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APPLICATION NUMBER:

203441Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	203441
Original Submission Dates	11/30/2011
PDUFA Due Date	12/30/2012
Brand Name	Gattex
Generic Name	Teduglutide
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OCP Division	DCP III
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Sponsor	NPS Pharmaceuticals
Relevant IND(s)	58,213
Submission Type	NME
Formulation; Strength(s)	Lyophilized powder; 5 mg/vial to be reconstituted with 0.5 mL sterile water for injection
Proposed indication	Treatment of Short Bowel Syndrome (SBS)
Proposed Dosage and Administration	0.05 mg/kg subcutaneous (SC) injection once daily, altering sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms.

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1 EXECUTIVE SUMMARY

GATTEX[®] (teduglutide [rDNA origin], ALX-0600) is a 33–amino acid recombinant analog of the human glucagon-like peptide-2 (GLP-2), a peptide that is secreted primarily from the lower gastrointestinal tract. Teduglutide is being proposed to treat adult patients with Short Bowel Syndrome (SBS), who need parenteral support (parenteral nutrition/intravenous hydration, PN/IV) to supplement nutrition, through improving intestinal absorption of fluid and nutrients. This proposed indication was granted Orphan Designation (OD) on June 29, 2000.

For treating patients with SBS, the FDA approved Zorbtive[™] [somatropin (rDNA origin) for injection, NDA 021597] in 2003. In 2004 the FDA approved NutreStore[™] [L-glutamine for oral solution, NDA 021667] which should be administered as a cotherapy with Zorbtive[™] together with optimal management of short bowel syndrome, such as a specialized oral diet.

The sponsor submitted an original New Drug Application for GATTEX[®] (teduglutide [rDNA origin], NDA 203441) on 11/30/2011. The submission contains a total of 14 completed clinical trials and an interim report of an ongoing open-label, extension study in SBS subjects (CL0600-021, Table 1). A total of 623 unique subjects received at least one dose of teduglutide and 198 subjects treated with placebo in the clinical program. Four *in vitro* drug-drug interaction study reports, six single-dose pharmacokinetic (PK) study reports, three multiple-dose pharmacokinetic/pharmacodynamic (PK/PD) study reports, PK/PD data and immunogenicity data from four Phase 3 studies with SBS subjects were reviewed in this clinical pharmacology review.

Data from four Phase 3 efficacy and safety studies form the basis to support the proposed indication. (1) The pivotal double blind, placebo-controlled study (CL0600-020) that compared one dose level, 0.05 mg/kg/day, of teduglutide to placebo and (2) its ongoing, open-label extension study (CL0600-021); and (3) a supportive double-blind, placebo-controlled study (CL0600-004) that compared two dose levels, 0.05 mg/kg/day and 0.10 mg/kg/day, of teduglutide to placebo and (4) its randomized, double-blind extension study CL0600-005 that studied the long term safety of 0.05 mg/kg/day and 0.10 mg/kg/day daily doses of teduglutide. Based on results from these studies, the sponsor proposed a daily teduglutide dose of 0.05 mg/kg for the proposed indication.

In this review, teduglutide and ALX-0600 were used interchangeable.

1.1 Recommendation

From a clinical pharmacology perspective, the information submitted to support this NDA is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Post-Marketing Requirements

The Clinical Pharmacology review team recommends the following post marketing requirement (PMR) as a sub-study of long term post-marketing safety trial(s):

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.

1.3 Post-Marketing Commitments

There are no post-marketing commitments for this submission.

1.4 Summary of Clinical Pharmacology Findings

The pharmacokinetics (PK) of teduglutide was evaluated in both healthy subjects and subjects with SBS. Teduglutide formulation strength (and/or SC injection volume) appears to have an impact on teduglutide PK upon SC administration (Study CL0600-022); therefore, the summary of clinical pharmacology findings are primarily based on data obtained with the to-be-marketed formulation strength (10 mg/mL).

Teduglutide PK after SC administration of the to-be-marketed formulation at the proposed clinical dose was characterized in the target patient population during Phase 3 study CL0600-004. Subjects with SBS appeared to have a lower drug exposure than healthy subjects. The overall summary of clinical pharmacology is presented below.

Pharmacokinetics (PK)

Absorption

Teduglutide was absorbed with a peak concentration at 3-5 hours after subcutaneous (SC) administration at abdomen, thigh, or arm with the to-be-marketed concentration (10 mg/mL). The maximal plasma concentration and exposure (C_{max} and AUC) of teduglutide was dose proportional over the dose range of 0.05 to 0.4 mg/kg. No accumulation of teduglutide was observed following repeated daily SC administration. In healthy subjects, teduglutide had an absolute bioavailability of 88% after abdominal SC administration (Study CL0600-006).

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 median area under the curve (AUC_{0-t}) was 0.15 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (Study CL0600-004).

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 $AUC_{0-\infty}$) in healthy subjects. The 90% confidence interval (CI) for AUC_{0-t} or $AUC_{0-\infty}$ was within the 80% to 125% range, indicating that exposure was similar after SC injection at these 3 sites (Study CL0600-015).

Distribution

Following IV 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 CL0600-006), similar to the 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 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 (CL0600-006). Teduglutide was rapidly eliminated with a mean terminal half life ($t_{1/2}$) of approximately 2 hours in healthy subjects and 1.3 hours in SBS subjects.

Special Population

Teduglutide PK was evaluated in healthy elderly subjects, subjects with renal impairment, and subjects with hepatic impairment. Plasma concentration-time profiles of teduglutide were similar for healthy non-elderly and elderly subjects (Study CL0600-018). 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.

Hepatic Impairment

Following a single SC administration of 20 mg teduglutide to subjects with moderate hepatic impairment, teduglutide C_{max} and AUC were lower (10 ~15%) compared to those in healthy matched control subjects; no dose adjustment is needed when administered to individuals with moderate hepatic impairment (CL0600-017). Teduglutide was not assessed in subjects with severe hepatic impairment.

