GIDAC Briefing Document

NDA:	203441
Applicant:	NPS Pharmaceuticals, Inc
Drug:	GATTEX®(teduglutide [rDNA origin]) powder for subcutaneous injection
Gastrointestinal Drug Advisory Committee Meeting	October 16, 2012
Location	White Oak, Maryland

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought teduglutide to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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I. Purpose of the Advisory Committee Meeting

The purpose of this Advisory Committee meeting is to discuss the safety and efficacy of the use of teduglutide (GATTEX) for the treatment of adult patients with Short Bowel Syndrome (SBS) to improve intestinal absorption of fluid and nutrients.

The Division of Gastroenterology in conjunction with the relevant review divisions in the Center for Drug Review and Evaluation has reviewed this NDA. Our preliminary findings regarding the primary efficacy data analyses and the identification of significant safety events of interest are in general agreement with those of NPS Pharmaceuticals, Inc. FDA hopes to benefit from advisory committee deliberations regarding the clinical importance/meaningfulness of the available efficacy data/measures especially as they relate to the intestinotrophic activity of teduglutide and its potential to accelerate neoplastic growth, including intestinal polyps; as well as the relevance of immunogenicity. We would appreciate the committee's thoughts regarding the risk benefit profile of this drug for treatment of adults with SBS. Additionally, in light of the issues raised above, discussion of the risk management strategy as proposed by the sponsor will be appreciated. (See Section IX. Issues for Committee)

II. Background

The applicant (NPS Pharmaceuticals, Inc.; previously, Allelix NPS Corporation) submitted NDA 203-441 for GATTEX (teduglutide), a new molecular entity (NME) that is a recombinant analogue of human glucagon-like peptide-2 (GLP-2). The to-be-marketed product is a sterile, single-use, 3 mL, glass vial containing 5 mg of teduglutide as a white lyophilized powder for reconstitution with 0.5 mL sterile water for subcutaneous (sc) injection (solvent provided in a pre-filled syringe). The recommended teduglutide dose is 0.05 mg/kg body weight.

Teduglutide is a 33 amino acid peptide that differs from GLP-2 in the substitution of alanine by glycine at the second position at the N-terminus. This substitution confers resistance to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) that results in a longer elimination half-life.

Teduglutide increases villus height and crypt depth of the intestinal epithelium. The applicant proposes that teduglutide accelerates intestinal adaption and enhances barrier function in the small intestine, thus enhancing absorption of fluids, electrolytes and nutrients, and reducing fecal fluid loss. Based on this mechanism of action, the applicant proposes that teduglutide would be supportive treatment for patients with SBS who are dependent on parenteral nutrition (PN).

Seriousness of Disease

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[1]:

> "Intestinal failure results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance. 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."

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 PN/I.V. 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 PN/I.V. support, it is unlikely the patient will be completely weaned from PN/I.V. support.[2]

Although lifesaving, PN/I.V. (parenteral nutrition/intravenous fluid) is associated with problems. These problems 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 PN/I.V. supplementation are associated with multiple long-term multi-organ system derangement ranging from mild to life threatening. In addition, being tethered to the infusion apparatus is a significant quality of life issue that directly affects mobility and lifestyle. Consequently, weaning PN/I.V. is a cornerstone of clinical management in SBS.

Intended population

The intended population for treatment with teduglutide is patients with SBS who are PN/I.V. dependent. There are approximately 40,000 patients in the United States who require total parenteral nutrition (TPN), and 26% of patients in the Oley Foundation Home TPN Registry had SBS[3]. 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). While use in children is possible, there is no

[1] 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

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

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

obligation under PREA for applicants of a drug or biologic with Orphan Designation to provide pediatric data at the time of submitting an initial marketing application.

Duration of treatment
The maximum duration of treatment with teduglutide in this development program is two years (24 weeks in the randomized efficacy trials plus up to 80 weeks in the open-label safety evaluation).

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

- **ZORBTIVE [somatropin (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 Bateriostatic 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

Only available in Europe:

REVESTIVE [teduglutide (rDNA) for subcutaneous injection; Class Name: GLP-2 Analog], Nycomed Danmark ApS) is proposed for the treatment of adult patients with SBS. The Committee for Medicinal Products for Human Use (CHMP) has recommended approval by the European Medicines Agency (EMA) as of June 21, 2012. A regulatory decision is pending from EMA.

III. Regulatory History

The following regulatory activity occurred for teduglutide:

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).
- 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. Immunogenicity to be monitored and a thorough QT study should be conducted (Study 001).

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 NPSP 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.

25 April 2011: Type B Pre-submission Meeting—clinical, nonclinical, submission logistics. Main points addressed:

- FDA recommended to delay submission until about 64 patients with at least 12 months of exposure are in the initial safety and efficacy databases
- NPS to characterize impact of immunogenicity on PK, efficacy, safety.

- 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 NDA."
- A pediatric waiver is not required based on Orphan Designation

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.

IV. Nonclinical 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, and *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.

V. Clinical Pharmacology

The pharmacokinetics (PK) of teduglutide was evaluated in both healthy subjects and patients with SBS. Patients with SBS had a lower drug exposure than healthy subjects. The overall summary of clinical pharmacology is presented below.

With the to-be-marketed concentration (10 mg/mL), teduglutide reached peak concentration 3-5 hours after subcutaneous (SC) administration. The median peak teduglutide concentration (C_{max}) was 36.8 ng/mL at 0.05 mg/kg/day SC dose. Teduglutide was rapidly eliminated with a mean terminal half life ($t_{1/2}$) of approximately 2 hours. No accumulation of teduglutide was observed following repeated daily SC administration. Dose proportionality was demonstrated over the range of 0.05 to 0.40 mg/kg both in terms of the maximal plasma concentration and the exposure measured as the area under the concentration-time curve of teduglutide. The exposure was similar after SC injection at the abdomen, the thigh, and the arm.

Following IV administration in healthy subjects, teduglutide plasma clearance (127 mL/hr/kg) was roughly equivalent to the GFR, suggesting that teduglutide is primarily cleared by the kidney. The mean volume of distribution at steady state (103 mL/kg) was similar to blood volume.

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.

Special Populations

In patients with moderate to severe renal impairment and end stage renal disease (ESRD), dosage reduction by 50% is recommended, because of decreased renal clearance. The primary PK parameters of teduglutide increased up to a factor of 2.6 ($AUC_{0-\infty}$) and 2.1 (C_{max}) in ESRD patients compared to healthy subjects.

In patients with moderate hepatic impairment, no dose adjustment is necessary because teduglutide C_{max} and AUC were only slightly lower (~10% to15%) compared to healthy matched control patients. Teduglutide PK was not assessed in severe hepatic impairment.

Age and gender did not have a significant effect on the PK of teduglutide.

QTc Prolongation

No significant QTc prolongation was detected at a supra-therapeutic teduglutide dose of 20 mg in the TQT study.

Drug-Drug Interaction (DDI)

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

C_{max} at the clinical dose of 0.05 mg/kg. This is acceptable given teduglutide is not a pro-inflammatory cytokine or cytokine modulator although the relevance of *in vitro* studies to *in vivo* setting is unclear. Additionally, teduglutide was neither a substrate nor an inhibitor of P-gp at concentrations above 2000 ng/mL (P10-005).

