEs considered to be related to study drug. The following subjects were discontinued in the SBS Placebo-controlled studies as a result of an AE related to study drug [ref: ISS, p. 198/472]:

- Placebo group (n=3)
 - 020-0109-1005: 48 yo white female after 3 months—Intestinal polyp in peristomal area
 - 020-0202-1001: 26 yo white male after 1.5 months—Increased ostomy output
 - 020-0205-1002: 47 yo white female after 3 days—frequent bowel movements (12/night)
- Teduglutide groups (n=9 in 0.05 group; n=1 in 0.10 group)

- 020-0106-1001 (0.05 mg/kg/day): 60 yo white female after 3 weeks—severe abdominal distension
- 020-0136-1010 (0.05 mg/kg/day): 37 yo white male 2 days—severe abdominal pain
- 004-0126-0001 (0.05 mg/kg/day): 56 yo white female after 2 days—dysgeusia, nausea, vomiting, asthenia
- 004-0132-0007 (0.05 mg/kg/day): 53 yo white female after 2 days—constipation, abdominal pain, nausea
- 004-0139-0002 (0.05 mg/kg/day): 59 yo white female after 2 days—severe abdominal distension and constipation
- 004-0139-0009 (0.05 mg/kg/day): 50 yo white female after (b) (6) days—congestive heart failure (SAE). At screening and baseline, noted to have had HR=121 bpm. On treatment day (b) (6), hospitalized for CHF. CXR—bilateral pulmonary edema. Cardiac ECHO—mild inferior hypokinesis, grade 2 mitral insufficiency, normal function, no LV dilation. Troponins <0.12 ng/mL and 1.15 ng/mL. Treated with bumetanide, perindopril, atenolol. Discharged after 6 days without dyspnea. Applicant or investigator felt that history and findings raise possibility of undiagnosed hypothyroidism and/or cardiac dysfunction [ref: ISS, p. 391/472].
- 004-0116-0002 (0.05 mg/kg/day): 51 yo white female after 123-198 days—hemorrhagic hemorrhoid (SAE). Multiple episodes of severe lower abdominal pain from days 123 through 198. Abdominal pain also felt to be related to exacerbation of SBS. Also diagnosed with Mallory-Weiss esophagus, focal trauma.
- 004-0135-0009 (0.05 mg/kg/day): 68 yo white female —coma, drug level increase, hypersomnia. Past history of type 2 diabetes mellitus, meningioma, epilepsy, hemorrhagic stroke, depression, anxiety, and insomnia. ‘Prazepam’ dose was increased on (b) (6) by her general practitioner. Started teduglutide 2 weeks later. During the first week on teduglutide, the patient’s mental status dramatically deteriorated and she was admitted to ICU for hypersomnolence, where she progressed to coma (Glasgow 8/15). She was found to have high serum benzodiazepine level (>300mcg/L). Study medication and benzodiazepine were discontinued. On unspecified date, patient’s neurologic status improved and she slowly awoke. 4 days later, she developed agitation and hallucinations from weaning of benzodiazepine. The next day after approximately 2 weeks in ICU, the patient had nearly normal state of consciousness and was discharged. Event was reported to have resolved the next month. [ref: ISS, p. 302/472].

- 004-0115-0003 (0.10 mg/kg/day): 62 yo white female after 1-5 days—small bowel obstruction (SAE). Medical history of Crohn’s disease (higher risk for bowel obstruction and amylase/lipase elevations). On day 2, developed abdominal bloating that lasted a week and progressed to severe abdominal pain and was not passing stool. In ER, CT showed dilated segments of small bowel. Hospitalized for possible bowel obstruction. Patient requested early study withdrawal and was given Early Termination visit. Laboratory test showed mildly elevated lipase and amylase levels secondary to small bowel obstruction rather than pancreatitis. Stoma size increased to point of having broke seal of stoma bag. Firm stool was passed followed by loose stool. Abdominal pain resolved and patient began drinking clear liquids. Stoma size decreased by 30% and she was discharged.

In the placebo group, the AEs leading to discontinuation (reported by more than 1 placebo-treated subject) included two cases of exacerbation of Crohn’s disease.

There were 65 of 71 study subjects who entered extension study 005 from 004. For extension study 021, all study 020 completers (n=76) entered study 021, and 12 additional subjects enrolled in 021 who had been screened but not randomized in study 020. This gave a total of 88 subjects enrolled in study 021.

7.3.4 Significant Adverse Events

These are discussed in the section 7.3.5 Submission Specific Primary Safety Concerns.

7.3.5 Submission Specific Primary Safety Concerns

Malignancy-related Events. There were patients diagnosed with malignancy following initiation of teduglutide therapy. These occurred in extension study 021 in sites in Poland [ref: ISS, Table 89]:

1. Metastatic adenocarcinoma—Subject 021-0155-1009 on Day (b) (6)
 - a. 47 year old male
 - b. Prior history of Hodgkin’s disease diagnosed in 1988 and treated with both radiation and chemotherapy had suggested high risk of a developing secondary malignancy of GI origin.
 - c. Two expert radiologist consultants agreed that patient had had a 2-cm left lobe hepatic lesion on CT scan (b) (6) performed prior to receiving teduglutide.

- d. In placebo/0.05 group (“NT, PBO/TED” group)
- e. Autopsy report (translation from Polish):
 - i. Intestines with extensive adhesions. “No malignancy was found in their sections”
 - ii. Liver: massive metastases of adenocarcinoma with necrosis, suppuration, and multiple emboli in almost all vascular spaces (blood and lymphatic). Multifocal liver necrosis with bile stasis. “Tumor morphology (including results of immunochemical staining) indicated intestinal cancer despite atypical liver changes.”
 - iii. Pancreas: marked autolysis. “Small emboli of cancer cells in the blood vessels”
 - iv. Lungs: “numerous emboli of cancer cells in blood vessels”, emphysema, tuberculous infiltrate with caseation necrosis.
 - v. Multiple other sites of massive metastasis of adenocarcinoma (pubic bone, vertebrae, lymph nodes)
 - vi. Diagnosis: “Natural death caused by the disease. Generalized malignancy (intestinal cancer with primary site difficult to localize – small intestine in the stomy region?) with massive metastases to the liver and regional abdominal lymph nodes and emboli in the vascular spaces, mainly in the lungs, was considered the primary cause of death.”
- 2. Right lung squamous cell carcinoma—Subject 021-0138-1002 on Day (b) (6)
 - a. 73 year old male with history of cigarette smoking
 - b. In 0.05/0.05 group
- 3. Left lung non-small cell carcinoma—Subject 021-0138-1011 on Day (b) (6)
 - a. 64 year old male with 30-year history of smoking 30 cigarettes per day
 - b. In placebo/0.05 group (“NT, PBO/TED” group)

Medical Reviewer Comment. A relationship between malignancy and teduglutide cannot be concluded based on these few reports, especially considering that all of these patients were at high risk for the type of malignancy with which they were diagnosed. It is unlikely that teduglutide was related to the lung cancers, which occurred in patients at very high risk. Lung pathology was not seen in the nonclinical studies, and GLP-2 receptors and nonclinical findings are mainly located in the GI tract.

GI Polyp-Related Events. GI polyp-related AEs (benign polyps) appear in Table 22. This table shows MedDRA terms, study identifier with country and treatment group, age/gender, severity, onset day representing totals days of study drug, and comments.

Table 22 GI Polyp-related adverse events

AE Preferred Term	AE Verbatim Term	Subject Number/ Country/ Treatment (mg/kg)	Severity/ Onset Day	Age/ Sex	Comments
Colonic polyp	Small polyp in sigmoideum	004-0138-0008/ Poland/ Teduglutide 0.05	Mild / 155	22/F	22-year-old female with verbatim term "small polyp in sigmoideum" occurring on treatment day 155 (3/2/06). There are 2 AE reports for this subject, the second of which was "GI tract adenoma" with verbatim term "large bowel adenoma" reported on 3/28/06 (005 treatment day 9). The pathology was reclassified to "hyperplastic colon polyp" in August 2008.
Intestinal polyp	Polyp growths (external peri-stomal area)	020-0109-1005/ USA/ Placebo	Severe / 79	48/F	47-year-old female with verbatim term "polyp growths (external peri-stomal area)" occurring on treatment day 79 (3/9/10). There are 2 "Intestinal polyp" AE reports for this subject, the second of which was reported on treatment day (b) (6). Subject discontinued participation on (b) (6) due to an AE (peri-stomal polyp growths).
Intestinal polyp ^a	Polipi at 20 and 40 cm from anus evidenced at colonoscopy	020-0207-1004/ Italy/ Teduglutide 0.05	Mild / 1	45/F	45-year-old female with verbatim term "polipi at 20 and 40 cm from anus evidenced at colonoscopy" occurring on treatment day 1 (4/9/10).
Rectal polyp	Rectal polyp	005-0103-0007/ USA/ Placebo/ Teduglutide 0.10	Mild / 189	58/F	50-year-old female with verbatim term "rectal polyp" occurring on treatment day 189 (5/24/07). Medical history of Crohn's disease.
Rectal polyp	Polyp in rectum	005-0145-0004/ Poland/ Placebo/ Teduglutide 0.10	Mild / 190	55/M	55-year-old male with verbatim term "polyp in rectum" occurring on treatment day 190 (10/26/07). Medical history of intestinal diverticulum. This subject had a non-treatment-emergent polyp during the PN stabilization phase of study 004.
Colorectal polyp ^b	3 Minipolyps in colon and rectum	021-0208-1001/ Italy/ Teduglutide 0.05/0.5	Mild / 230	49/F	49-year-old female with verbatim term "3 minipolyps in colon and rectum" occurring after 230 days on teduglutide when the patient discontinued because of weight loss.
Duodenal polyp	Duodenal polyp	021-0138-1011/ Poland/ Placebo/ Teduglutide 0.05	Mild / (b) (6)	64/M	64-year-old male with diagnosed lung cancer underwent upper GI endoscopy which revealed a small duodenal polyp. Subsequently the subject died from lung cancer.