Renal Impairment

Following a single SC administration of 10 mg teduglutide to subjects with moderate to severe renal impairment or end stage renal disease (ESRD), teduglutide C_{max} and AUC_{0-∞} increased with increasing degree of renal impairment. The primary PK parameters of teduglutide increased up to a factor of 2.6 (AUC_{0-∞}) and 2.1 (C_{max}) in ESRD subjects compared to healthy subjects (Study CL0600-018).

Based on these results, SBS patients with renal impairment would be exposed to higher levels of teduglutide due to a decrease in the renal clearance of the drug. Therefore, a dose reduction by 50% is recommended in patients with moderate to severe renal impairment and ESRD

Comparability Assessment

The phase 3 studies used the to-be-marketed formulation. However, the formulation strength appears to have impact on the extent of exposure following SC injection based on data in one single study that evaluated the same dose of teduglutide administered in two different formulation strengths (Study CL0600-022).

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.

QTc Prolongation

No significant QTc prolongation was detected at a supra-therapeutic teduglutide dose of 20 mg in the TQT study (Study C09-001).

Exposure-Response Relationship

Overall, the dose-response relationship indicates the proposed dose, i.e., 0.05 mg/kg/day, had better efficacy and safety profiles compared to 0.1 mg/kg/day.

Efficacy

In the 24-week study (CL0600-004), changes in weekly PN/IV volume were evaluated with two dose levels of teduglutide (0.05 and 0.10 mg/kg/day) in subjects with PN/IV-dependent SBS. For the primary efficacy endpoint, i.e., the proportion of subjects achieving a 20% to 100% reduction in PN/IV at Weeks 20 and 24 (responder), the teduglutide 0.05 mg/kg/day group, was statistically significantly higher compared with the placebo group (45.7% vs. 6.3%; $p = 0.005$). However, the teduglutide 0.10 mg/kg/day group did not have statistically significant difference compared to the placebo group (25.0% vs. 6.3%; $p = 0.172$). The sponsor proposed several arguments to explain why the responder rate of the 0.10 mg/kg/day group was lower than that of the 0.05 mg/kg/day group, including higher baseline PN/IV in 0.10 mg/kg/day group.

As to the secondary efficacy endpoint, the absolute change from baseline in weekly PN/IV volume at Week 24, both active treatment groups demonstrated a mean weekly decrease in PN/IV volume of 2.5 L compared to 0.9 L in the placebo group ($p = 0.08$ for each comparison) indicating that both active doses have similar efficacy ($p = 0.98$).

Altogether, it seems that the teduglutide efficacy reached the plateau around 0.05 mg/kg/day dose.

Safety

The percentage of subjects who experienced a treatment-emergent adverse event (TEAE) in the teduglutide 0.10 mg/kg/day group (97%, 31/32) was numerically higher than in either the teduglutide 0.05 mg/kg/day group (88%, 68/77) or the placebo group (83%, 49/59) based on combined data from Studies CL0600-004 and CL0600-020. However, the overall high incidence and nature of the TEAEs in this population across both the teduglutide-treated and placebo-treated subjects most likely represent both the underlying disease and parenteral support complications often observed in the SBS population.

Immunogenicity

Immunogenicity incidence – anti-drug antibody (ADA)

In the pivotal Phase 3 study (CL0600-020), the incidence of anti-teduglutide IgG antibody was 0% (0/16) at Week 12 and 18% (6/34) at Week 24 in subjects who received SC administration of 0.05 mg/kg teduglutide once a day. Of the 16 subjects, who were ADA negative (ADA-) at Week 12, 2 subjects were confirmed to be ADA positive (ADA+) at Week 24. This suggests that the immunogenicity incidence rate increased with the duration of treatment. One additional subject (Patient 0136-1002) had positive ADA at baseline however remained negative post-baseline during Study CL-0600-020 and the extension Study CL0600-021.

In the Phase 3 open label extension study (CL0600-021) where subjects had the option to continue taking teduglutide 0.05 mg/kg/day for up to 2 years. Twenty-seven out of 85 subjects (27/85, 32%) was ADA positive at one or more time points post baseline up to the approximate 1-year cut (currently ongoing). Among 34 subjects who were treated with teduglutide in both the pivotal study and the extension study, 6 subjects tested ADA+ at baseline (of which 5 continued to be ADA+) in the extension study and 8 additional subjects became ADA+ post-baseline. The incidence rate was 38% (13/34) for subjects who received teduglutide treatment for the duration of 18 months. Among 51 subjects who initiated teduglutide treatment in the extension study, 14 subjects were ADA+ (14/51, 27%) during the extension study after teduglutide treatment of 12 months.

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

Of note, the immunogenicity assessment was based on a validated (b) (4) discovery electrochemiluminescent (b) (4) ECL) assay which has a drug tolerance significantly higher than the observed mean C_{max} at the clinical dose, 0.05 mg/kg.

Cross-reactivity of ADA to GLP-2

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

Immunogenicity incidence – neutralizing antibody

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

Immunogenicity Impact on PK, Efficacy and Safety

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

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

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

In summary, the sponsor should assess the long term safety impact of ADA in post-marketing studies, as immunogenicity incidence rate increased with treatment duration during clinical trials. Furthermore, 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.