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

Immunogenicity

Overall, the immunogenicity incidence rate increased with the duration of treatment (18% at 6 months, 27% at 12 months and 38% at 18 months) and the majority of patients had the first occurrence of anti-drug antibody (ADA+) finding at 6 months after treatment initiation. Among 34 patients who were treated with teduglutide in both the pivotal study and the extension study, 6 patients tested ADA + at baseline (of which 5 continued to be ADA+) in the extension study and 8 additional patients became ADA+ post-baseline. The incidence rate was 38% (13/34) for patients who received teduglutide treatment for the duration of 18 months. Among 51 patients who initiated teduglutide treatment in the extension study, 14 patients were ADA+ (14/51, 27%) during the extension study after teduglutide treatment of 12 months.

Anti-teduglutide specific antibodies showed evidence of cross reactivity against the native GLP-2 protein in 5 out of 6 ADA+ patients at 6 months post treatment in the pivotal study. It has not been established if these antibodies are neutralizing because the assay is uninterpretable in the presence of circulating drug. The data regarding the timing of administration of teduglutide and the collection of the samples was not captured. Therefore, we are unable to determine whether or not the antibodies are neutralizing. (See Hypersensitivity Reactions in Safety Section below)

In order to explore this issue, we analyzed the average weekly response in Study 020 and Study 021 for those six patients who had a positive ADA at month 6. In general the weekly trend improved for all of these patients and appeared to stabilize in the extension study. This was similar to the mean response in the other patients who did not have an ADA positive status at week 24.

The impact of ADA on PK is unknown as it has not been adequately assessed. All ADA+ patients were responders during the controlled treatment period; however, the long term impact is unknown.

VI. Efficacy

Efficacy was assessed using the data from the two SBS placebo-controlled trials (Study 004 and Study 020). Each of these studies had a non-randomized open-label extension study (Study 005 and Study 021, respectively). These studies are listed in Table 1. These were multinational trials conducted in the US, Canada, and Europe.

Table 1 SBS Efficacy and Safety Trials

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 patients 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 related to PN volume reduction and duration
021 (25 sites) Open-label extension of 020	09/21/09 to ongoing	Open-label	A. Ted 0.05 mg/kg/day (88)	2 years	Patients 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 to 2 different doses	A,C. Ted 0.05 mg/kg/day (6+25=31) B,D. Ted 0.10 mg/kg/day (7+27=34)	28 weeks	Patients who completed or stopped dosing (due to ADR) in 020	Long-term safety

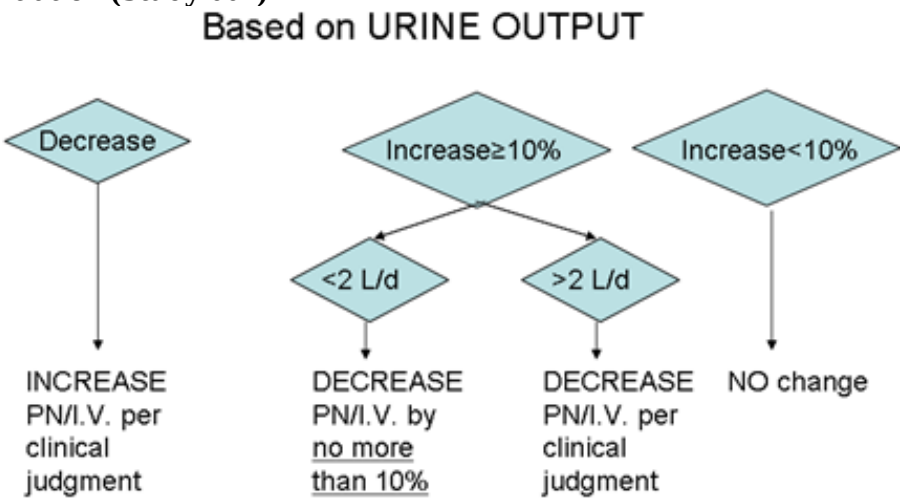
[Ref: Adopted from Applicant's ISE, Table 3.1, p 24/124.]

Study 004 and Study 020 were conducted sequentially, and the preliminary results of 004 were available during discussions of the design of the primary endpoint and statistical analysis 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.

Study 004 had a different fluid optimization/stabilization algorithm to guide the clinicians in the selection of PN/I.V. fluid administered during the trial. 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 (Figure 1). In Study 020, an additional fluid adjustment occurred at Week 2.

Figure 1 PN/I.V. adjustment algorithm based on urine output after treatment initiation (Study 004)



In Figure 1, note that the diamond boxes (decision tree nodes) are for urine output percent change (decrease versus <10% versus ≥10%) and absolute urine daily volume (<2L/day versus >2L/day). For 020, a similar fluid weaning algorithm was used, except that the first fluid adjustment in 020 occurred at Week 2 rather than Week 4; and up to 30% volume reduction was permitted in 020 (compared to 10% in 004). The weaning algorithm in 020 was as follows:

- Increase PN/I.V. volume for urine output <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 reason for the 10% limitation in 004 was to prevent dehydration. When dehydration turned out not to be a significant problem in 004, the 30% limit was specified.

Efficacy Results (Study 004, Study 020)

This section presents the efficacy results of Study 004 and subsequent Study 020. First, Study 004 and Study 020 are discussed together, since the null efficacy results of Study 004 affected the design of Study 020. Then efficacy results from Study 004 are presented, followed by Study 020 results.

Efficacy 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 ≥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
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.

Based on the preceding considerations during the design of Study 020, 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.

Efficacy Results, Study 004

Study 004 contained 3 arms, and there were two dose comparisons to placebo for 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 endpoints is listed below with additional descriptions following.

1) Primary endpoint: graded categorical response
2) Key secondary endpoint (PRIMARY ENDPOINT IN 020 STUDY): Number and percentage of patients who demonstrate a response at Week 20, and who maintain that response through Week 24. Response is defined as the achievement of at least a 20% reduction from baseline in weekly PN volume. The weekly actual PN/IV volume will be used in the analyses.
3) Other secondary endpoints in the following order
    a. Number and percentage of patients who achieve at least a one day reduction in weekly PN
    b. Absolute reduction from baseline in weekly PN kilocalories
    c. Absolute reduction from baseline in weekly volume of PN
    d. Change from baseline in plasma citrulline at dosing Week 24

The 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 2, which allows an integer score to be calculated for each patient based on response at Weeks 16, 20, and 24. Recall that this primary endpoint was amended to replace the original "≥20% responder" primary endpoint which was moved to the key secondary efficacy endpoint in the hypothesis testing order.

To use Table 2 first note that the column headings would be more accurate as "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 patient, 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". The integer at the intersection of this row and column is the graded response score for this patient.

Table 2 Primary efficacy endpoint (graded response score) in Study 004

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

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

The graded response score was analyzed using ranks-ANCOVA, which is for ordinal data. However, this scoring system is not ordinal. A 100% reduction at Weeks 20 and 24 (last column) and a <20% reduction at Weeks 16 to 20 (first row) is scored as a 3. However, a 4 (should be better than a 3) can be achieved with only a 40% reduction at Weeks 16, 20, and 24 (second to last column and last row). Because a 3 can actually be 'better' than a 4 violates the ordinality assumption and the ranks analysis procedure. Other similar examples can also be found in this table.

The results for trial 004 in the pre-specified efficacy hypothesis testing order were as follows:

1. **Primary**: an ordered categorical (or graded) response score for the 0.10 mg/kg/day group versus placebo
    i. Teduglutide 0.10mg vs placebo: p=0.161 (rank-ANCOVA):

    TESTING STOPS HERE. Statistical significance was not demonstrated and hence all subsequent reported p-values are deemed exploratory in nature.

    ii. Teduglutide 0.05mg vs placebo: p=0.007 (rank-ANCOVA) significance not established due to prespecified hierarchical multiplicity adjustment testing strategy.

The distribution of graded response scores in Study 004 is shown in Table 3.