AE = adverse event; F = female; GI = gastrointestinal; M = male

^aSubject 020-0207-1004, a 45-year-old female, enrolled in study 020 in the teduglutide 0.05 mg/kg/day treatment group had an AE of "Intestinal polyp" reported on treatment (b) (6). This was the result of the baseline colonoscopy and reported on the baseline day. Therefore, this subject is not included in the treatment-emergent GI polyp-related adverse event tables.

^bPolyps found on colonoscopy performed 36 days after discontinuing teduglutide.

[ref: ISS-4mo Update, Table 90, p. 330]

In Table 22, the top 3 rows indicate that polyps were found in 3 patients after treatment initiation (i.e., treatment-emergent) in the SBS placebo-controlled studies 004 and 020. However, the third case (020-0207-1004) was discovered on Day-1. Further details on this case are not available at this time. Pathology reports for all but 2 cases (021-0138-1011 and 020-0207-1004) in Table 22 are listed below:

- Subject 004-0138-0008: 0.05 group

- Pathology: Hyperplastic colon polyp (initially read as “Tubular adenoma with low-grade dysplasia”)
- Subject 020-0109-1005: placebo
 - Pathology: “Inflammatory polyp...small bowel, ... with associated ulceration and fibrosis”
- Subject 005-0103-0007: placebo/0.10 group
 - Pathology: “Fragments of benign focally hyperplastic colonic mucosa with focal ulceration, acute and chronic inflammation and reactive...consistent with rectal prolapse/solitary rectal ulcer syndrome/proctitis cystica profunda”
- Subject 005-0145-0004: placebo/0.10 group
 - Pathology: “Villous adenoma. Low grade dysplasia.”
- Subject 021-0208-1001: 0.05/0.05 group
 - Pathology: Colon Polyp (110 cm): “Tubular adenoma with low-grade dysplasia”; Rectal polyp: “Tubulo-villous adenoma with low-grade dysplasia”

Medical Reviewer Comment. The polyp in subject 020-0207-1004 is not likely related to teduglutide because of its Day-1 onset, and was likely missed at screening. No details on this case are available at this time.

In the extension studies, there were two patients with adenomas with villous features. Villous features have been associated with a higher risk of colonic malignancy compared to adenoma without these features.² The recently updated (2012) colonoscopic surveillance guidelines recommend 3-year interval colonoscopic follow-up for tubular or villous polyps, and indicate that since the 2006 version, there is now stronger evidence for this association and recommendation.³

Although the guidelines recommend 3-year follow-up for adenomatous polyps, they are for the general population. However, the teduglutide population might potentially be different in terms of risk for polyps. Labeling negotiations are to be held with the Applicant. At that time, I feel consideration should be given to the possible non-

² DAVID A. LIEBERMAN, DOUGLAS K. REX, SIDNEY J. WINAWER, FRANCIS M. GIARDIELLO, DAVID A. JOHNSON, THEODORE R. LEVIN. Guidelines for colonoscopy surveillance after screening and polypectomy: A consensus update by the US Multi-Society Task Force on colorectal cancer. GASTROENTEROLOGY 2012;143:844–857.

³ DAVID A. LIEBERMAN, DOUGLAS K. REX, SIDNEY J. WINAWER, FRANCIS M. GIARDIELLO, DAVID A. JOHNSON, THEODORE R. LEVIN. Guidelines for colonoscopy surveillance after screening and polypectomy: A consensus update by the US Multi-Society Task Force on colorectal cancer. GASTROENTEROLOGY 2012;143:844–857.

comparability of the teduglutide and general populations in terms of polyps; the frequency of colonoscopic follow-up in patients where polyps are or are not found; and the risk of the washout prep for colonoscopy in patients subject to fluid/electrolyte imbalance and multisystem organ pathology. Consideration might be given to doing a colonoscopy at one year in all GATTEX patients, or perhaps just those with a polyp at baseline. Consideration might also be given to performing more frequent colonoscopy than in the guidelines if polyps are found and less frequently if the patient has remained polyp-free after one year of teduglutide. These and other issues will be discussed with the Applicant with regard to labeling.

Cholecystitis. In the SBS Placebo-controlled trials, the following biliary events were reported [ref: ISS 4-month update, Table 91, p.333]:

- Placebo: None
- Teduglutide: 4/109 (3.7%)
 - Subject 004-0101-0007 (0.05 mg/kg/day, Canada): acute cholecystitis with gallbladder perforation (severe AE)
 - 32 year old male with onset at 103 days
 - History: Crohn's disease, cholelithiasis, jaundice, hepatitis, recurrent abdominal abscesses
 - Concomitant medications: ursodeoxycholic acid, levocarnitine, codeine, amitriptyline, pamidronate
 - CT scan—markedly distended gallbladder with wall thickening, gallstones, a 2-cm calculus in neck
 - Cholecystectomy 2 days later
 - Completed studies 004 and 005
 - Subject 004-0132-0008 (0.05 mg/kg/day, Great Britain): cholecystitis (SAE)
 - 38 year old male with repeat episodes with onset at 143 days through 153 days. Events lasted 3 to 15 days
 - History: Crohn's disease, colitis, cholestasis secondary to TPN
 - Abdominal U/S showed sludge, pericholecystic fluid, and findings consistent with acute cholecystitis
 - Discharged on ciprofloxacin and scheduled for elective cholecystectomy. Completed Study 004.
 - Subject 004-0138-0001 (0.10 mg/kg/day, Poland): cholecystitis (AE)
 - 49 year old female with onset at 12 days and lasted 2 days

- History: metabolic bone disease, renal colic. No history of cholestasis
- “No objective imaging or laboratory data is documented corroborating the diagnosis of cholecystitis”. Completed study 004 and did not enter Study 005
- Subject 020-0109-1001 (0.05 mg/kg/day, USA): acute cholecystitis (SAE)
 - 70 year old male with onset at 30 days and lasted 105 days
 - History of cholelithiasis and “sludge”
 - Cholecystostomy tube placed next day. Open cholecystectomy 3 months later. Completed study 020 and entered 021

In study 020, there was also a case of exacerbation of cholestatic hepatitis at 146 days that occurred the placebo group in a 49 year old female patient (Subject 020-0203-1004) with history of cholecystectomy.

In the open-label extension studies (005, 021), the following additional patients experienced gallbladder events [ref: ISS 4-month update, Table 93, p. 340]:

- Subject 005-0109-0001 (0.05/0.05 group, USA): acute cholecystitis (SAE)
 - 66 year old male after 10 days of teduglutide and lasted 5 days (repeat hospital admission for acute cholecystitis 3 months later when cholecystectomy was performed)
 - History: lower GI hemorrhage, deep vein thrombosis, aortic dissection, hypertension.
 - Concomitant medications: amlodipine, olmesartan, metoprolol and lisinopril
 - CT scan showed inflamed gallbladder
 - Cholecystostomy drainage tube placed on first episode. 3 months later cholecystectomy performed
- Subject 005-0145-0004 (placebo/0.10 group, Poland): cholecystitis (SAE)
 - 56 year old male after 153 days of teduglutide and lasted 12 days
 - History: MI, CABG, chronic renal failure, and atrial fibrillation.
 - Concomitant medications: quianrpil, vivacor, and theophylline
 - Admitted for severe event of “cholecystitis” and “chronic pancreatitis” that lasted 12 days. No other information on hospitalization available.
- Subject 021-0144-1001 (0.05/0.05 group, USA): acute cholecystitis (AE)
 - 40 year old female after 21 days of teduglutide in 021 and lasted 5 months
 - History: ulcerative colitis, pancreatic insufficiency, ileostomy, renal failure
 - Medications: loperamide, morphine, fludrocortisone, lasix, reclast

- Mild event of acute cholecystitis reported as an AE
- Subject 021-0155-1004 (0.05/0.05 group, Poland): cholestasis secondary to obstructed biliary stent (SAE)
 - 78 year old female after 197 days of teduglutide and lasted 2 days
 - History: jaundice, cholecystectomy with biliary stent, papillotomy, biliary tract calculosis, and 4 years of elevated ALP, GGT, AST, ALT (since 2006)
 - Concomitant medications: lactulose
 - Two weeks before this event, patient had worsening liver enzyme elevation—ALP from 430 to 567 IU/L; GGT from 286 to 534 IU/L; Dbili=6.0 micromol/L. On day of event, patient underwent ERCP--biliary stent obstructed and was removed. Six weeks later biliary function tests reduced (Dbili=0.1).
- Subject 021-0209-1002 (plac/0.05 group, France): cholecystitis
 - 82 year old male after 16 days of teduglutide and lasted 12 days
 - History: cholelithiasis, chronic renal failure
 - Concomitant medications: fluindione
 - Admitted to hospital for abdominal pain and fever. CT showed evidence of portal hypertension. Study drug discontinued. Patient dropped from study 5 days later. Gastroscopy on (b) (6) c/w cholelithiasis. Treated with cephalosporin, metronidazole.