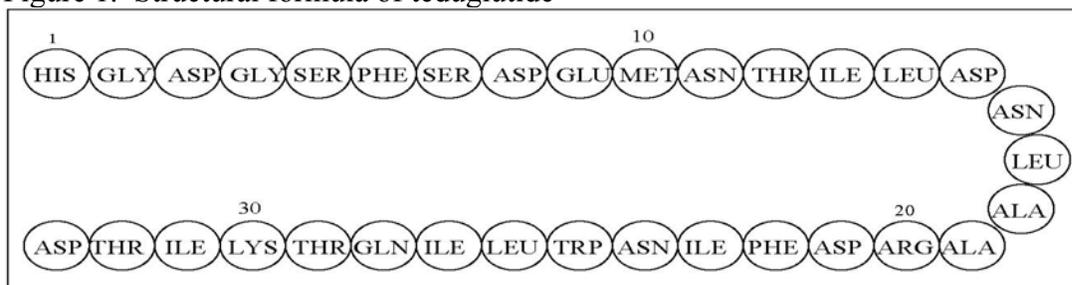
2 QUESTION-BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Teduglutide (rDNA origin) is a 33 amino acid glucagon-like peptide-2 (GLP-2) analog manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. Its chemical name 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. The structural formula is:

Figure 1. Structural formula of teduglutide



Teduglutide has a molecular weight of 3752 Daltons. Teduglutide drug substance is a clear, colorless to light-straw-colored liquid.

Teduglutide has one amino acid substitution of alanine by glycine at the second position of the N-terminus of GLP-2. The single amino acid substitution relative to naturally occurring GLP-2 results in resistance to in vivo degradation by the enzyme dipeptidyl peptidase-IV (DPP-IV), resulting in an extended half-life.

Each vial of GATTEX contains 5 mg of teduglutide as a white lyophilized powder for solution for subcutaneous injection. In addition to the active pharmaceutical ingredient (teduglutide), each vial of GATTEX contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate heptahydrate as excipients. No preservatives are present.

At the time of administration the product is reconstituted with 0.5 mL of sterile water for injection, which is provided in a prefilled syringe. A nominal 10 mg/mL solution concentration is obtained after reconstitution. Up to 0.38 mL of solution can be withdrawn for subcutaneous injection upon reconstitution with the 0.5 mL sterile water for injection (sWFI) provided in the prefilled syringe.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Teduglutide is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. Teduglutide binds to the glucagon-like peptide-2 receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of multiple mediators including insulin-like growth factor (IGF)-1, nitric oxide, and keratinocyte growth factor (KGF).

As with GLP-2, teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine. Teduglutide increases villus height and crypt depth of the intestinal epithelium resulting in enhanced intestinal absorptive capacity as demonstrated by greater absorption of fluids, electrolytes and nutrients, and reduced fecal fluid loss. Therefore, GATTEX[®] (teduglutide [rDNA origin]) powder for subcutaneous injection is used to improve intestinal absorption of fluid and nutrients, thus is proposed to be indicated for the treatment of adult patients with Short Bowel Syndrome (SBS).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended daily dose of GATTEX is 0.05 mg/kg body weight. GATTEX should be administered by subcutaneous (SC) injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen, or alternating thighs, or alternating arms. GATTEX should **not** be administered intravenously or intramuscularly.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 1 is a summary of clinical pharmacology studies and clinical studies (a total of 15 studies) that provide PK, PD, efficacy, and safety information. There are 9 clinical pharmacology studies (6 in healthy subjects and 2 in otherwise healthy subjects with organ dysfunction), 1 Phase 2 dose-ranging study in subjects with SBS, 2 Phase 3 efficacy and safety studies (both placebo-controlled, 1 pivotal study and 1 supportive study) with PK and/or PD components in subjects with SBS, 2 extension studies (1 uncontrolled, blinded extension, and 1 [ongoing] uncontrolled, open-label) of the Phase 3 studies, and 2 studies in subjects with Crohn's Disease (CD). With the exception of one open-label (2-year) study in SBS subjects, all studies have been completed.

Table 1. Outline of Clinical Pharmacology Studies and Clinical Studies with PK and/or PD Components

Type of Study	Study Number	Study objective	Study Design and Type of Control	Teduglutide dose and routes (site); Control	Number of Subjects enrolled	Healthy Subjects or Diagnosis of Patients	Total duration of Treatment	PK Assay Method
Bioavailability (SC vs. IV)	CL0600-006	PK, absolute bioavailability of SC relative to a 1-hour IV infusion in fasted	Phase 1, single centre, open-label, randomized, 2-way crossover (two treatment, two sequence) trial	0.12 mg/kg IV or SC	14 (all teduglutide)	Healthy male and female subjects	Single dose (IV as 1-hour infusion)	ELISA
Bioavailability (thigh, arm vs. abdomen)	CL0600-015	PK, relative bioavailability (thigh and arm, relative to abdomen)	Phase 1, randomized, open-label, 3-way crossover trial	10 mg SC	18 (all teduglutide)	Healthy male and female subjects	Single dose on 3 occasions separated by 3 days	ELISA LC-MS/MS
Bioavailability (single & multiple dose)	1621/13	PK, ascending single SC doses	Phase 1, single-blind, placebo-controlled trial	2.5, 5, 7 and 10 mg SC; placebo control	32 (8 placebo; 24 teduglutide)	Healthy male subjects	Single dose	ELISA
	CL0600-022	PK, multiple SC doses	Phase 1, double-blind, randomized, placebo-controlled, multi-dose trial	10, 15, 20, 25, 30, 50, 80 mg SC (abdomen); placebo control	95 (24 placebo 71 teduglutide)	Healthy male and female subjects	qd for 8 days	LC-MS/MS (US)
Intrinsic Factor PK	CL0600-017	PK, single dose, hepatic impairment	Phase 1, open-label, parallel-group, prospective, controlled trial	20 mg SC (abdomen)	24 (12 impaired; 12 healthy)	Hepatically impaired subjects and healthy matched control subjects	Single dose	LC-MS/MS (US)
	CL0600-018	PK, single dose, renal impairment	Phase 1, open-label, parallel group, prospective trial	10 mg SC (abdomen)	36 (18 impaired; 18 healthy)	Subjects with renal impairment (moderate or severe renal impairment, or end stage renal disease) or healthy subjects	Single dose	LC-MS/MS (EU)
PK/PD in healthy subjects	C09-001	QTC study	Phase 1, single centre, single dose, placebo and positive controlled, 4-period, change over design	5 and 20 mg SC; Positive control moxifloxacin 400 mg PO Placebo negative control	72 (all treated w/ teduglutide)	Healthy male or female subjects	Single dose in 4 treatment periods	LC-MS/MS (EU)
	C10-003	PD, gastric emptying (using acetaminophen absorption kinetics)	Phase 1, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group study	4 mg SC Placebo control Other agent: Acetaminophen 1000 mg	36 (13 placebo 23 teduglutide)	Healthy male or female subjects	qd for 10 days Acetaminophen at Days 0 and 10	LC-MS/MS (US)
PK/PD in SBS patients	ALX-0600-92001	PK and PD, multiple SC doses	Phase 2, open-label, multicentre, dose-ranging, pilot study	0.03, 0.1, 0.15 mg/kg/day SC (abdomen)	17 (all treated w/ teduglutide)	Male or female SBS patients without colon or with ≥ 50 of their colon continuity	qd or bid for 21 days	ELISA