Table 3 Distribution of graded response scores (Study 004, ITT)

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

PN/I.V. = parenteral nutrition/intravenous fluids

Note: Subject # 0126-0001 was missing the baseline value and could not be ranked.

2. **Key Secondary**: ≥20% reduction from Baseline in weekly PN/I.V. volume at Weeks 20 and 24
    i. Result *[ref: CSR for Study 004]*
        a) Teduglutide 0.10 mg/kg/day group versus placebo: p=0.172 (Fisher's exact test): 8/32 (25%) vs. 1/16 (6.3%)
        b) Teduglutide 0.05 mg/kg/day group versus placebo: p=0.005 (Fisher's exact test): 16/35 (45.7%) vs. 1/16 (6.3%)
            1. Applicant reanalysis using methods of Study 020 gives: 16/35 (45.7%) vs. 1/16 (6.3%): p=0.009

The key secondary endpoint (20% response) is shown in Table 4

Table 4 Key secondary endpoint in Study 004: Responder endpoint

	Treatment Group, n (%) of subjects			
		Teduglutide		
Binary Responder Status	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 32	Total N = 67
Response ≥ 20% PN Reduction from Baseline to Week 20 and maintained to Week 24.				
Responders	1 (6.3)	16 (45.7)	8 (25.0)	24 (35.8)
Non-Responders	15 (93.8)	19 (54.3)	24 (75.0)	43 (64.2)
95% CI of % Responders	0, 18.1	29.2, 62.2	10.0, 40.0	
Difference from Placebo for % Responders		39.5	18.8	
p-value for Treatment Comparison		0.009	0.238	
ANCOVA (on the rank) test:			**p-value***	
0.10 mg/kg/d teduglutide vs. Placebo			0.172	
0.05 mg/kg/d teduglutide vs Placebo			0.005	
0.10 mg/kg/d teduglutide vs. 0.05 mg/kg/d teduglutide			0.053	

Note: Treatment comparisons for difference from placebo are based on Fisher's Exact test

* Test Statistic is based on Pairwise rank ANCOVA after adjustment for the Baseline PN consumption level and Baseline PN volume as a covariate. Subject # 0126-0001 is missing Baseline and cannot be ranked. Therefore, this subject is not included in the calculation of the test statistic for Rank ANCOVA 0.05 mg/kg/day – Placebo and 0.10 mg/kg/day – 0.05 mg/kg/day.

Source: Table 14.2.2.15, Listing 16.2.6.9

[ref: CSR for 004, Table 11-9]

3. Other Secondary Endpoints

1) Number and percentage of patients who achieved at least a 1-day reduction in weekly PN (Table 5)
2) Absolute reduction from Baseline in weekly PN kilojoules (transformed from kilocalories). For results see Applicant background package.
3) Absolute reduction from Baseline in weekly volume of PN
   - Results (Week 24):
     a) Teduglutide 0.10 mg group: 2.5 L decrease
     b) Teduglutide 0.05 mg group: 2.5 L decrease
     c) Placebo: 0.9 L decrease

In Study 004, the mean PN/I.V. volumes at Baseline and Week 24 are as follows:

- 0.10 group
  - 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
- 0.05 group
  - 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
- Placebo group

- 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

The results for the one-day reduction endpoint are shown in Table 5.

Table 5 One-day reduction in PN/I.V. (Study 004)

	Treatment Group, n (%) of subjects			
		Teduglutide		
Response Status	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 32	Total N = 67
Yes	4 (25.0)	11 (31.4)	3 (9.4)	14 (20.9)
No	12 (75.0)	24 (68.6)	29 (90.6)	53 (79.1)
95% CI of % Responders	3.8, 46.2	16.0, 46.8	0.0, 19.5	
Difference from Placebo for %Achievers		6.4%	– 15.6%	
p-value for Treatment Comparison		0.749	0.201	
ANCOVA (on the rank) test:			**p-value**	
0.10 mg/kg/day teduglutide vs. Placebo			0.120	
0.05 mg/kg/day teduglutide vs. Placebo			0.684	
0.10 mg/kg/day teduglutide vs. 0.05 mg/kg/day teduglutide			0.031	

Note: Treatment comparisons for difference from placebo are based on Fisher's Exact test.
*Test statistic is based on Pairwise rank ANCOVA after adjustment for the Baseline PN consumption level and Baseline PN volume as a covariate.
Source: Table 14.2.3.13, Listing 16.2.6.9

[ref: CSR for 004, Table 11-10]

The Applicant also did an analysis of change in the "fluid composite effect" (defined as PN/I.V. volume + Oral Fluid Intake volume – Urine Output volume). See Applicant background package. However, FDA questions the validity of this analysis because fluid composite effect as defined here does not account for stool fluid output and other fluid ingestion.

Efficacy Results, Study 020

The following results are in the prespecified statistical testing order:

1. **Primary endpoint**: percent responders (at least 20% reduction by Weeks 20 and 24)

The primary efficacy hypothesis test result was statistically significant (p=0.002) as shown in Table 6**.**

Table 6 Primary efficacy results of Study 020

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

N, n = number

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

[ref: ISE, p. 32]

2. **Secondary endpoints**:

a. Percent change from baseline in PN/I.V. volume at Week 24.

In 020, the mean PN/I.V. volumes at Baseline and Week 24 are as follows:

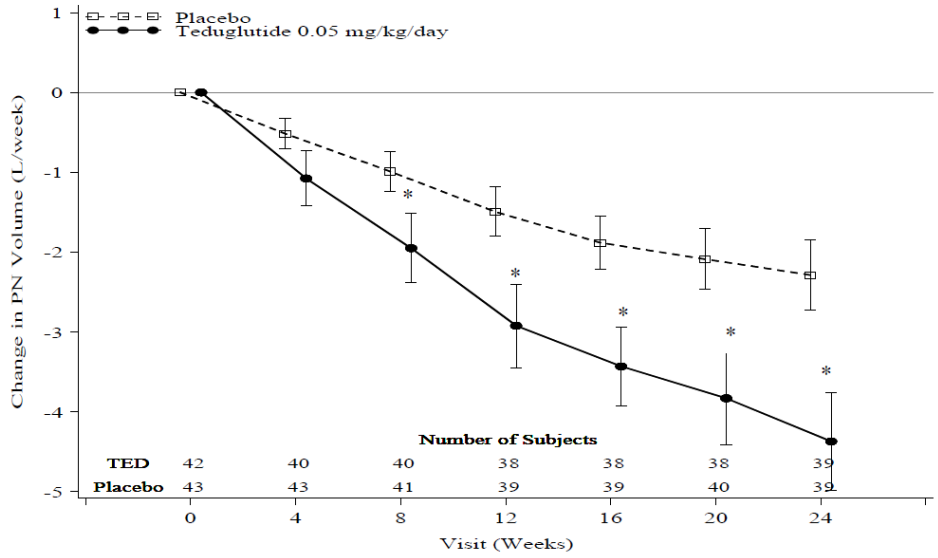
- 0.05 group
  - Baseline (n=39 completers): 12.92 L/week (n=43 randomized and dosed once: 12.45 L/week)
  - Week 24 (n=39 completers): 8.55 L/week
- Placebo group
  - Baseline (n=39 completers): 13.20 L/week (n=43 randomized and dosed once: 13.37 L/week)
  - Week 24 (n=39 completers): 10.91 L/week

b. Absolute change from baseline in PN/I.V. volume at Week 24

A plot of absolute PN/I.V. volume change from baseline is shown in

Figure 2. Mean absolute change from Baseline in PN/I.V. volume at Week 24 was greater in the teduglutide group compared with placebo (-4.4L/week and -2.3L/week, respectively; $p<0.001$, completers analysis).