Cholelithiasis was reported in the following subjects:

- Subject 021-0109-1004 (plac/0.05 group, USA): new onset cholelithiasis
 - 46 year old female after 171 days of teduglutide and lasted 1 day. “Bile duct stenosis” was reported a month later
 - History: Crohn’s disease, cholelithiasis, cholecystectomy (8 years ago), asthma
 - Concomitant medications: omeprazole, fluticasone, alprazolam and zoledronic acid
- Subject 021-0144-1003 (plac/0.05 group, USA): cholelithiasis
 - 64 year old male after 83 days of teduglutide and no end-date reported
 - History: diabetes mellitus, chronic renal failure
 - Concomitant medications: colecalciferol, esomeprazole, Procet, and dilaudid
 - On same day, also had abdominal distention, nephrolithiasis, hydronephrosis and hydroureter reported, and symptoms could have been attributable to ureter dysfunction
- Subject 021-0207-1001 (plac/0.05 group, Italy): new onset cholelithiasis

- 21 year old female after 206 days of teduglutide and lasted 101 days
- History: (volvulus), gastrectomy, biliary sludge, osteoporosis, multiple risk factors for cholelithiasis
- Concomitant medications: carnitine, ursodeoxycholic acid
- Rising liver enzymes and bilirubin. Study drug discontinuation. PN lipid content increased. Biliary ultrasound showed multiple gallstones with normal ducts (confirmed by MRI one month later).
- Cholecystectomy 4 months later (after event onset)

Medical Reviewer Comment. Rates of cholecystitis in the SBS placebo-controlled trials suggest a safety signal: 4% of patients on teduglutide and none on placebo. However, the numbers are small, and gallbladder/pancreas pathology is common in SBS patients on PN/I.V. support. However, the nonclinical finding of subacute inflammation of the gallbladder is not in consistent with cholecystitis in humans. Providers and patients need to be made aware of this potential safety issue.

GI Stenosis and Obstruction-Related Events.

In the SBS Placebo-controlled trials (004, 020), the following rates of GI obstruction were reported, and none required surgical intervention:

- Placebo group: 0/ 59 (0.0%)
- Teduglutide groups: 6/109 (5.5%): none required surgical intervention
 - Teduglutide 0.05 mg/kg/day: 3/77 (3.9%): onsets at 4-6 months
 - Subject 004-0101-0007 (SAE, Canada): small intestinal obstruction (SAE)
 - 32 year old male with onset at 156 days lasted 8 days
 - History: Crohn's disease, bowel obstructions, gallstones, cholestasis, cholecystectomy
 - Partial small bowel obstruction that resolved in 8 days. Cholecystectomy 2 months before this obstruction event occurred.
 - Subject 004-0155-0001 (SAE, Poland): colonic stenosis (SAE)
 - 49 year old male with onset at 176 days and lasted 10 days
 - History: chronic pancreatitis, deep vein thrombosis, pneumonia
 - Stricture of sigmoid colon seen on colonoscopy. Admitted on (b) (6) for endoscopic dilation of fibrous stenosis, patient underwent dilation of stricture (regular ring shaped narrowing). Pathology showed mucous membrane hyperemia and small hemorrhages in superficial lamina

propria. Event lasted (b) (6) days. In study 005 (345 days of teduglutide), repeat colonoscopy showed [asymptomatic] stenosis at same site, which was diagnosed as moderately severe colonic stenosis.

- Subject 020-0201-1004 (SAE, USA)
 - 54 year old female with multiple events with onsets at 120, 125, and 144 days
 - History of cholecystectomy, hypothyroidism, glucocorticoid deficiency, oophorectomy
 - Multiple events of “small intestinal stenosis” (worsening of jejunum stricture). Stricture was dilated after third event. Patient completed study 020.
- Teduglutide 0.10 mg/kg/day: 3/32 (9.4%): onsets at 1 day to 2 months
 - Subject 004-0115-0003 (SAE, USA)
 - 62 year old female with onset at 8 days
 - History of Crohn’s disease, stricturoplasty, cholecystectomy, GERD, GI hemorrhage
 - On 12/12/06 (2 days after initiation of teduglutide), patient developed abdominal bloating followed within the week (12/16/06) with inability to pass stool. CT scan showed dilated small intestine loops. Admitted on (b) (6) and study drug discontinued. Stoma size increased and broke seal of stoma bag. KUB c/w small bowel obstruction. Firm stool passed followed by loose stools. Obstruction resolved, stoma size decreased by 30%, and she was discharged on (b) (6). Early discontinuation secondary to a second small bowel obstruction event on (b) (6).
 - Subject 004-0132-0001 (SAE, Great Britain)
 - 53 year old female with onset at 49 days
 - History of Crohn’s disease, recurrent small bowel obstruction, intestinal perforation and abscess, cholecystectomy.
 - Hospitalized on (b) (6) with abdominal pain and diagnosis of subacute intestinal obstruction; abdominal X-ray reported as being normal. Study medication temporarily stopped. Treated with morphine, saline, cyclizine. Event resolved next day (b) (6), study medication was restarted, and patient was discharged. Completed study 004.
 - Subject 004-0156-0001 (moderate AE, Germany)
 - 39 year old female with onset at 1 day

- History of Crohn's disease, intestinal stenosis, cholecystectomy
- Early discontinuation from study secondary to infusion port infection

As of April-2012 in the SBS extension studies (Study 005 and Study 021), 8 additional patients experienced GI obstruction/stenosis, none of whom required surgical intervention. One patient underwent endoscopic dilation of stenosis. Time to onset of these events was 6 days to 7 months. Here are the patients with intestinal obstruction/stenosis, and all were on the teduglutide 0.05 mg/kg/day dose:

- Subject 005-0105-0001 (SAE, USA): partial small bowel obstruction
 - TED 0.05/0.05 group
 - Onset at 205 days
 - 55 year old female
 - History: multiple intestinal obstructions, cholecystectomy
 - Resolved after 4 days
 - Completed study 005
- Subject 005-0155-0001 (SAE, Poland): Restenosis of sigmoid colon
 - TED 0.05/0.05 group
 - Onset at 164 days
 - 48 year old male
 - History: chronic pancreatitis
 - Found during elective colonoscopy in study 004
 - Balloon dilatation twice within 6 months
- Subject 021-0106-1005 (Severe AE, Canada): Ileal stenosis
 - Placebo/0.05 group
 - Onset at 199 days
 - 37 year old female
 - History: Crohn's disease, cholecystectomy, duodenal ulcer and stenosis
 - Continued in study 021
- Subject 021-0106-1006 (Mild AE, Canada): Partial blockage of small bowel
 - Placebo/0.05 group
 - Onset at 226 days
 - 67 year old female
 - History: Crohn's disease, IBS, cirrhosis, hyperthyroidism, radiotherapy to thyroid and hypothyroidism
 - Continued in study 021

- Subject 021-0136-1013 (Severe AE, Denmark): bowel obstruction
 - NT/0.05 group
 - Onset at 6 days
 - 76 year old male
 - History: ulcerative colitis, carcinoid tumor
 - Early termination from “abdominal pain” 2 weeks later
- Subject 021-0138-1006 (SAE): stenosis of jejunorectal anastomosis
 - TED 0.05/0.05 group
 - Onset at 60 days
 - 41 year old male
 - History: congenital megacolon
 - Resolved in 2 weeks
 - Continued in study 021
- Subject 021-0201-1004 (Mild AE): worsening jejunal stricture
 - TED 0.05/0.05 group
 - Onset at 30 days
 - 54 year old female
 - History: cholecystectomy, glucocorticoid deficiency, hypothyroidism
 - Continued in study 021
- Subject 021-0209-1002 (SAE): bowel obstruction
 - Placebo/0.05 group
 - Onset at 16 days
 - 82 year old male
 - History: cholelithiasis
 - Diagnosis was based on hypertrophied ileal stoma

In the extension study obstruction/stenosis cases, one patient underwent single endoscopic dilation and there were no patients that received surgical intervention.

Medical Reviewer Comment. Although prior bowel surgery increases the risk for intestinal obstruction, it was not reported for the placebo group. And although intestinal obstruction was not reported in the nonclinical studies, it is not inconsistent with the mechanism of action of teduglutide (bowel wall thickening and/or stool dessication). Although somewhat reassuring that no patients in these trials required surgical intervention, the number of patients was small and additional data needs to be gathered for this and other adverse events in the post-market setting, especially considering the already critically limited intestinal capacity of these patients. This will be addressed in the REMS and patient registry.