Type of Study	Study Number	Study objective	Study Design and Type of Control	Teduglutide dose and routes (site); Control	Number of Subjects enrolled	Healthy Subjects or Diagnosis of Patients	Total duration of Treatment	PK Assay Method
Efficacy and safety studies in SBS patients Placebo controlled	CL0600-020 (Pivotal)	To evaluate the efficacy, safety, tolerability and pharmacokinetics of Teduglutide compared with placebo in patients with parenteral nutrition-dependent SBS	Pivotal Phase 3, placebo-controlled study	0.05 mg/kg SC Placebo control	85 dosed (43 placebo 42 teduglutide)	Male and female parenteral nutrition-dependent SBS patients	qd for 24 weeks	No PK
	CL0600-004 (Supportive)	To evaluate the efficacy, safety, tolerability and pharmacokinetics of Teduglutide compared with placebo in patients with parenteral nutrition-dependent SBS	Phase 3, placebo-controlled study	0.05, 0.10 mg/kg SC placebo control	83 (16 placebo 67 teduglutide)	Male and female parenteral nutrition-dependent SBS patients	qd for 24 weeks	LC-MS/MS (US)
Efficacy and safety studies in SBS patients Open-label extension	CL0600-021	A Study of the Safety and Efficacy of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome Who Completed Protocol CL0600-020	Phase 3, extension study of CL0600-020	0.05 mg/kg/day SC	88 (all teduglutide)	Patients with parenteral nutrition-dependent SBS who completed study CL0600-020	qd for 28 weeks (on-going study)	No PK
	CL0600-005	A Study of the Safety and Efficacy of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome Who Completed Protocol CL0600-004	Phase 3, extension study of CL0600-004	0.05, 0.10 mg/kg/day SC	65 (all teduglutide)	Patients with parenteral nutrition-dependent SBS who completed study CL0600-004	qd for 28 weeks	No PK
Efficacy and safety studies in CD patients	CL0600-008	To assess the efficacy of different doses of Teduglutide in subjects with moderately active Crohn's disease (CD) as compared to placebo	Phase 2, randomized, double-blind, placebo-controlled study	0.05, 0.10, or 0.20 mg/kg/day SC; placebo	100 (25 placebo 75 teduglutide)	Male and female subjects with moderately active Crohn's disease	qd for 8 weeks (self-administered)	LC-MS/MS (US)
	CL0600-009	An open label extension study of the safety & efficacy of Teduglutide (ALX-0600) in subjects with Crohn's Disease who completed the study protocol CL0600-008	Phase 2, open-label extension of the study CL0600-008	0.10 mg/kg/day SC	67 (all teduglutide)	Patients who completed study CL0600-008	qd for 12 weeks	No PK

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Primary Efficacy Endpoint:

The primary efficacy endpoint in the pivotal Phase 3 study (CL0600-020) and the supportive Phase 3 study (CL-0600-004) was based on the percentage of subjects who achieved a reduction of 20% to 100% in PN/IV volume from baseline. This endpoint was used to support the US approval for Zorbtive. The primary efficacy endpoints of Studies CL0600-020 and CL0600-004 are below:

- Study CL0600-020 utilized a binary (responder and non-responder) endpoint that assessed the difference between treatment groups (teduglutide 0.05 mg/kg/day and placebo) in the number and percentage of subjects who achieved a reduction of 20% to 100% from baseline in PN/IV volume response at Week 20 and at Week 24.
- Study CL0600-004 used a graded response endpoint that accounted for the intensity and duration of the PN/IV volume reduction at the end of the 24-week treatment period.
- Each study included the endpoint from the other study as a secondary efficacy endpoint.

Clinically Meaningful Exploratory Biomarkers

Exploratory PD biomarkers were assessed during the clinical development process. Two clinically meaningful ones are listed below (refer to section 2.2.6 for study results):

1. Parameters of gastrointestinal absorption

A 72-hour nutrient absorption sub-study was included in Studies ALX-0600-92001 and CL0600-004 to evaluate effects of teduglutide administration on absolute and relative absorption of fat, nitrogen, sodium, potassium, calories and g.i. fluid. The studies also provide information on stomal or fecal output of fat, nitrogen, sodium, potassium, calories and fluid.

2. Structural/histological mucosal changes of small and large intestine

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.

Other Exploratory Biomarkers:

Several other biomarkers were also assessed, but the clinical relevance was questionable in that the assessment was conducted in healthy subjects rather than the SBS patients or the study results were not different between placebo and treatment groups. As such, the data and the associated bioanalytical assays from these biomarkers were not reviewed in depth.