Figure 2 Absolute change (+/- SE) in PN/I.V. volume (L/week)



L=liter; SE=standard error, TED=teduglutide
* p < 0.05
[ref: CSR for Study 020, Fig 11-2]

c. Patients achieving at least 20% reduction in PN/I.V. volume by duration (0, 1, 2, 3+ days)

d. Patients with at least 20% or 2L reduction in PN/I.V. volume at Weeks 20 and 24

The results for the one-day reduction in PN/I.V. volume at week 24 was 53.8% (21/39) for patients receiving teduglutide 0.05 mg/kg/day and 23.1% (9/390 for patients receiving placebo).

In Study 020 1 patient came off PN/I.V. by Week 24; it was because of hospitalization and catheter replacement. On the other hand, in Study 004, there were 2 patients who were actually weaned completely off PN/I.V., both in the teduglutide group.

The Applicant also did an analysis of change in the "fluid composite effect" (defined as PN/I.V. volume + Oral Fluid Intake volume – Urine Output volume). See Applicant background package. However, FDA questions the validity of this analysis because fluid composite effect as defined here does not account for stool fluid output and fluid content of ingested food.

In summary, 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 findings in 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.

Efficacy Results in Open-label Extension Studies (Study 005, Study 021)

For Study 005, the main efficacy results were *[ref: Applicant ISE. P.54-6]*:

- Response Maintainers: 75% (18/24) of patients in the 1-Year Active Group (patients treated with teduglutide in both Study 004 and Study 005) maintained 'response' from Study 004 through Study 005 in each treatment subgroup (12/16 in 0.05 mg/kg/day group and 6/8 in 0.10 mg/kg/day group).
- Mean reduction of PN/I.V. volume from baseline to Week-28 (of Study 005):
    - Teduglutide 0.05 mg group: 4.9 L/wk reduction (57%)
    - Teduglutide 0.10mg group: 3.3 L/wk reduction (27%)
- In the 1-Year Active Group (received teduglutide in both studies 004 and 005 for one year): 68% (17/25) patients in the 0.05 mg/kg/day group and 37% (10/27) in the 0.10 mg/kg/day group achieved at least a 1-day reduction in PN/I.V. fluid use.
- 1 patient was completely weaned off PN/I.V. during Study 005
    - The 2 patients previously weaned off PN/I.V. in Study 004 did not require PN/I.V. during study 005.

For ongoing Study 021, the main efficacy results (interim report) are *[ref: Applicant ISE. P.54-6]*:

- 7 patients were completely weaned off PN/I.V. during study 021 (cutoff 31 May 2012)
- Teduglutide/Teduglutide
    - Month-6 of Study 021 (total 12 months of teduglutide): 91% (31/34) response rate (at least 20% reduction in baseline PN/I.V.)
- No Treatment, Placebo/Teduglutide
    - Month-6 of Study 021 (total 6 months of teduglutide): 40% (17/43) response rate (at least 20% reduction in baseline PN/I.V.)

For Study 005 and Study 021, days reduction of PN/I.V. are summarized in Table 7.

Table 7 Days reduction in PN (Study 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]

Eight teduglutide patients were weaned completely off PN/I.V. in the SBS long term extension trials.

Efficacy Summary

The benefits of Gattex® include its ability to reduce parenteral nutrition requirements in patients with Short Bowel Syndrome. In the pivotal study (Study 020), the proportion of teduglutide-treated patients achieving a 20% reduction of parenteral nutrition at Weeks 20 and 24 was statistically significantly different from placebo. Treatment with teduglutide was associated with a 4.4 Liter/week (L/wk) reduction in parenteral nutrition requirements (from a pre-treatment baseline of 12.45 L/wk) versus 2.3 L/wk (from a pre-treatment baseline of 13.37 L/wk) for placebo at 24 weeks. More patients (53.8%) on teduglutide compared to placebo (23.1%) were able to obtain at least a 1-day reduction in parenteral nutrition. In Study 004, two patients were weaned off parenteral nutrition/I.V. In the extension studies to-date (021 ongoing), an additional 8 patients have been weaned off PN/I.V. Key secondary endpoint analysis of data from Study 004 supports the efficacy findings of Study 020.

The clinical meaningfulness of the primary outcome measure is the subject of this GIDAC (October 2012). However, during the European Medicines Agency expert group meeting of the CHMP (May 8, 2012) experts concluded that reduction in parenteral fluid requirements was clinically meaningful in this population. The CHMP issued a positive opinion for granting Marketing Authorization on June 21, 2012 and the Commission adopted this decision on August 30, 2012 granting marketing authorization for “Revestive-teduglutide”, and an orphan medicinal product for human use.

VII. Safety

In this section, the safety results are presented. For purposes of identifying safety signals, data from the SBS placebo-controlled studies (Study 004, Study 020) are presented. Additionally, data from the SBS extension studies (Study 005, Study 021) are shown.

Overall, 566 (safety population) patients were exposed to teduglutide and 198 to placebo across 15 clinical studies. Exposure statistics for all patients exposed to teduglutide (n=566, safety population) are as follows:

- Mean duration of exposure to teduglutide: 16 weeks
- Person-years of exposure: 168 person-years
- Exposure in SBS Efficacy and Safety studies : 142 person-years

The distribution of exposure in these 566 teduglutide-treated patients was distributed as follows:

- 299 patients in the clinical pharmacology studies
  - 89 (16% of 566) for less than 6 months
  - 135 (24% of 566) for at least 6 months but no more than 12 months
  - 75 (13% of 566) for at least 12 months
- 173 patients in the SBS Efficacy and Safety trials
- 94 patients in other studies (Crohn's Disease)

In the SBS Placebo-controlled trials (004, 020), exposure to teduglutide appears in Table 8

Table 8 Exposure to teduglutide in SBS Placebo-controlled Trials (Study 004, Study 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%)

In terms of discontinuation because of an AE, the following numbers of patients were reported in the SBS placebo-controlled studies (Table 9).

Table 9 Discontinuations from AE, SBS Placebo-controlled trials (Study 004, Study 020)

		Teduglutide in mg/kg/day	
Patient Disposition	Placebo (n=59) n (%)	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

[ref: ISS, p. 197]

In the pooled teduglutide group in the SBS Placebo-controlled study data, the most common reasons for discontinuation included constipation and abdominal distension, for which there were no discontinuations in the placebo group. In the pooled placebo group, all 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.

In extension study 005, 7 of 8 discontinuations from AE were in patients previously treated with teduglutide in 004. The reasons for discontinuation in these 7 patients included abdominal pain, hyperplastic colon polyp, irritable bowel disease, vomiting, nausea, cough, and cerebrovascular accident (CVA). The case of CVA occurred in a 64 year old white female (005-0145-0005) with history of stroke, who had been on teduglutide for 59 days.

Deaths

There were 3 deaths reported during the drug development program. The two treated with teduglutide died during the extension studies.

- Patient 021-0155-1009. The patient was a 47 year-old man with a history in the 1980's of Hodgkin's disease, cecal necrosis secondary to radiation, and primary liver disease. He was diagnosed with metastatic adenocarcinoma after 11 months of treatment with 0.05 mg/kg/day teduglutide. Study drug was discontinued. The primary tumor was considered to be probably in the gastrointestinal tract but its precise location was unknown. The patient expired 10 days after diagnosis. Six months prior to starting teduglutide therapy, CT scan had shown liver enlargement without focal lesions and an edematous gallbladder with dense bile and 2 soft tissue foci of 10 and 15 mm diameter in the splenic field suspected to be accessory spleen. A subsequent review of a pre-teduglutide CT scan by 2 independent radiologists revealed a focal liver lesion of unclear significance. The primary tumor was considered to be probably in the gastrointestinal tract, but its precise location was unknown. A biopsy revealed metastatic adenocarcinoma. The patient died 10 days after diagnosis of

adenocarcinoma. An autopsy was inconclusive as to the primary site of the cancer; primary cause of death was "generalised malignancy (Intestinal cancer with primary site difficult to localize – small intestine in the stomy region?) with massive metastases". The event was considered by the investigator to be severe and related to treatment.