Pancreatic Disease-Related Events. A total of 2 subjects in the placebo-controlled trials, both on teduglutide, had pancreatitis AEs as follows:

- Placebo: None
- Teduglutide: 2/109 (1.8%)
 - Subject 004-0115-0003 (teduglutide 0.10 group, USA): moderate AE; asymptomatic pancreatitis
 - 62 year old female with onset at 8 days and lasted 68 days
 - History: Crohn's disease, cholecystectomy, GI hemorrhage, multiple small bowel obstructions and surgeries confer higher risk for amylase/lipase elevation secondary to small bowel obstruction.
 - Diagnosis of pancreatitis was likely small bowel obstruction with secondary amylase and lipase elevations, although reported as pancreatitis initially
 - Presented with severe abdominal pain and failure to pass stool through stoma (12/16/06). Amylase and lipase had been normal 4 days earlier. At this presentation, CT and KUB showed dilated segments of small bowel most consistent with small bowel obstruction
 - 3 days later (12/19/06), patient developed elevation of amylase (to 600 IU/L) and lipase (to 588 IU/L). Stoma increasing to point where it broke seal of stoma bag
 - Passed large firm stool, stoma decreased in size, abdominal pain resolved, and patient began taking food orally.
 - Repeat amylase (93 IU/L) and lipase (82 IU/L) two months later
 - Subject 004-0155-0001 (teduglutide 0.05 group, Poland)
 - 48 year old male with onset at 113 days
 - History of chronic pancreatitis with ductal stenosis and pseudocyst
 - Amylase already elevated prior to baseline
 - After 113 days patient presented with abdominal pain
 - Abdominal ultrasound and CT: pancreatic head pseudocyst with mild dilation of intrahepatic biliary and common bile ducts c/w chronic pancreatitis.
 - A month later ERCP showed stenosis of papilla of Vater and distal duct of Wirsung and two pancreatic pseudocysts. Papillotomy and insertion of duct prostheses performed.

- Another month passed at screening visit for 005. ERCP showed occluded prosthesis so a new one was placed. Amylase and lipase levels at 005 screening were normal and remained so through 005.
- Final diagnosis was chronic pancreatitis during a simultaneous event of cholecystitis.

In the extension studies 005 and 021, there was a single case of chronic pancreatitis (005-0145-0004) with onset at 6 months, diagnosed in a 56 year old male in the placebo/TED 0.10 group; likely ongoing prior to teduglutide based on prior episodic amylase and lipase elevations. An acute pancreatitis episode occurred in another patient (TED 0.05 group) with onset at 15 months. Both patients had a prior history of pancreatitis.

Medical Reviewer Comment. These few pancreatitis cases are not convincing of a relationship between teduglutide and pancreatitis, and do not represent new-onset disease. Patients on chronic PN therapy are prone to pancreatic and other diseases, and one patient already had chronic pancreatitis prior to starting teduglutide. The other pancreatic case was in a patient with concurrent bowel obstruction with elevated amylase and lipase that were the basis of the diagnosis in this patient. On the other hand, the number of patients in these trials was small (orphan disease), but the nonclinical studies did show that teduglutide affected the pancreato-biliary system. In consideration of these issues and the potential seriousness of pancreatitis, physicians and patients need to be made aware of it.

Volume Expansion-Related Events. Based on its mechanism of action, teduglutide increases GI luminal fluid reabsorption into the circulatory system. Fluid imbalance is a common complication of PN in this population. General signs of fluid overload include weight gain, edema (e.g., peripheral, periorbital), bloating, pulmonary edema with or without dyspnea/hypoxia, jugular-venous distension, organomegaly, and frank heart failure. In the SBS placebo-controlled trials (004, 020), these MedDRA preferred terms were analyzed:

- Cardiac failure congestive
- Face edema
- Fluid retention
- Generalized edema
- Jugular vein distension
- Edema
- Edema peripheral
- Periorbital edema

- Fluid overload
- Weight increased

The following rates of fluid overload and weight gain were observed in the SBS Placebo-controlled trials [ref: ISS, Table 137, p. 447]:

- Fluid Overload
 - Placebo: 4/59 (6.8%)
 - Teduglutide 0.05 group: 9/77 (11.7%)
- Weight Increased
 - Placebo: 3/59 (5.1%)
 - Teduglutide 0.05 group: 4/77 (5.2%)

Also in the SBS Placebo-controlled trials, 2 teduglutide-treated subjects had an AE of “Cardiac failure, congestive” as follows:

1. Subject 004-0139-0009 (0.05 mg/kg/day): SAE of congestive heart failure (CHF) on day (b) (6)
 - a. 50 year-old female
 - b. Medications—pantoprazole, erythromycin. No thyroid supplement is documented for this patient.
 - c. Medical history—thyroidectomy, hyperparathyroidism, no cardiac history recorded, but tachycardia of 121 bpm was noted at screening and baseline.
 - d. Hospitalized on treatment day (b) (6) for congestive heart failure (CHF). Chest x-ray (CXR) revealed bilateral pulmonary edema. Echocardiography showed mild inferior hypokinesis and Grade-2 mitral insufficiency, normal function, no LV dilatation. Troponin level of <0.12 ng/mL and 1.15 ng/mL. Treated with bumetanide, perindopril, and atenolol. Discharged (b) (6) CXR (b) (6) days later (b) (6) was within normal limits. Discharged from study on (b) (6)
 - e. History and findings suggest possibility of undiagnosed hypothyroidism and/or cardiac dysfunction.
2. Subject 020-0109-1001 (0.05 mg/kg/day). Not reported as an SAE. Clinical details not available.

***Medical Reviewer Comment.** The data suggest a possible safety signal (12% vs 7%) for fluid overload, which is common in this population and not inconsistent with the mechanism of action. One of the two CHF cases was reported as an SAE, but occurred*

in a patient with likely cardiac dysfunction secondary to previously undiagnosed hypothyroidism. Nonetheless, patients in this population and their healthcare providers need to be made aware of the potential for fluid overload, especially those with any type of cardiac disease.

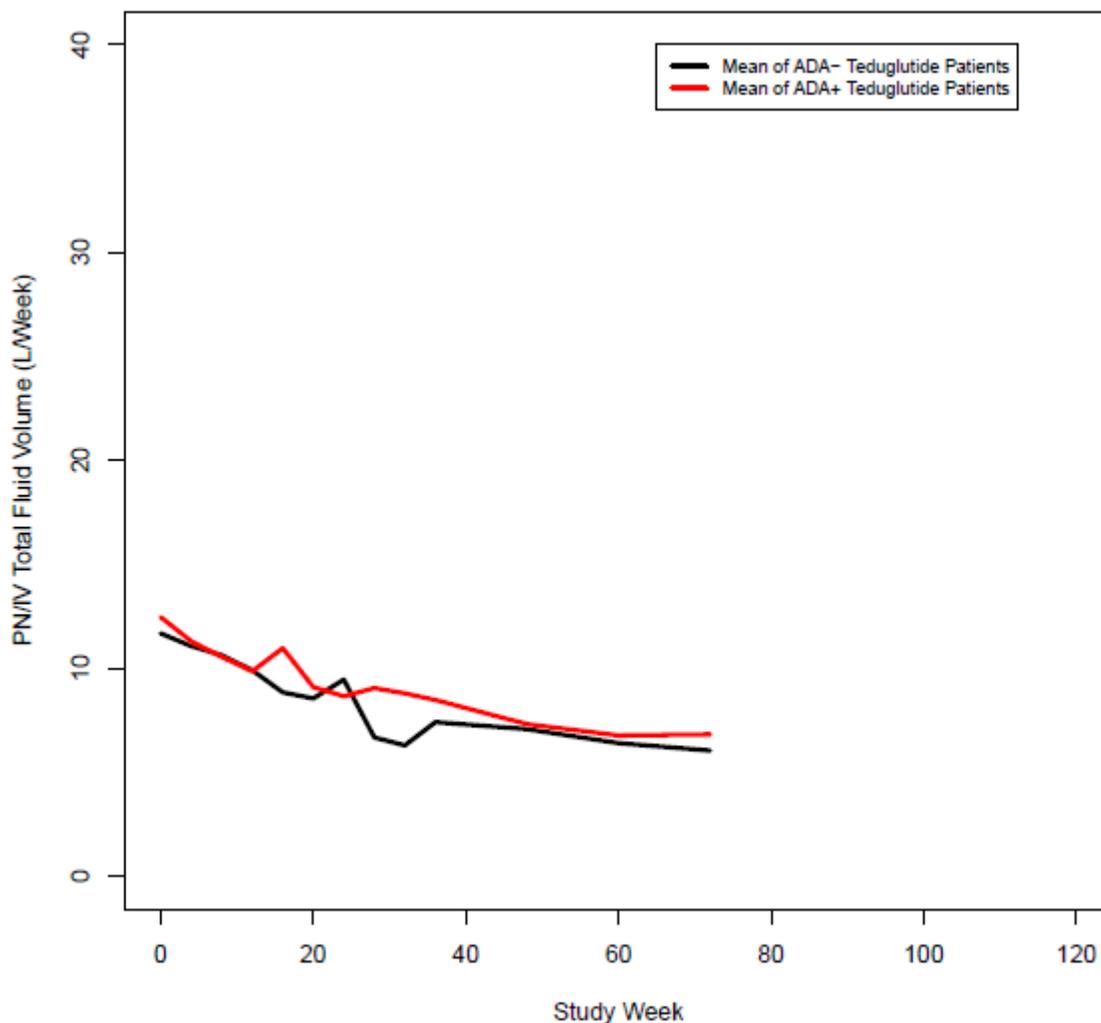
Immunogenicity-Related Events. Also see section 7.4.6 Immunogenicity. The following rates of anti-drug antibody (ADA) positivity were observed in trials 020 and 021:

- Month-3 (study 020): 0/16 (0%)
- Month-6 (study 020): 6/34 (18%)
- Month-12 (study 021): 14/51 (27%)
 - These patients were on placebo in study 020
- Month-18 (study 021): 13/34 (38%)
 - These patients were on teduglutide in 020 and 021

Cross-reactivity with endogenous GLP-2 was seen in 5/6 (83%) of patients.