1. Gastric emptying

The effect of teduglutide on gastric emptying was examined in healthy subjects in Study C10-003 where acetaminophen absorption kinetics was determined at before teduglutide treatment and after once daily dosing of teduglutide at 4 mg for 10 consecutive days. An LC-MS/MS assay was used for the quantification of acetaminophen in human plasma.

Reviewer's comment:

The sponsor should have conducted this study in subjects with SBS rather than in healthy subjects. As reported in Gut. 1993 Sep;34(9):1171-6, SBS subjects had disturbed gastric emptying: rapid gastric emptying of liquid resulting in large stomal output of liquid and nutrients. As teduglutide was shown to increase the absorptive epithelium (as evidenced by increase in villus height and crypt depth) of gastrointestinal tract in SBS subjects, it may potentially correct the disturbed gastric emptying in this patient population. On the other hand, healthy subjects have normal gastric empty and may not be a relevant population to assess the impact of teduglutide on gastric emptying. As such, the data gained from healthy subjects after short-term treatment (10 days) are not relevant and can not be used for labeling purpose.

2. Effect on insulin, glucagon and glucose

Gastric emptying study C10-003 also included analyses of the PD of teduglutide on insulin, glucagon and glucose. Fasting blood samples for biomarkers were collected at screening. Pre- and post-prandial blood samples were collected on Day 0 prior to the meal at -3, -2.75, -2.5, -2, -1, and 0 hours, and following the meal at 15 and 30 minutes and at 1, 2, 3, 3.5, 4, 5, 6, 7, 8, 10, and 14 hours. On Day 10, pre- and post-prandial blood samples were taken at 0 hour (predose) and at 15 and 30 minutes and at 1, 2, 3, 3.5, 4, 5, 6, 8, 10, and 14 hours following teduglutide administration, with a meal given immediately following the 3-hour blood draw. A validated competitive radioimmunoassay for the quantitation of glucagon in human plasma was used. Plasma insulin and glucose levels were based on commercially available kits.

Reviewer's comment:

Similarly, the sponsor should have conducted this study in subjects with SBS rather than in healthy subjects. As reported in Gut. 1979 20:806-810, SBS subjects had disturbed pancreatic endocrine function such as persistent low insulin secretion. As such, the data gained from healthy subjects after short term treatment (10 days) are not clinically meaningful and can not be used for labeling purpose. However, according to the medical officer, Dr. John Troiani, there were no clinically significant differences between teduglutide treated and placebo subjects in terms of glucose change from baseline after 6-month teduglutide treatment (please refer to clinical review for more details).

3. Plasma citrulline

Plasma citrulline was measured in several clinical studies and was considered as a potential biomarker for absorptive enterocyte mass in patients with malabsorption syndrome, including intestinal failure and villous atrophy. An LC-MS/MS method was used to quantify plasma levels of L-citrulline.

Reviewer's comment:

It was found that plasma levels of citrulline increased after teduglutide treatment. However, the increase of plasma citrulline was not associated with a decrease in parenteral nutrition volume. Therefore, the role of plasma citrulline as a biomarker in assessing the PD effect of teduglutide is questionable.

4. Bone turn-over markers

Bone markers and effects on bone density and lean tissue were assessed in the pivotal study CL-0600-004. Several parameters such as bone-specific alkaline phosphate (BASP), pyridinoline cross-linked N-telopeptide (NTx), or the whole body mineral content were used.

Reviewer's comment:

Teduglutide treatment resulted in no statistically difference between placebo and teduglutide treatment group and the role of these biomarkers in assessing the PD effect of teduglutide is unknown.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic (PK) parameters and exposure response relationships?

Yes, three different assays were used to measure the plasma concentrations of teduglutide, the active moiety, including an enzyme-linked immunosorbent assay (ELISA) and two assays based on liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). One LC-MS/MS assay was developed for studies conducted in USA in which plasma samples were prepared with tripotassium ethylenediaminetetraacetic acid [K₃EDTA]) and one for studies conducted in European Union in which plasma samples were obtained from potassium-EDTA anticoagulated blood. Please refer to Section **2.6 Analytical** for more information about the performance of these bioanalytical assays.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Effect on PN/IV (Primary Clinical Endpoint)

In the 24-week Study CL0600-004, changes in weekly PN/IV volume were evaluated with two dose levels of teduglutide (0.05 and 0.10 mg/kg/day) in subjects with PN/IV-dependent SBS. For the teduglutide 0.05 mg/kg/day group, the proportion of subjects achieving a 20% to 100% reduction in PN/IV at Weeks 20 and 24 (responder) was statistically significantly higher compared with the placebo group (45.7% vs. 6.3%; p = 0.005). However, no statistical difference was observed between the 0.10 mg/kg/day group and placebo (25.0% vs. 6.3%; p = 0.172).

Reviewer's comments:

The sponsor proposed several arguments why the responder rate of the 0.10 mg/kg/day group was even lower than that of the 0.05 mg/kg/day group. They included:

- PN/IV reductions were limited to $\leq 10\%$
- PN/IV changes were not made until week 4
- Higher Baseline PN/IV in 0.10 mg/kg/day group
 - Numeric effect of large denominator on calculation of response percentages
 - 0.10 group: 12.7 L/wk decreased 2.5 L at Week-24: (-14%)
 - 0.05 group: 9.6 L/wk decreased 2.5 L at Week-24: (-25%)
 - Placebo group: 10.7 L/wk decreased 0.9 L at Week-24: (-8%)

The clinical reviewer, Dr. John Troiani, reviewed these arguments and found them acceptable. Additionally, adjustments were made in the pivotal trial (CL0600-020), such as allowing PN/IV reductions up to 30% and changes could be made at Week 2.

For the secondary efficacy endpoint, at Week 24, both active treatment groups demonstrated a mean weekly decrease in PN/IV volume of 2.5 L versus 0.9 L in the placebo group ($p = 0.08$ for each comparison) indicating that both doses have similar efficacy ($p = 0.98$).