- Patient 021-0138-1011. After the study cutoff date of 30-Jun-2011, it was reported that this patient expired during ongoing Study CL0600-021. 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 87 days of teduglutide 0.05 mg/kg/day therapy. Teduglutide was permanently discontinued by the Investigator and subsequently received chemotherapy. The investigator reported that the stage of the cancer was T2BN2M0. The investigator did not attribute the SAE to teduglutide treatment. An autopsy report is not available at this time.
- Patient 004-0139-0003. This patient expired during the screening period of Study 004, prior to randomization. This patient's death was attributed to a massive upper GI tract hemorrhage.

Adverse Events of special interest

Areas of special interest to evaluate the safety of teduglutide were selected based on mechanism of action, nonclinical safety data, adverse events in clinical studies, clinical laboratory data and literature review. The following areas were selected:

- Acceleration of neoplastic growth including intestinal polyps
- GI stenosis and Intestinal obstruction
- Cholecystitis
- Pancreatic disease
- Increased absorption of fluid absorption and risk of hypervolemia
- Hypersensitivity Reactions

Acceleration of neoplastic growth including intestinal polyps.

Neoplasia

No treatment-emergent malignancies were reported in teduglutide placebo-controlled studies.

Three patients in the ongoing extension Study CL0600-021 were reported with neoplasms of the GI tract and lung.

1. Metastatic adenocarcinoma—Patient 021-0155-1009 on Day 326
    a. 47 year old male with Hodgkin's disease
    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. Treated with radiation therapy and chemotherapy for Hodgkin's disease 22 years prior to study entry, and consequently was at very high risk for developing secondary malignancies, particularly those of gastrointestinal origin. Autopsy revealed massive

metastasis of adenocarcinoma to liver, bone, lung, and regional nodes, with a primary site that was "difficult to localize – small intestine in the stomy region?".

c. Expert radiology consultants agreed that a liver lesion was present on the CT scan performed prior to teduglutide therapy.
d. Two expert radiologist consultants agreed that patient had a 2-cm left lobe hepatic lesion on CT scan (21-jan-2010) performed prior to receiving teduglutide.
e. In placebo/0.05 mg/kg/day group ("NT, PBO/TED" group)

2. Right lung squamous cell carcinoma—Patient 021-0138-1002 on Day 379
   a. 73 year old male with history of cigarette smoking
   b. In 0.05/0.05 mg/kg/day group
3. Left lung non-small cell carcinoma—Patient 021-0138-1011 on Day 87
   a. 64 year old male with 30-year history of smoking 30 cigarettes per day
   b. In placebo/0.05 mg/kg/day group ("NT, PBO/TED" group)

A relationship between malignancy and teduglutide cannot be determined based on these cases, all of whom were at high risk for cancer. It is impossible to know whether the drug had a role in increasing tumor growth in these patients. In the metastatic adenocarcinoma case, a liver lesion had already been present on CT scan prior to starting teduglutide. At autopsy, "massive metastases" (liver, nodes, bone, lung) of adenocarcinoma were reported probably of GI origin (although the intestine was free of malignancy at autopsy). The patient had received irradiation to the abdomen (developed cecal necrosis) about 20 years earlier. The patients with lung cancer from Poland were cigarette smokers, and lived in an area of Poland with very high risk of lung cancer. In these cases it is unknown if teduglutide had any role in the clinical manifestation of these malignancies. GLP-2 receptors are mainly located in the GI tract.

Intestinal Polyps

In the pooled SBS Placebo-controlled study (Study 004, Study 020) data, the following patients were diagnosed with GI polyps:

- Teduglutide 0.10 mg/kg/day: none
- Teduglutide 0.05 mg/kg/day: 2/109 (1.8%)
  - Patient 004-0138-0008 (Poland)
    - 22 year old female with sigmoid polyp
    - Onset at 155 days
    - Pathology: Hyperplastic colon polyp
  - Patient 020-0207-1004 (Italy)
    - 45 year old female with 2 colonic polyps (at 20 and 40 cm proximal to anus)
    - Onset at 1 day (discovered at baseline colonoscopy)
    - Pathology: not provided
- Placebo: 1/59 (1.7%)
  - Patient 020-0109-1005
    - 48 year old female with 2 peristomal polyps

- Onset at 87 days
- Pathology: Colostomy site—intestinal polyp; small bowel—inflammatory polyp with ulceration and fibrosis

In the SBS extension studies (Study 005, Study 021), the following 4 polyp cases have been reported:

- Patient 005-0103-0007: 0.10/0.10 mg/kg/day group (USA)
  - 58 year old female with 1 rectal polyp
  - Onset at 189 days
  - Pathology: benign focally hyperplastic colonic polyp with ulceration and inflammation
- Patient 005-0145-0004: placebo/0.10 mg/kg/day group (Poland)
  - 55 year old male with 1 rectal polyp
  - Onset at 190 days
  - Pathology: not provided
- Patient 021-0208-1001: 0.05/0.05 mg/kg/day group (Italy)
  - 49 year old female with 3 small colorectal polyps
  - Onset at 230 days (36 days after discontinuing teduglutide)
  - Pathology: tubular adenomata with low-grade dysplasia
- Patient 021-0138-1011: 0.05/0.05 mg/kg/day group (Poland)
  - 64 year old male (death from lung cancer) also had 1 small duodenal polyp
  - Onset at 87 days
  - Pathology: not provided

From the 3 polyp cases (1.8% in teduglutide and 1.7% in placebo group) in the SBS Placebo-controlled studies, it is difficult to conclude a relationship between teduglutide and the development of GI epithelial polyps through exposures for 6 months or less. GI polyps, especially at stomy sites, are not uncommon in patients who have undergone bowel resection. On the other hand, the finding of polyps is not inconsistent with the mechanism of action of teduglutide and the nonclinical findings. As for the cases in the long-term studies, which exposed patients to more than 6 months of teduglutide, the absence of a concurrent control group makes it difficult to determine the role of teduglutide in polyp formation and growth. Although biologically plausible a definitive statement regarding the relationship of polyps and treatment with teduglutide cannot be made based on these data.