Mean and individual PN volume in study 020 in antibody-positive (red) and –negative (black) patients were compared (Figure 8).

Figure 8 Mean PN/I.V. volume by antidrug antibody (ADA) positivity status



None of the 6 ADA+ subjects in study 020 study experienced AEs related to hypersensitivity reactions. In study 021, 3 of 27 ADA+ subjects experienced an injection site reaction but no other hypersensitivity reactions.

Medical Reviewer Comment. Although the ADA+ curve seems to lie slightly above the ADA- curve in Figure 8, the difference is small. From these data through approximately 18 months, the long-term effects on safety and efficacy of ADA cannot be determined. Continued study of the effect of ADAs on efficacy and safety will need to be done in the post-market setting in the patient registry. Additionally, if a patient fails to respond to teduglutide or loses efficacy while on it, ADA levels should be drawn and stored in the patient registry database.

Respiratory Tract Infections: Lower and upper respiratory tract infections were reported. None resulted in study discontinuation.

For lower respiratory tract infection in the SBS Placebo-controlled trials (004, 020), the following rates were observed:

- Placebo: 3/ 59 (5.1%)
- Teduglutide: 6/109 (5.5%)
 - 0.05 mg/kg/day: 4/ 77 (5.2%)
 - 0.10 mg/kg/day: 2/ 32 (6.3%)

Medical Reviewer Comment. For lower respiratory infection, there does not appear to be a safety signal based on nearly equal rates in treatment groups.

For upper respiratory infections (URI) in the SBS Placebo-controlled trials (004, 020), the following rates were observed:

- Placebo: 8/ 59 (13.6%)
- Teduglutide: 30/109 (27.5%)
 - 0.05 mg/kg/day: 20/ 77 (26.0%)
 - 0.10 mg/kg/day: 10/ 32 (31.3%)

The frequency of Crohn's disease history, splenectomy, asthma, and emphysema and concomitant corticosteroid use in subjects with URI-related AEs was no higher in the teduglutide group compared to the placebo group.

Medical Reviewer Comment. For upper respiratory infection, there appears to be a dose-response relationship. In most patients URI is not expected to be a serious clinical issue. Some patients with SBS could be immune compromised secondary to other concomitant medications as well as liver dysfunction. Therefore, this information should be included in the label.

Mood, Anxiety, and Sleep Disorder-Related Events. Teduglutide has the potential to affect absorption of other medications absorbed in the GI tract, such as benzodiazepines and psychotropic agents. In the safety database in this program, the following AEs by MedDRA Preferred Term (PT) were reported: agitation, anxiety, depression, dysthymic disorder, hypomania, insomnia, libido increased, nervousness, sleep disorder and suicide attempt.

In the SBS placebo-controlled trials (004, 020), the following rates for this class of events were observed:

- Depression, dysthymia, suicide attempt

- Placebo: 1 (1.7%): suicide attempt (SAE)
 - Subject 020-0218-1001: 55 year old male. Onset at 43 days. History: Crohn's disease, IBS, depression, low testosterone. Concomitant medications—doxepin, testosterone, clonazepam, codeine, fentanyl, oxycodone.
- Teduglutide: 2 (1.8%)
 - Subject 004-0101-0004 (teduglutide 0.05 group): 39 year old female. Depression. History—Crohn's disease, migraine, hypoglycemia. Concomitant medications—codeine, estradiol, fentanyl, morphine, sumatriptan. Completed Studies 004 and 005.
 - Subject 004-0111-0007 (teduglutide 0.10 group): 64 year old female. Depression. Onset after 8 weeks of teduglutide. History—ulcerative colitis, radiation enteritis, peripheral neuropathy. Concomitant medications—meclizine, oxybutynin.
- Insomnia, sleep disorder (no SAEs):
 - Placebo: None
 - Teduglutide: 5 (4.6%)
 - One subject with Crohn's disease and one with head injury on piracetam
- Anxiety, nervousness (no SAEs)
 - Placebo: None
 - Teduglutide (all at 0.05 mg/kg/day dose): 3 (2.8%)
 - Two of these patients had Crohn's disease and 2 had history of nervousness and/or depression

Broken out by benzodiazepine use, the following rates of "Cognition and attention disorders and disturbances" (MedDRA Preferred Term) were observed [ref: ISS, Table 82, p. 306/472] in the SBS Placebo-controlled trials:

- Placebo (n=109)
 - Benzodiazepine (n=5): 20.0% (1/ 5)
 - No benzodiazepine (n=54): 5.6% (3 /54)
- Teduglutide 0.05 mg/kg/day (n=134)
 - Benzodiazepine (n=28): 14.3% (4/ 28)
 - No benzodiazepine (n=106): 3.8% (4/106)
- Teduglutide 0.10 mg/kg/day (n=39)
 - Benzodiazepine (n=14): 21.4% (3/ 14)
 - No benzodiazepine (n=25): 4.0% (1/ 25)

Subject 004-0135-0009 (teduglutide 0.05 mg/kg/day) had been on a benzodiazepine for a few years prior to starting teduglutide. She was a 68-year-old white female with history of Type 2 diabetes mellitus, elevated GGT, frontal meningioma, epilepsy, ischemic hemorrhagic stroke, depression, anxiety, and insomnia. The patient experienced TESAEs of coma, drug level (benzodiazepine, prazepam) increase, and hypersomnia, which were all considered by the investigator to have been related to study medication (attributed to possibly increased absorption of prazepam). Prazepam had been started in Sep-2005. Her dose was increased by her general practitioner a year later. (b) (6) days later teduglutide was started. In her (b) (6) week on teduglutide, the patient reportedly experienced dramatic deterioration in mental status with episodes of spontaneously falling asleep. At the end of the week she was hospitalized in ICU for hypersomnia that progressed to coma (Glasgow 8/15) within a few days. Her benzodiazepine level was >300 mcg/L. Teduglutide and prazepam were discontinued, and after 5 days the coma resolved and the patient experienced agitation and hallucinations secondary to weaning of the benzodiazepine. the “coma abated”, neurologic status improved, and the patient slowly awakened. She was discharged on (b) (6) with a nearly normal state of consciousness (though increased periods of sleep). In (b) (6) the event of high level of benzodiazepine resolved.

***Medical Reviewer Comment.** The relatively sparse data (above) broken out by benzodiazepine use do not suggest a dose-response relationship because the placebo group had a higher rate of cognition/attention disorder events (20%) than the teduglutide 0.05 mg/kg/day group (14%). However, because of the potential risk of this class of events and how common they are in this population, patients and all of their healthcare providers need to be made aware of this potential effect of teduglutide on the absorption of other medications.*

Liver Disease-Related Events. In the SBS population, liver disease is very common. Cholestasis and elevated liver disease markers (AST, ALT, GGT, Alk Phos, bilirubin fractions) occur frequently. Consequently, quantitative assessment of the effect of teduglutide on the liver can be difficult to assess.

Here it is assessed by looking for temporal effects on liver function tests before and after starting teduglutide. In the SBS placebo-controlled trials, the following rates of liver-disease related events were observed:

- Placebo: 1/ 59 (1.7%)
 - Pretreatment elevation of ALT, AST, and bilirubin worsened during study, and hepatic fibrosis was found during study that had probably been probably long-standing
- Teduglutide: 4/109 (3.7%)

- 3 subjects with pretreatment elevations of liver enzymes and bilirubin values that persisted during the study

In the SBS extension studies, hepatic cyst infection and portal hypertension were also reported, both in study 021. In study 005, hepatic enzyme elevations were reported in 3 subjects, all on teduglutide 0.10 mg/kg/day and with baseline liver enzyme elevations. In study 021, there were 6 patients with AST and/or ALT elevations, all of whom had histories of the same including elevated baseline liver enzyme tests.

Medical Reviewer Comment. A safety signal is not suggested in these sparse data, especially in light of how common liver function tests are elevated in the SBS population on PN.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events appear in Table 23.