Altogether, these results seem to suggest that the maximum efficacy reached plateau around 0.05 mg/kg/day.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

In the 2 SBS Placebo-Controlled Studies (CL0600-004 and CL0600-020), 99 of the 109 subjects treated with teduglutide (91%) reported a total of 778 treatment-emergent adverse event (TEAEs), and 49 of the 59 subjects treated with placebo (83%) reported a total of 369 TEAEs. The percentage of subjects who experienced a TEAE in the teduglutide 0.05 mg/kg/day group (88%, 68/77) was comparable to that in the placebo group (83%, 49/59). The percentage of subjects who experienced a TEAE in the teduglutide 0.10 mg/kg/day group (97%, 31/32) was higher than in either of the other 2 treatment groups. However, the overall high incidence and nature of the TEAEs in this population across both the teduglutide-treated and placebo-treated subjects most likely represents both the underlying disease and parenteral support complications often observed in the SBS population.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No significant QTc prolongation effect of teduglutide (5 mg and 20 mg) was detected in the TQT study C09-001. In this randomized, partially blinded, single-dose, four-way crossover, active- and placebo-controlled study, 70 healthy subjects received teduglutide 5 mg, teduglutide 20 mg, placebo, and moxifloxacin 400 mg (positive control). Overall summary of findings is presented in Table 2 (Please refer to the interdisciplinary QT review).

Table 2. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Teduglutide 5 mg, Teduglutide 20 mg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Teduglutide 5 mg	24	1.2	(-0.7, 3.0)
Teduglutide 20 mg	5	3.0	(0.8, 5.2)
Moxifloxacin 400 mg*	4	14.1	(12.1, 16.1)

- Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 10.5 ms.
- $\Delta\Delta\text{QTcF}$: difference between teduglutide and placebo on the baseline-corrected QT interval using Fridericia's formula)

The largest upper bounds of the 2-sided 90% CI for the mean differences between teduglutide (5 mg and 20 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The positive control, moxifloxacin did produce QTc prolongation as the largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 10 ms.

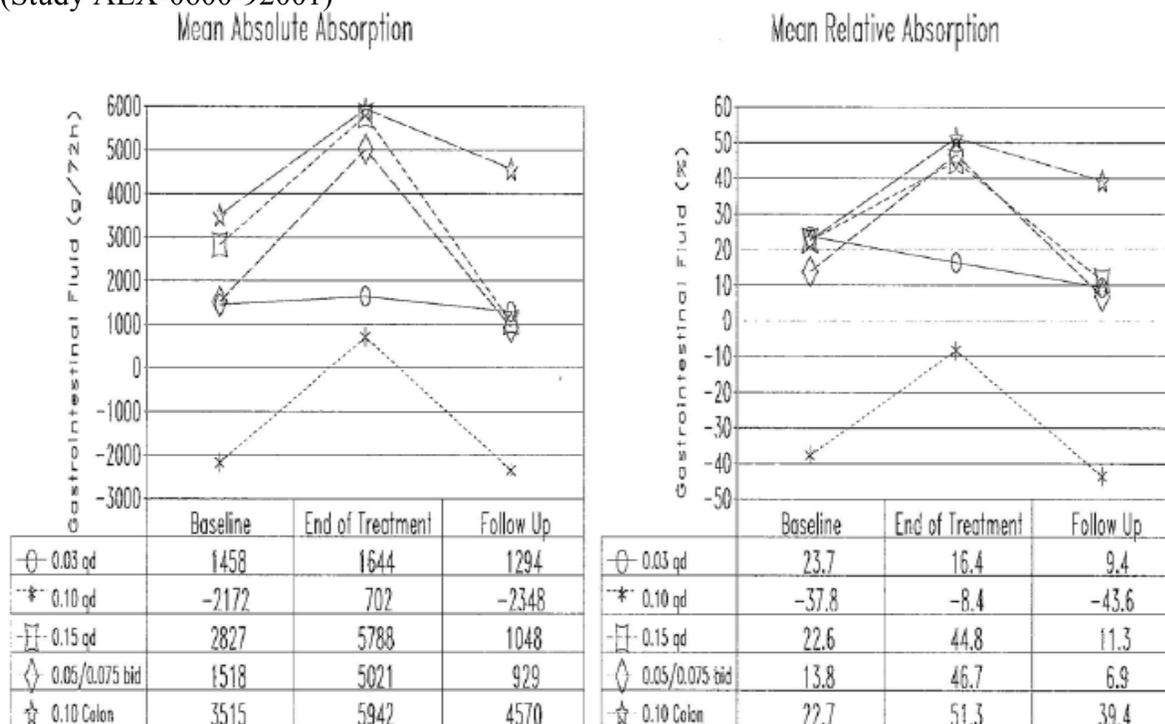
The supra-therapeutic dose (a single 20-mg dose) produces mean C_{max} value of 242 ng/mL which is significantly higher than the median C_{max} (36 ng/mL) for the therapeutic dose (0.05 mg/kg/day). Altogether, there are no detectable prolongations of the QT-interval at a dose significantly greater than the proposed dose.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes. The selected dosing regimen, 0.05 mg/kg once a day SC injection, was the dosing regimen studied in the pivotal Phase 3 study, CL0600-020, and was consistent with the dose-response relationship for both efficacy and safety. There are no unresolved issues on dosing or administration.

The dose-response data from a dose-ranging Phase 2 study (ALX-0600-92001) guided the choice of doses (0.05 and 0.1 mg/kg) for Phase 3 Study CL0600-004. In Study ALX-0600-92001, a highly significant ($p < 0.05$) increase in gastrointestinal fluid absorption (approximately 750 to 1000 mL/day, corresponding to a relative increase of up to 30%) was observed at the end of treatment with both teduglutide doses of 0.10 and 0.15 mg/kg/day, but not with the dose of 0.03 mg/kg/day. Additionally, there were no differences between the 0.10 mg/kg/day group and the 0.15 mg/kg/day group (Figure 2). Therefore, in the Phase 3 Study CL0600-004, 0.10 mg/kg/day dose was selected as the high dose and 0.05 mg/kg/day was selected as the low dose to investigate whether a dose lower than 0.10 mg/kg/day but greater than 0.03 mg/kg/day was effective.