GI Stenosis and Intestinal Obstruction

In the SBS Placebo-controlled trials (Study 004, Study 020), the cases of GI obstruction were reported:

Placebo group: none

Teduglutide groups: 6/109 (5.5%): none required surgical intervention

- 0.05 mg/kg/day: 3/77 (3.9%)
  - Patient 004-0101-0007 (severe SAE, Canada)

        - 32 year old male with onset at 156 days
        - History of Crohn's disease and bowel obstructions
        - Cholecystectomy. On 05/22/07 patient developed partial small bowel obstruction that resolved in 8 days
    - Patient 004-0155-0001 (moderate SAE, Poland)
        - 49 year old male with onset at 176 days
        - History of chronic pancreatitis, deep vein thrombosis, pneumonia
        - Colonic stenosis diagnosed on 01/24/07 with stricture of sigmoid colon seen on colonoscopy. Admitted 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 10 days. In Study 005 (345 days of teduglutide), repeat colonoscopy showed [asymptomatic] stenosis at same site, which was diagnosed as moderately severe colonic stenosis.
    - Patient 020-0201-1004 (severe SAE, USA)
        - 54 year old female with multiple events with onsets at 120, 125, and 144 days
        - History of cholecystectomy, hypothyroidism, glucorticoid deficiency, oophorectomy
        - Multiple events of "small intestinal stenosis" (worsening of jejunum stricture). Stricture was dilated after third event. Patient completed study 020.
- 0.10 mg/kg/day: 3/32 (9.4%)
    - Patient 004-0115-0003 (severe 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 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 after 4 days. Early discontinuation secondary to a second small bowel obstruction event on 2/23/07.
    - Patient 004-0132-0001 (severe 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 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, study medication was restarted, and patient was discharged. Completed study 004.
    - Patient 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

In the SBS extension studies (Study 005 and Study 021), 6 new patients experienced GI stenosis/obstruction. In the SBS Placebo-controlled studies (Study 004, Study 020), no patients required surgical intervention. In the extension studies, 1 patient required endoscopic dilation.

In summary, in the SBS Placebo-controlled Studies, a higher incidence of GI stenosis or obstruction-related AEs was observed compared with placebo with frequencies of 0% (0/59), 3.9% (3/77), and 9.4% (3/32) for placebo, teduglutide 0.05, and 0.10 mg/kg/d treatment groups, respectively. The highest frequency was noted in the teduglutide 0.10 mg/kg/d group. In both SBS Placebo-controlled Studies and the extension studies, none of the patients with GI stenosis or obstruction-related AEs required surgical intervention, and three required an endoscopic procedural treatment.

Although prior bowel surgery increases the risk for intestinal obstruction, these data suggest a dose-response relationship. An obstructive clinical presentation (obstruction or pseudo-obstruction) is not inconsistent with the mechanism of action of teduglutide—increased luminal fluid reabsorption (stool dessication) and bowel wall thickening (slower transit and lead points). The obstruction cases are associated with a history of recurrent obstruction, stricture/adhesions from previous surgery, and firm dry stool which when passed resulted in resolution of the obstruction. A concern with bowel obstruction in patients with SBS is that there is little bowel to spare if surgery is needed.

Acute Cholecystitis

In the SBS Placebo-controlled studies, the following biliary events occurred. None of the following cases resulted in study withdrawal:

Placebo: 0/59 (0%)

Teduglutide: 4/109 (3.7%)

- Patient 004-0101-0007 (0.05 mg/kg/day, Canada)
  - 32 year old male with onset at 103 days
  - GB perforation
  - History of cholelithiasis, hepatitis, beta thalassemia
  - Cholecystectomy performed on Day 105. Completed 004 and 005.
- Patient 004-0132-0008 (0.05 mg/kg/day, Great Britain)
  - 38 year old male with onset at 143 days with events lasting 3 to 15 days
  - History of cholestasis
  - Gallbladder sludge also found. Discharged on ciprofloxicin Elective cholecystectomy scheduled. Completed 004.
- Patient 004-0138-0001 (0.10 mg/kg/day, Poland):
  - 49 year old female with onset at 12 days and lasted 2 days
  - No history of cholestasis; history positive for renal colic and metabolic bone disease
  - This episode of cholecystitis was not documented (no "objective imaging or laboratory data" is documented to establish diagnosis)

- Patient 020-0109-1001 (0.05 mg/kg/day, USA)
  - 70 year old male with onset at 30 days and reported with duration of 105 days
  - History of cholelithiasis and ”sludge”
  - Cholecystectomy tube placed. Open cholecystectomy was performed 4 months later. Study drug interrupted for one week and entered study 021 after completing 020.

In the open-label extension studies (Study 005, Study 021), the following additional gallbladder events were reported:

- Patient 005-0145-0004 (placebo/0.10 mg/kg/day group, Poland): cholecystitis
  - 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
  - Patient was hospitalized for acute bronchitis. 3 weeks later, he was admitted for severe event of “cholecystitis” and “chronic pancreatitis” that lasted 12 days
- Patient 021-0144-1001 (0.05/0.05 mg/kg/day group, USA): acute cholecystitis
  - 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, fludrocortisones, Lasix, Reclast
  - On 5/11/10 mild event of acute cholecystitis was reported as an AE with end date of 10/10/10
- Patient 021-0155-1004 (0.05/0.05 mg/kg/day group, Poland): cholestasis secondary to obstructed biliary stent
  - 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: included lactulose
  - On 12/6/10, worsening enzyme elevations—ALP from 430 to 567 IU/L; GGT from 286 to 534 IU/L; Direct bilirubin = 6.0 micromol/L. On 12/21/10 got ERCP-- biliary stent obstructed so was removed. On 2/8/11, biliary function tests reduced (Direct bilirubin = 0.1).
- Patient 021-0207-1001 (placbo/0.05 mg/kg/day group, Italy): new onset cholelithiasis
  - 21 year old female after 206 days of teduglutide and lasted 101 days
  - History: (volvulus), gastrectomy, biliary sludge, osteoporosis
  - Concomitant medications: carnitine, ursodeoxycholic acid
  - Onset on 10/27/10. On 11/24/10 due to rising liver function tests, study drug was discontinued and PN lipid content decreased. Biliary U/S showed multiple gall stones with normal ducts. Cholecystectomy performed.
- Patient 005-0109-0001 (0.05/0.05 mg/kg/day group, USA)
  - 66 year old male with 3 events—10, 16, and 104 days into Study 005
  - No prior history of gallbladder problems (past history of lower GI bleed, DVT, aortic dissection)
  - Meds-- amlodipine, olmesartan, metoprolol, lisinopril
- Patient 005-0145-0004 (placebo/0.10 mg/kg/day, Poland)
  - 56 year old male with onset 153 days into Study 005

  - Also diagnosed with pancreatitis on this episode
  - No prior history of gallbladder problems (past history of MI, CABG, chronic renal failure, atrial fibrillation)
  - Meds—quinapril, vivacor, theophylline

- Patient 021-0209-1002 (plac/0.05 group mg/kg/day, France): cholecystitis
  - 82 year old male after 16 days of teduglutide and lasted 12 days
  - History: cholelithiasis, chronic renal failure
  - Concomitant medications: included fluindione
  - Patient was admitted to hospital for abdominal pain and fever. CT showed evidence of portal hypertension. Study drug discontinued on 9/22/10 and dropped from study on 9/28/10. Gastoscopy on 9/23/10 c/w cholelithiasis. Treated with Rocephin, Flagyl, danaparoid. Resolved on 9/28/10.

In the extension studies (Study 005, Study 021), the following cases of cholecystitis were reported:

- Patient 021-0209-1002 (placebo/0.05, France)
  - 82 year old male with onset 16 days into Study 021
  - History of cholelithiasis and chronic renal failure

The absence of cholecystitis cases in the placebo group of the SBS Placebo-controlled studies suggests a safety signal for cholecystitis. However, the numbers are small and gallbladder/liver/pancreatic disease is very common in PN-dependent SBS patients.

Pancreatic Disease The following cases of pancreatitis were reported in the SBS Placebo-controlled trials:

Teduglutide: 2/109 (1.8%)

- Patient 004-0115-0003 (0.10 mg/kg/day group, USA)
  - 62 year old female with onset at 8 days and lasted 68 days
  - History of multiple small bowel obstructions and surgeries confer higher risk for amylase/lipase elevation secondary to small bowel obstruction. Also history of cholecystectomy and GI hemorrhage
  - Meds-- Etrafon-d, alprazolam, calcitonin, esomeprazole, Lomotil
  - 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

- Patient 004-0155-0001 (0.05 mg/kg/day group, Poland)
  - 48 year old male with onset at 113 days
  - History of chronic pancreatitis with ductal stenosis and pseudocyst
  - Meds—Kreon, cimetidine, insulin
  - 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.