Table 23 Common AEs (in at least 5% of subjects on 0.05 mg/kg/day) and more frequent with teduglutide, SBS Placebo-controlled studies

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) [ref: ISS, Table 67, p. 238]

7.4.2 Laboratory Findings

The following laboratory tests were assessed during these trials: BUN, creatinine, albumin, bicarbonate, calcium, chloride, CRP, glucose, magnesium, phosphate, potassium, sodium, and uric acid. Markers for liver function and pancreatic enzymes such as ALP, ALT, AST, total bilirubin, GGT, amylase, and lipase.

Selected nutritional, pancreatic, biliary, and hepatic laboratory test results in the SBS Placebo-controlled trials are summarized in Table 24.

Table 24 Selected laboratory values (studies 004, 020)

Lab Test	Visit	Mean (SD)		
		Placebo	Teduglutide dose in mg/kg/day	
			0.05	0.10
Amylase IU/L	Baseline	96.4 (57)	87.2 (46)	84 (33)
	Week-24	94.3 (61)	89.5 (49)	84.2 (33)
	Change	-2.9 (28)	1.5 (37)	1.6 (19)
Lipase IU/L	Baseline	46.5 (25)	38.4 (19)	54.9 (42)
	Week-24	47.6 (31)	57.2 (70)	57.2 (34)
	Change	2.2 (19)	17.9 (65)	6.7 (26)
Albumin g/L	Baseline	41.5 (4)	41.0 (4)	38.3 (4)
	Week-24	39.8 (4)	39.8 (6)	37.5 (5)
	Change	-1.7 (3)	-1.3 (4)	-0.9 (4)
Calcium mmoL/L	Baseline	2.28 (0.12)	2.28 (0.13)	2.35 (0.11)
	Week-24	2.26 (0.12)	2.26 (0.15)	2.34 (0.11)
	Change	-0.037 (0.12)	-0.006 (0.16)	-0.012 (0.14)
Phosphate mmoL/L	Baseline	1.19 (0.2)	1.17 (0.2)	1.17 (0.2)
	Week-24	1.14 (0.2)	1.15 (0.2)	21.20 (0.2)
	Change	-0.053 (0.2)	-0.016 (0.3)	0.031 (0.3)
Glucose mmoL/L	Baseline	5.6 (1.0)	5.4 (1.1)	5.2 (0.7)
	Week-24	5.3 (0.8)	5.5 (1.5)	5.3 (0.8)
	Change	-0.25 (0.8)	0.14 (1.0)	0.10 (0.80)
Alk Phos IU/L	Baseline	154.6 (95)	155.8 (83)	158.9 (79)
	Week-24	142.4 (75)	132.0 (140)	136.7 (86)
	Change	-8.6 (60)	-22.3 (107)	-18.9 (67)
ALT (SGPT) IU/L	Baseline	41.8 (32)	44.6 (31)	50.2 (36)
	Week-24	39.8 (31)	29.8 (21)	42.2 (27)
	Change	0.3 (16)	-13.8 (21)	-7.3 (33)
AST (SGOT) IU/L	Baseline	34.4 (19)	34.9 (19)	41.1 (22)
	Week-24	25.5 (25)	26.6 (11)	35.2 (19)
	Change	1.6 (20)	-6.3 (12)	-4.8 (23)
Total Bilirubin mcmoL/L	Baseline	10.2 (8)	11.5 (9)	12.8 (22)
	Week-24	12.7 (13)	8.8 (6)	10.7 (12)
	Change	2.5 (8)	-2.5 (6)	-2.4 (12)
GGT IU/L	Baseline	85.8 (78)	76 (66)	78.9 (83)
	Week-24	82.7 (88)	61.5 (52)	81.0 (94)
	Change	-2.8 (44)	-11.4 (44)	7.2 (61)

[adopted from ISS-4mo Update, end-of-text Tables 10.1.2, 10.3.2]

Medical Reviewer Comment. Changes in these lab values are generally on the order of 2% and in the range of the size of the between-group differences.

7.4.3 Vital Signs

No clinically significant differences were observed between-groups.

7.4.4 Electrocardiograms (ECGs)

Across all studies, two subjects, both on teduglutide 0.05 m/kg/day, had endpoint ECGs categorized as Abnormal, Clinically Significant. These cases were as follows:

Subject 020-0106-1003. “72-year-old female with SBS and history of left atrial septal defect. ECG tracings were normal at screening, baseline and Week 4. ECG tracings showed a finding of right atrial enlargement at Weeks 20 and 24. A diagnosis and adverse event report of right atrial dilatation was made at the end-of-study visit, and the investigator deemed the event mild in severity and not related to teduglutide use; no treatment was given. The subject enrolled in the long-term study CL0600-021 and the event is ongoing.” [ref: ISS-4mo update, p. 274]

Subject 020-0147-1001. “40-year-old female with SBS and a negative cardiac history enrolled in the teduglutide 0.05 mg/kg/d group with Endpoint assessment of abnormal/CS. The ECG at screening is read as normal with ventricular rate of 68 bpm and QTc 465 ms (at the upper limit of normal). The Week 24 ECG shows “nonspecific ST abnormality” and “QT prolongation; the ventricular rate is 90 bpm and the QTc is 484 ms. This subject entered the study with a borderline prolonged QTc; the slightly longer QTc at endpoint may be an artifact of heart rate and correction formula. Review of the ECG tracings shows no significant differences in ST segment morphology between screening and Week 24. This subject likely has no clinically significant ECG changes from baseline to endpoint.” [ref: ISS-4mo update, p. 274]

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT study (Study C09-001) was conducted, in which the effect of teduglutide on cardiac repolarization (QTcF interval) was comparable to placebo.

Study CL0600-022. This was a double-blind, randomized, placebo-controlled, multiple dose (8 consecutive days) study in healthy subjects. Subjects received either placebo, 10 mg/d, 15 mg/d, 25 mg/d, 30 mg/d, 50 mg/d, or 80 mg/d teduglutide SC. Results were used to design the TQT study.

Study C10-003. This was a single center, randomized, double-blind, placebo-controlled, multiple dosing, parallel group study to assess the effects of teduglutide on gastric emptying in 36 healthy subjects. A total of 36 healthy subjects were randomized to receive 10 days of either once-daily 4 mg teduglutide (n=23) or placebo (n=13) as single daily SC injections for 10 days.

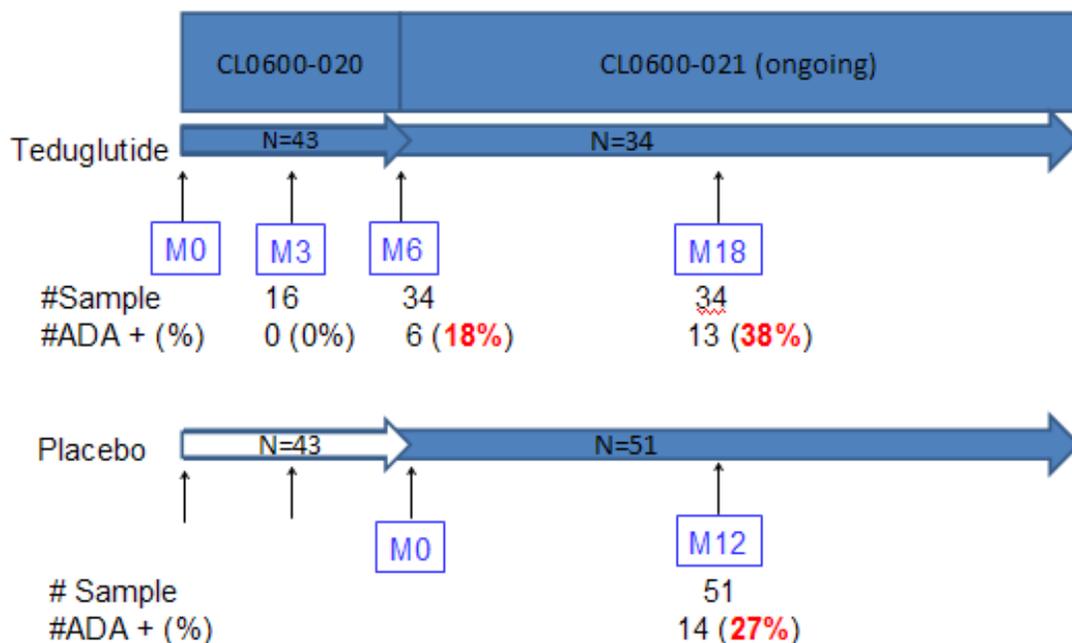
7.4.6 Immunogenicity

Immunogenicity. The immunogenicity assessment was based on a validated meso-scale discovery electrochemiluminescent (MSD ECL) assay with a drug tolerance of 1.5 ng/mL, which exceeds the observed mean C_{max} at the clinical dose of 0.05 mg/kg.