Figure 2. Mean Absolute and Relative Absorption of Gastrointestinal Fluid by Treatment Groups (Study ALX-0600-92001)



Results of Study CL600-004 showed unexpectedly no apparent dose-response relationship in terms of the percentage of responders (as described in Section 2.2.4.1). For the teduglutide 0.05 mg/kg/day group, the proportion of subjects achieving a 20% to 100% reduction in PN/IV at Weeks 20 and 24 (responder) was statistically significantly higher compared with the placebo group (45.7% vs. 6.3%; $p = 0.005$). However, no statistical difference was observed between the 0.10 mg/kg/day group and placebo (25.0% vs. 6.3%; $p = 0.172$).

Subsequently, 0.05 mg/kg/day dose was selected for further confirmation in the pivotal study CL0600-020.

Overall, efficacy results from studies CL0600-004 and CL0600-020 provided substantial and reproducible evidence of the effectiveness of teduglutide at the proposed dose of 0.05 mg/kg/day administered SC for the treatment of adults with SBS.

With respect to dose-response relationship for safety, as stated in Section 2.2.4.2, the percentage of subjects who experienced a TEAE in the teduglutide 0.05 mg/kg/day group (88%, 68/77) was comparable to that in the placebo group (83%, 49/59). The percentage of subjects who experienced a TEAE in the teduglutide 0.10 mg/kg/day group (97%, 31/32) was numerically higher than placebo or 0.05 mg/kg/day group.

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

Pharmacokinetic properties of teduglutide were characterized in multiple studies in which teduglutide of different formulation strengths were administered and teduglutide plasma

concentrations were quantified using different assay methods. Table 3 is a summary of these features and the key assessments of the teduglutide clinical pharmacology studies.

Table 3. Summary of Studies Providing Teduglutide PK Information

Study #	PK Assay	Form. Conc. (mg/mL)	Key clinical pharmacology findings
CL0600-006	ELISA	10	%F, t _{1/2} , Vd, CL, C _{max} , AUC, T _{max} (HV)
CL0600-015	ELISA & LC-MS/MS	20	Relative %F in thigh & arm versus abdomen (HV)
1621/13	ELISA	3.5	C _{max} , AUC, T _{max} , linear PK (HV)
CL0600-017	LC-MS/MS (US)	20	Hepatic impairment impact on PK
CL0600-018	LC-MS/MS (EU)	10	Renal impairment impact on PK
C09-001	LC-MS/MS (EU)	10	No QTc prolongation, linear PK (HV)
CL0600-022	LC- MS/MS (US)	20/50	No accumulation, linear PK, , formulation strength impact on PK (HV)
CI0-003	LC- MS/MS (US)	8	No accumulation (HV)
ALX-0600-92001	ELISA	10	Linear PK and no accumulation (SBS patients)
CL0600-004	LC- MS/MS (US)	10/20	Linear PK and no accumulation (SBS patients)

Of note, teduglutide formulation strength appears to have an impact on teduglutide PK upon SC administration (Study CL0600-022). Therefore, the summary of clinical pharmacology findings are primarily based on data obtained with the to-be-marketed formulation strength (10 mg/mL).

Teduglutide PK for the to-be-marketed formulation after SC administration of the proposed clinical dose was characterized in the target patient population during Phase 3 study CL0600-004 using LC/MS/MS method.

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Single/Multiple Dose PK in Healthy Subjects (Study CL0600-022)

Study CL0600-022 was a Phase 1, double-blind, randomized, placebo-controlled study conducted to investigate the PK, safety, and tolerability of teduglutide following once daily SC injection to abdomen for 8 consecutive days in healthy subjects. Teduglutide was provided as 20 and 50 mg/vial lyophilized powder, reconstituted prior to administration with 1.0 and 1.2 mL of sterile water, respectively. A total of 95 male and female subjects were randomized (71 received teduglutide and 24 received placebo). The teduglutide treatments that were administered are summarized in below Table 4.