Two more patients (one teduglutide and one placebo) experienced elevations of amylase and/or lipase. All four cases above had pre-existing disease prior to entering these trials in which amylase and lipase elevations had occurred.

In the extension studies 005 and 021, there was a single case of chronic pancreatitis (005-0145-0004) diagnosed in a 56 year old male in the placebo/teduglutide 0.10 mg/kg/day group on Day 153 of teduglutide; likely ongoing prior to teduglutide based on episodic amylase and lipase elevations.

Considering additional information such as medical history, other adverse events, clinical laboratory values and SAE narratives, the evidence shows that these patients had such events or signs of the events prior to treatment, due to non-pancreatic illness or abnormality or were contributed to by an underlying medical condition. An association between pancreatitis and teduglutide cannot be established based on these cases.

Increased absorption of fluid absorption and risk of hypervolemia.

In the SBS placebo-controlled trials (004, 020), these MedDRA preferred terms were used to identify cases of fluid overload:

- 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 were observed in the SBS Placebo-controlled trials (004, 020) *[ref: ISS, Table 137, p. 447]*:

- Fluid Overload
  - Placebo: 4/59 (6.8%)
  - Teduglutide 0.05 mg/kg/day group: 9/77 (11.7%)

The following AEs of "Cardiac failure congestive" were reported:

1. Patient 004-0139-0009 (0.05 mg/kg/day): SAE of congestive heart failure (CHF) on day 186
   a. 50 year-old female
   b. Medical history—thyroidectomy, hyperparathyroidism, no cardiac history recorded, but tachycardia of 121 bpm was noted at screening and baseline.
   c. Medications—pantoprazole, erythromycin. No thyroid hormone supplementation is documented for this patient.
   d. Hospitalized on treatment day 186 for congestive heart failure (CHF). Chest x-ray (CXR) revealed bilateral pulmonary edema. Echocardiography showed mild inferior hypokinesis and Gr 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 6 days later. CXR 10 days later (05/04/06) was within normal limits. Discharged from study on 05/04/06.
   e. History and findings suggest possibility of undiagnosed hypothyroidism and/or cardiac dysfunction.
2. Patient 020-0109-1001 (0.05 mg/kg/day). Not reported as an SAE. Clinical details not available.

These data suggest that fluid overload should be considered when administering teduglutide. Not only is its mechanism of action to increase fluid reabsorption but the data show that the rate of fluid overload was nearly twice that in the placebo group. The CHF cases are not clearly related to teduglutide. The applicant addresses this issue in labeling.

Hypersensitivity Reactions

In the SBS Placebo-controlled trials, hypersensitivity as a Preferred Term (PT, MedDRA) was reported as follows *[ref: ISS, Table 62, p. 223]*:

- Teduglutide (0.10 mg/kg/day): 3/32 (9.4%)
- Teduglutide (0.05 mg/kg/day): 6/77 (7.8%)
- Placebo: 3/59 (5.1%)

None of these patients was ADA positive. FDA also conducted a search in the adverse event safety data for possible anaphylactic reactions to teduglutide. No instances of possible anaphylactic reactions to teduglutide were found in the safety data submitted by the Applicant, using the search terms of hives, urticaria, pruritis, flushing, edema, swelling,

respiratory compromise (dyspnea, wheeze, bronchospasm, stridor, hypoxemia, shortness of breath, chest tightness), hypotension, and low blood pressure.[4]

VIII. Risk Evaluation and Mitigation Strategy (REMS)

Background Regarding REMS

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified

[4] HA Sampson et al. Second symposium on the definition and management of anaphylaxis: summary report—Second national institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis network symposium. American Academy of Allergy, Asthma and Immunology. 2006.

- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be patient to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, section 505-1(f)(2) of the FDCA specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

Discussion of GATTEX for Short Bowel Syndrome and Risk Management

The three key serious risks observed with teduglutide in the SBS clinical development program include: 1) acceleration of neoplastic growth and enhancement of colon polyp growth, 2) gastrointestinal obstruction, and 3) biliary and pancreatic disorders. As cited in Section IV. Nonclinical Pharmacology-Toxicology, in this GIDAC Briefing Package, the majority of the observed non-clinical study findings are associated with the mechanism of action of teduglutide, which is to promote growth and repair of gastrointestinal epithelium with increased villus height and crypt depth of the intestinal epithelium.

Based on the three key serious risks, risk mitigation in the Phase 3 teduglutide clinical trial protocols excluded high-risk patients with the following history:

- Cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state (not including cutaneous basal or squamous cell carcinoma, or in situ non-aggressive and surgically resected cancer)
- Crohn's disease who had been treated with biological therapy (e.g., anti-tumor necrosis factor [anti-TNF] or natalizumab) within the 6 months prior to screening
- Inflammatory bowel disease (IBD) who required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months
- Untreated pre-malignant or malignant change on colonoscopy biopsy or polypectomy
- Chronic pancreatitis or cholecystitis
- Signs of severe hepatic impairment or disturbed renal function including:
    - Total bilirubin $\geq$ 2 x upper limit of normal (ULN)
    - Patients with Gilbert's disease, direct (conjugated) bilirubin $\geq$ 2 x ULN

- Aspartate aminotransferase (AST) ≥ 5 x ULN
- Serum creatinine ≥ 2x ULN

The applicant's proposed labeling for GATTEX includes risk mitigation information and recommendations for administration in the following sections: Monitoring to Assess Safety (Section 2.3), Dosage Modifications in Specific Patient Populations (Section 2.4), CONTRAINDICATIONS (Section 4.), and a WARNINGS and PRECAUTIONS (Section 5.1 through 5.6).

Applicant's Proposed Risk Evaluation and Mitigation Strategy

NPS Pharmaceuticals has proposed a REMS that includes the following goals and elements:

I. GOAL

The goal of the proposed REMS for GATTEX for the treatment of adults with short bowel syndrome (SBS) to improve intestinal absorption of fluid and nutrients is:

- 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.

II. REMS ELEMENTS

A. Communication Plan

The communication plan includes a **Dear Healthcare Professional (DHCP) letter** that includes potential and known risks associated with the use of GATTEX. The DHCP letter will be sent to target providers, defined as gastroenterologists and gastrointestinal (GI) surgeons, likely to prescribe GATTEX to treat adult patients with SBS. The Dear Healthcare professional letter will be disseminated to target providers within 60 days of approval of GATTEX or at the time of launch, whichever is sooner, bi-annually, for three-years.

To support prescriber training and education about key serious risks with GATTEX, NPS Pharmaceuticals will disseminate a **Dear Professional Society letter** to leadership of select professional organizations with outreach to healthcare providers likely to prescribe GATTEX in patients with SBS. NPS Pharmaceuticals proposes distribution of the Dear Professional Society letter as a one-time dissemination, within 60 days of product approval or at the time of product launch, whichever is sooner, to the following professional organizations:

- American Society for Parenteral and Enteral Nutrition
- American Gastroenterological Association
- American College of Gastroenterology
- Society for Surgery of the Alimentary Tract
- American Society of Colon and Rectal Surgery

The **Dear Healthcare Provider letter** and the **Dear Professional Society letter** will be appended to and part of the REMS.

B. Timetable for Submission of REMS Assessment

NPS proposes to submit REMS assessments to FDA at 18 months, 3 years and 7 years form the date of initial approval of the REMS.