Through studies 020 (CL-0600-020) and 021 (CL-0600-021), the rate of development of anti-drug antibody (ADA) increased with the duration of treatment (18% at 6 months, 27% at 12 months, and 38% at 18 months). All patients had their first occurrence of anti-drug antibody positivity (ADA+) sometime after 12 weeks of teduglutide exposure. In Study 020, 0% (0/16) patients were ADA+ at Week-12, and 18% (6/34) were ADA+ at Week-24. Two of the 16 patients who were ADA- at Week-12 subsequently turned ADA+ at the Week-24 testing. Five of the 6 ADA+ patients at Week-24 had evidence of cross-reactivity to native GLP-2 protein. A single patient (Subject 0136-1002) was ADA+ at Baseline but remained negative through studies 020 and 021.

In extension study 021, 32% (27/85) patients became ADA+. Of the 34 subjects who entered study 021 from study 020, 8 subjects (in addition to the 6 who became ADA+ in study 020) became ADA+ in study 021. Thus based on the pooled data from studies 020 and 021, by 18 months of teduglutide exposure, 38% (13/34) of patients had become ADA+ (Figure 9). Because the placebo group did not receive teduglutide in study 020, it is portrayed as an open arrow in Figure 9.

Figure 9 Antibody positivity by months of teduglutide exposure (studies 020, 021)



M=month following initiation of treatment in Study 020

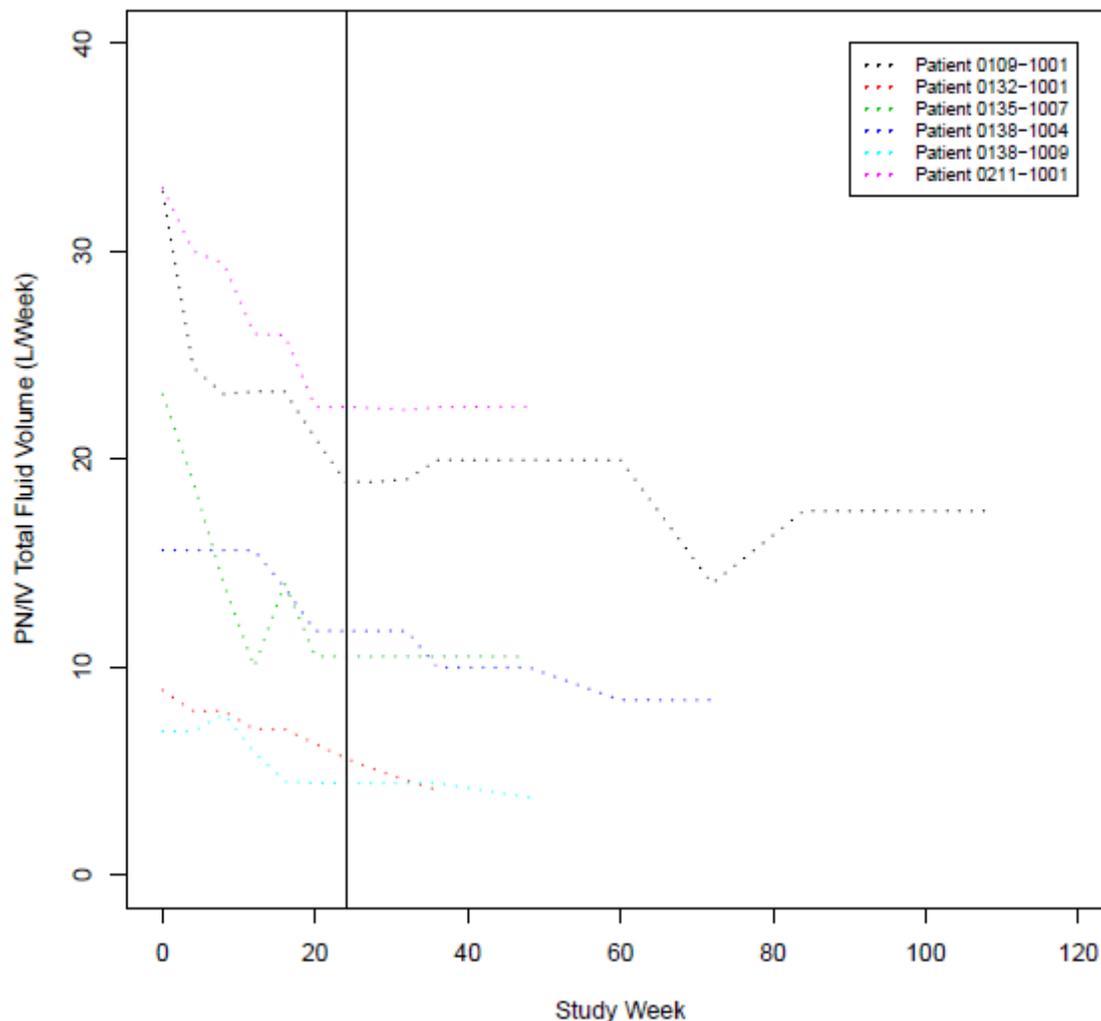
Red percentages in parentheses are percent of study population at that visit who were ADA(+)

No subjects in the SBS population developed neutralizing antibodies. However, circulating drug could have interfered with the neutralizing antibody assay, whose drug tolerance was 1.5 ng/mL, which exceeds the observed mean C_{max} of the 0.05 mg/kg dose.

The impact of ADA on PK has not been adequately assessed. The Applicant's population PK analysis was unsuccessful in evaluating the effect of ADA on teduglutide PK because of an inadequate design.

Regarding the affect of immunogenicity on efficacy, the 6 subjects who were ADA+ at Week-24 were primary endpoint responders (Figure 10). Additionally, in study 021, 25/26 patients who were ADA+ had experienced PN/I.V. reduction by their last dosing visit.

Figure 10 ADA(+) subjects' weekly PN/I.V. volume (Studies 020, 021)
Study CL0600-020/CL0600-021 – Average Weekly PN By Study Week



Medical Reviewer Comment. The effect of immunogenicity on PK has not yet been determined. At this time, there is no convincing evidence that immunogenicity adversely affects efficacy or safety, at least through 18 months of teduglutide exposure. In consideration of the favorable risk-benefit profile of teduglutide, it is acceptable for the Applicant to collect these data in the post-market setting. In the post-market setting, it will be required to continue to study ADA and its impact on safety and efficacy. If a patient fails to respond to teduglutide or loses efficacy while on it, ADA levels should be drawn and recorded in the patient registry.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See individual adverse events.

7.5.2 Time Dependency for Adverse Events

The rate of antibody development seems to increase with duration of exposure to teduglutide. See section 7.4.6 Immunogenicity.

7.5.3 Drug-Demographic Interactions

The effect of gender, age, and race on AE rates was examined, and the results are summarized in this section.

Gender. Of 232 patients in the SBS Efficacy and Safety studies, there were 128 females (95 on teduglutide) and 104 males (78 on teduglutide). The rate of AEs was slightly higher for females than males.

Age. In the SBS Efficacy and Safety Studies, about 13% (31/232) of patients in each treatment group were at least 65 years of age (9 patients were at least 75 years of age). The pediatric population has not been studied.

All subjects at least 65 years of age, regardless of treatment group, experienced an AE [ref: Table 72 in ISS-4mo Update]. Approximately 50% of subjects at least 65 years of age experienced an SAE. Whereas no patients on placebo had an AE leading to discontinuation, 20% of patients on teduglutide (same rate at each dose level) did. In general, AEs occurred more frequently in patients at least 65 years of age in the placebo group.

Race. In the teduglutide groups of the SBS Efficacy and Safety studies, 94.2% of subjects were White, 4.6% were Black, and 1.2% were classified as "Other". In the placebo groups, 94.9% were White, 3.4% were Black, and 1.7% were "Other". Over all AEs, there are sporadic single occurrences in the Black and Other categories. Because of the very small sample sizes, trends cannot be identified.

Medical Reviewer Comment. *There are too few patients to conclude whether there are any drug-demographic interactions.*

7.5.4 Drug-Disease Interactions

In the SBS Efficacy and Safety studies, the following percentages of study subjects had a history of Crohn's disease:

- Placebo: 15/ 59 (25%)
- Teduglutide: 33/109 (33%)

In the SBS Placebo-controlled studies, nearly all subjects with a history of Crohn's disease had at least one AE (100% teduglutide vs 93% placebo). In the placebo groups of the SBS Efficacy and Safety Studies, more subjects with a history of Crohn's disease experienced at least one AE (94%) compared to subjects without Crohn's disease (79%). All subjects (with or without Crohn's disease) in the teduglutide groups experienced at least one AE. In the teduglutide groups, slightly more patients (22% vs 15%) with Crohn's disease experienced an AE leading to discontinuation compared to those without Crohn's disease.

AEs that occurred in teduglutide subjects with rates at least 10% higher than placebo included abdominal pain, upper respiratory infection, nausea, abdominal distension, and injection site reactions.

7.5.5 Drug-Drug Interactions

Drug-drug interactions do not occur in this GLP-2 analog. However, teduglutide has the potential to alter the absorption of other drugs such as benzodiazepines because of its enhancement of intestinal absorption. See 7.3.5 Submission Specific Primary Safety Concerns (Mood, Anxiety and Sleep-related disorders).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See section 7.3.5 Submission Specific Primary Safety Concerns.

7.6.2 Human Reproduction and Pregnancy Data

The effect of teduglutide on human reproduction and pregnancy is unknown.

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no drug abuse potential directly related to teduglutide, other than its effect on the absorption of other drugs with abuse potential such as the benzodiazepines.

7.7 Additional Submissions / Safety Issues

There are no additional submission or safety issues other than those already presented.

8 Postmarket Experience

There is no postmarket experience with this drug because it is not approved at the time of this review.

9 Appendices

9.1 Literature Review/References

See footnotes.

9.2 Labeling Recommendations

The Applicant's proposed label already incorporates all of the major recommendations to date. The main issues were the risk of malignancy and polyps, gallbladder/pancreatic disease, intestinal obstruction, and fluid overload in cardiac patients. Baseline studies including endoscopies with polyp removal as well as biliary/pancreatic laboratory tests are specified, along with a schedule of follow-up (every (b) (4) 6 months for labs and no less frequently than every 5 years for endoscopy, and other investigations as needed for clinical management).

Medical Reviewer Comment. The issue of surveillance colonoscopy will be discussed with the Applicant in labeling discussions after finalization of this review. See earlier comment.

Selections from the Applicant's proposed labeling for the AEs of special interest (August 03, 2012 version) are as follows:

2.3 Monitoring to Assess Safety

A colonoscopy (or alternate imaging) of the entire colon with removal of polyps must be done within 6 months prior to starting treatment with GATTEX. Subsequent colonoscopies (or alternate imaging) (b) (4) recommended at intervals of no more than 5 years. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Patients must undergo initial (b) (4) laboratory assessments (bilirubin, alkaline phosphatase, lipase and amylase). Subsequent laboratory assessments are recommended every 6 months; if (b) (4) clinically meaningful elevation is seen, (b) (4)

Medical Reviewer Comment. The issue of surveillance colonoscopies is to be discussed in regard to labeling with the Applicant after finalization of this review. See earlier comments.

4 CONTRAINDICATIONS

[Redacted] (b) (4)

5 WARNINGS AND PRECAUTIONS

5.1 Acceleration of Neoplastic Growth

[Redacted] (b) (4)

5.2 Colorectal Polyps

(b) (4) colonoscopy [Redacted] (b) (4) of the entire colon with removal of polyps (b) (4) be done within 6 months prior to starting treatment with GATTEX. [Redacted] (b) (4)

[Redacted]

Medical Reviewer Comment. Colonoscopy surveillance to be discussed in relation to labeling after finalization of this review. See earlier comments.

5.3 Small Bowel Neoplasia

Based on [Redacted] (b) (4) benign tumor findings in the rat carcinogenicity study, patients should be monitored clinically for small bowel neoplasia. If a benign neoplasia is found, it should be removed. In case of [Redacted] (b) (4), GATTEX therapy should be discontinued. [see [Redacted] (b) (4) (13.1)]

[Redacted] (b) (4)

[Redacted] (b) (4)

5.6 Gallbladder and Bile Duct Diseases

Cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies.

(b) (4)

5.7 Pancreatic Diseases

Pancreatitis has been reported in clinical studies.

(b) (4)

5.8 Intestinal Obstruction

Intestinal obstruction has been reported in clinical trials.

(b) (4)

9.3 Advisory Committee Meeting

An FDA Advisory Committee Meeting was held on 16-Oct-2012. The results of that meeting were as follows, organized by question:

1. Primary Efficacy Endpoint:

Given that a response was defined as greater-than or equal to a 20% reduction in parenteral nutrition/ intravenous fluids, or PN/I.V., as used in Trial 020, discuss the clinical meaningfulness of this outcome in adult patients with short-bowel Syndrome (SBS).

Discussion: 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.

2. Efficacy Results:

VOTE: Considering all the efficacy data from Trials 004 and 020, do you agree that a clinically meaningful benefit has been demonstrated in adult patients with SBS treated with teduglutide? Please explain your answer.

Discussion: Unanimous agreement. 12 YES, 0 NO.

3. Safety Results:

a. Potential Tumor Promoting Concerns:

- i. Considering the potential tumor promoting effects of teduglutide, discuss the adequacy of the recommended safety monitoring described in the label proposed by the applicant for monitoring the development of malignancy for colon and other gastrointestinal tract sites.

Discussion. Members of the panel noted that the Applicant's recommendations for colonoscopy might be reasonable, as in a registry. With respect to small bowel cancers, currently there is not a good way to screen for them, so the current proposal involving clinical awareness and vigilance should be reasonable. Regarding the potentially long latency period for onset and identification of intestinal and non-intestinal (gallbladder, pancreas, lung, possibly others) malignancy, many members felt that the 7-year follow-up proposed in the REMS is probably insufficient; and that decades of follow-up would be better. One member stated that longer-term data related to malignancy were needed. One member mentioned that perhaps serial colonoscopy every two years with multiple biopsies looking for dysplasia is needed, and would provide a better way of assessing cancer risk.

- ii. Considering the extra-intestinal malignancies reported in the safety database, what additional safety monitoring would you recommend, if any, for patients receiving teduglutide?

Discussion. The committee felt that no additional scheduled safety monitoring would be needed. Rather, adherence to standard of care which is labwork every 3 to 6 months, history and physical exam, nutritional assessments, and imaging as needed should suffice.

b. Other Gastrointestinal-Related Safety Concerns:

Considering the potential side effects of teduglutide that include biliary disease, pancreatic disease, gastrointestinal stenosis and obstruction, discuss the

adequacy of the recommended laboratory and imaging studies described in the label proposed by the applicant.

Discussion. Members agreed that standard-of-care monitoring for these events is sufficient, consisting of liver and pancreatic enzymes every 3 to 6 months, clinical history and physical exam, and imaging as indicated by the status of the patient. It was mentioned that bile duct lesions are very difficult to identify ‘in advance’, and the pancreas is also hard to screen other than looking at the development of signs and symptoms and deciding to pursue further investigation (ie, imaging) based on that.

c. Immunogenicity Concerns:

Please comment on the potential long term safety risk, if any, associated with the cross-reactivity of anti-Gattex antibody to endogenous GLP-2. If evaluation of the long-term impact is warranted, please comment on which clinical endpoints to monitor.

Discussion. In general, the panel felt there was nothing to specifically recommend at this time. One member noted that he was reassured by the Applicant’s nonclinical data that there is no evidence of any phenotypic change to interfere with GLP-2 pathway. The Applicant stated they would test for antibodies for 6 months after discontinuation of teduglutide in Study 021.

4. Risk Evaluation and Mitigation Strategy (REMS):

VOTE: Do you agree that the proposed REMS element, a Communication Plan directed to prescribers, is adequate to address the safety concerns with teduglutide? Please explain your answer.

Discussion. 10 YES, 1 NO, 1 ABSTAIN. Those who voted “Yes” commented that teduglutide is generally a safe drug and the current REMS Communication Plan is appropriate and the registry can be done as a post marketing study. One member noted some concern with a registry in terms of required data collection and its enforcement in the registry. Another member mentioned that the plan needs to be not burdensome but more than just a mass mailing to physicians. Another member commented on the need for patient education to be clear and for the plan to be inclusive of patients.

The member who voted “No” commented that, although the outline for the prescriber is good, the REMS does not require evaluating the patient’s level of knowledge or informing the patient and care team as part of the evaluation.

One member abstained from voting as he does not know how physicians respond to mail.

5. Benefits-Risk Considerations:

VOTE: Do the benefits of teduglutide outweigh the potential risks in patients with SBS?
Please explain your answer.

Discussion. 11 YES, 1 NO. The NO vote mistakenly hit the NO button, so the vote was actually a unanimous 12 YES. All members agreed that the benefits outweigh the risks associated with teduglutide in the study population. Some members noted that half of the clinical benefit in these trials was from the PN/I.V. optimization/stabilization protocol. Another member commented that his YES vote only applies to this population and not to other conditions where teduglutide might be used off-label.

6. Post-Approval Studies:

If teduglutide is approved, describe any additional studies that you would recommend post-approval?

Discussion. Panel members expressed the need for a registry for colorectal and other cancers that follows patients for at least 10 years in addition to the REMS and post-marketing survey oversight. It was commented that there should be a mandatory registry and the frequency of reporting needs to be defined. One member noted the need for rigorous data collection, where compliance or participation would not be an issue. Besides safety surveillance, collection of data on quality of life and other behavioral assessments was also recommended. A few members also noted the importance of patient education, and recommended additional data in pediatrics. One member also wanted to see studies and data on pre- and post treatment colonoscopy and biopsies for dysplasia to see any premalignant changes.

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/s/

JOHN S TROIANI
10/31/2012

RUYI HE
10/31/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2: 020 Indication: treatment of SBS				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			SBS is treated the same worldwide
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	No worldwide marketing experience exists for teduglutide
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested based on Orphan drug status (no PREA obligation)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		Statistical Review has indicated that datasets for study 004 have not been submitted; nor have stratified analyses by gender/age/race been submitted
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			No conflicts
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ YES ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

John Troiani, MD, PhD	04-Jan-2012
Reviewing Medical Officer	Date
Ruyi He, MD	04-Jan-2012
Clinical Team Leader	Date

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

/s/

JOHN S TROIANI
01/09/2012

RUYI HE
01/09/2012