REMS Assessment Plan

The Applicant's REMS assessment plan will provide the following information that will be used to assess whether or not the REMS is meeting its intended goals:

1. Evaluation of prescriber understanding of the potential risks associated with GATTEX and the importance of appropriate patient selection and monitoring will be conducted by prescriber Knowledge, Attitude, and Behavior (KAB) surveys.

    a. The survey instrument will include questions assessing whether HCPs understand the key risk messages in the REMS educational materials.

    b. Surveys will be conducted with a random sample of prescribers as identified in market research data in order to assess their awareness and understanding of the risks with GATTEX.

    c. The protocol will include: expected sample size and confidence intervals associated with that sample size, description of the methodology for recruitment and selection of the prescriber sample, specific selection criteria for inclusion into the survey, a description of how and when the survey will be administered, and an explanation of the design features and controls that will be included to minimize bias and compensate for any limitations in the methodology

2. Results of the prescriber surveys will be included in REMS Assessment Reports beginning at 18 months after REMS approval; subsequent reports will be submitted at 3 years and 7 years after REMS approval.

Discussion of REMS

The Agency believes that GATTEX proposed for treatment of adult patients with SBS warrants a REMS. The Agency, in general, agrees with the applicant's proposed REMS elements that include a communication plan and a timetable for submission of assessments.

The Agency does not believe that access to GATTEX for SBS should be restricted or require elements to assure safe use based on the following rationale:

- Target prescribers for teduglutide will most likely be subspecialty physicians, specifically, gastroenterologists and colorectal surgeons who have expertise in the complex management of adult patients with SBS post-surgical resection.

- Target subspecialty physicians are trained to manage complications of SBS including dehydration, diarrhea, chronic weight loss, and life-threatening complications of gastrointestinal obstruction, sepsis, blood clots, and the ongoing risks of hepatobiliary disease. These subspecialists have training to manage venous access for chronic parenteral nutrition as well as preventive screening and follow-up colonoscopies over the lifetime of a patient with SBS.
- Target subspecialists understand the potential and known serious risks with teduglutide, some of which are inherent complications of SBS.
- A collaborative team approach led by a gastroenterologist is used in many settings for the care of patients with SBS. Other team providers may include nutritionists, clinical pharmacists, nurse practitioners and/or physician assistants. Follow-up requires frequent doctor visits and monitoring to avoid septic episodes and treatment of small bowel bacterial overgrowth.
- Long-term care burden for patients with SBS is substantial including chronic parenteral nutrition. The added burden of required participation in a restricted distribution program for access to a potentially beneficial product will likely be excessive for target subspecialty physicians.

In general, the Agency supports the applicant's proposed REMS elements (a communication plan and timetable for submission of assessments). However, the Agency recommends strengthening the communication plan educational materials directed to prescribers. Additional focused prescriber educational materials that emphasize the three key serious risks with GATTEX, summarize the key non-clinical study findings, including results of carcinogenicity studies that support the potential and observed serious risks with teduglutide, and underscore the recommended pre-treatment screening colonoscopy and vigilant laboratory monitoring with use of GATTEX should be considered.

By example, consider the following:

- A prescriber educational slide deck for face-to-face presentation by a NPS Medical Science Liaison to gastroenterologists, colorectal surgeons, as well as other providers that may support a collaborative team for care of patients with SBS.
- Educational materials (directed to patients) that prescribers may use to educate a SBS patient considering treatment with GATTEX. Note that proposed labeling includes a Medication Guide directed to patients.
- Expand target healthcare prescribers to include internal medicine physicians and general surgeons.

It will be challenging to determine the impact of such a proposed REMS; however, prescriber KAB survey results, long-term post marketing pharmacovigilance to monitor for potential malignancies as well as the other key serious risks (potential, known, and unknown), and a required postmarketing study to be discussed by the GIDAC.

IX. Issues for Committee

The following are preliminary questions for your consideration as you review the AC materials.

1. Are the efficacy results (>20% reduction in PN/I.V.) clinically meaningful in patients with short-bowel syndrome?

2. Is there a group of patients who might benefit from treatment for longer than 24 weeks, since some patients were weaned off PN/I.V. during the extension study after more than 24 weeks of therapy? How long should teduglutide be administered?

3. What considerations should be given to the potential tumor promoting effects of teduglutide?
    a. colon/GI track,
    b. other sites

4. How do you view the hepatobiliary and pancreatic safety of this drug? Non-clinical studies revealed hyperplastic and/or hypertrophic effects of teduglutide on intrahepatic and extrahepatic bile ducts, gall bladder, and pancreatic ducts.

5. Please comment on the relevance of the presence of ADA and cross-reactivity with endogenous GLP-2.

6. Considering the benefits and risks for Gattex described above would you recommend approval?

7. Regarding the safety profile of Gattex: if Gattex is approved, please comment whether additional measures beyond professional labeling, including a Medication Guide, will be necessary to ensure the benefits outweigh the risks.

8. Please comment on the applicant's Communication Plan.

9. Would you recommend additional studies for safety or efficacy be conducted?

X. Appendix

Applicant's proposed labeling (April 20, 2012)

2.1 Laboratory and Colonoscopy Assessments

A colonoscopy of the entire colon with removal of polyps must be done within 6 months prior to starting treatment with GATTEX. Subsequent colonoscopies are recommended at a minimum of 5-year intervals. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Patients must also undergo initial (within 6 months prior) and subsequent laboratory assessments (bilirubin, alkaline phosphatase, lipase and amylase). If a clinically meaningful elevation is seen imaging of the biliary tract or pancreas is recommended. In case of malignancy, GATTEX therapy should be discontinued.

4 CONTRAINDICATIONS

GATTEX is contraindicated in patients with currently suspected or active malignancy and in patients with a history of malignancies (excluding basal cell carcinoma).

5 WARNINGS AND PRECAUTIONS

5.1 Acceleration of Neoplastic Growth

The possibility that GATTEX may accelerate the growth of neoplasms cannot be ruled out. In case of malignancy, GATTEX therapy should be discontinued.

5.2 Colorectal Polyps

A colonoscopy of the entire colon with removal of polyps must be done within 6 months prior to starting treatment with GATTEX. Subsequent colonoscopies are recommended at a minimum of 5-year intervals. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, GATTEX therapy should be discontinued.

5.3 Small Bowel Neoplasia

Based on small bowel 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 malignancy, GATTEX therapy should be discontinued.

5.4 Cardiovascular Disease

Due to increased intestinal fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to fluid overload, especially during initiation of therapy. Parenteral nutrition/intravenous (PN/I.V.) fluid volume should be reassessed relative to signs of fluid overload. In case of a significant deterioration of the cardiovascular disease, the need for continued GATTEX treatment should be reassessed.

5.5 Risks Resulting from Increased Absorption of Concomitant Oral Medication

Concomitant oral drugs requiring titration or with a narrow therapeutic index may require dose adjustment due to increased absorption.

5.6 Gallbladder and Bile Duct Diseases

Cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. Patients must undergo initial (within 6 months prior) and subsequent laboratory assessment of bilirubin and alkaline phosphatase. If a clinically meaningful elevation is seen imaging of the biliary tract is recommended.

5.7 Pancreatic Diseases

Pancreatitis has been reported in clinical studies. Patients must undergo initial (within 6 months prior) and subsequent laboratory assessment of lipase and amylase. If a clinically meaningful elevation is seen imaging of the pancreas is recommended.

5.8 Intestinal Obstruction

Intestinal obstruction has been reported in clinical trials. Patients presenting with symptoms suggestive of these conditions should be closely monitored. Caution should be exercised when prescribing GATTEX.