Table 4. Teduglutide Treatments in Study CL0600-022

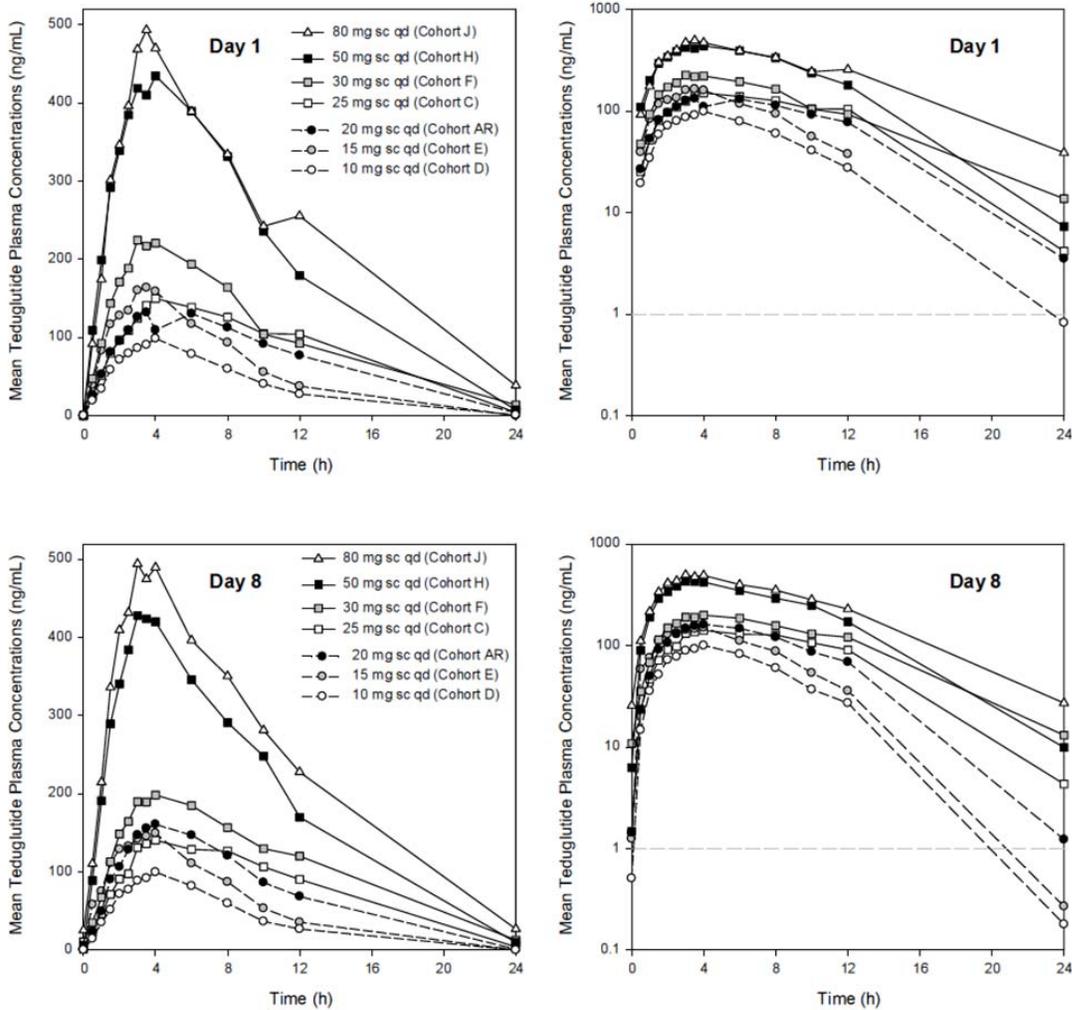
Cohort	Teduglutide (mg/dose)	Daily Dose (mg)	Formulation (mg/mL)	Volume per Injection (mL)
A	20	20	20	1.0
AR	20	20	50	0.4
C	25	25	50	0.5
D	10	10	50	0.2
E	15	15	50	0.3
F	30	30	50	0.6
H	50	50	50	1.0
J	80	80	50	0.8 (2x) ^a

^aEach 80-mg dose was administered as 2 injections of 0.8 mL given 3- to 4-cm apart within a single quadrant of the abdomen.

Blood samples were collected on Days 1 and 8 as follows: 0 hour (within 30 minutes of dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours postdose. Teduglutide plasma levels were assessed using a validated LC-MS/MS assay with a linear range of 1.00 to 120 ng/mL. The timing of blood samples was judged appropriate for characterizing the PK of teduglutide given its route of administration and its $t_{1/2}$.

Mean plasma concentration–time profiles of teduglutide on Days 1 and 8 following SC administration of the 50 mg/mL formulations are presented on linear and semi-log scales in below Figure 3.

Figure 3. Pharmacokinetic Profiles of Teduglutide on Days 1 and 8 Following SC Administration of the 50 mg/mL Formulation Over 10 to 80 mg Dose Range



Pharmacokinetic parameters of teduglutide were calculated using non-compartmental methods. Descriptive statistics of PK parameters of teduglutide following SC administration of the 50 mg/mL formulations on Days 1 and 8 are presented below (Table 5).

Table 5. Descriptive Statistics of PK Parameters of Teduglutide (in 50 mg/mL formulation) On Days 1 (Top) and 8 (Bottom) (Study CL0600-022)

CL0600-022 Teduglutide PK parameters							
Arithmetic Mean (±SD)							
Median (Minimum-Maximum)							
Dose Level	C _{max} (ng/mL)	T _{max} (h)	t _½ (h)	AUC _{0-last} (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	CL/F (L/h)	Vd _{ss} (L)
10 mg Day 1 (n=9)	100.789	4.169 (±1.1159)	3.198	773.550	857.036	11.98 (±2.08)	55.81 (±24.5)
	(±38.0606)	4.000	(±1.2971)	(±128.3251)	(±146.1475)	11.67	55.02 (17.36-87.33)
	90.300	(3.00-6.00)	3.269	736.908	857.159	(9.04-15.12)	
	(52.80-157.00)		(1.11-5.63)	(628.93-952.94)	(661.39-1106.50)		
15 mg Day 1 (n=9)	175.011	4.111 (±3.0391)	3.166	1172.131	1422.632	11.35 (±2.84)	50.83
	(±89.3289)	3.500	(±1.7743) ¹	(±444.3884)	(±483.1919)	11.52	(±32.74)
	158.000	(1.50-12.00)	3.039	1018.527	1305.993	(5.93-15.44)	34.05 (19.57-114.19)
	(71.10-360.00)		(1.33-5.94) ¹	(647.73-2129.99)	(971.51-2527.38)		
20 mg Day 1 (n=9)	152.333	5.278 (±2.9907)	3.377	1429.759	1528.052	13.29 (±1.65)	65.82
	(±54.4771)	4.000	(±2.3078) ¹	(±162.1779)	(±213.2013)	14.01	(±50.05)
	137.000	(3.00-12.00)	2.573	1415.266	1427.372	(10.44-14.9)	50.49 (23.17-184.7)
	(101.00-288.00)		(1.45-8.59) ¹	(1126.68-1751.48)	(1342.38-1915.69)		
25 mg Day 1 (n=9)	162.222	6.111 (±2.8370)	3.600	1657.661	1784.353	15.21 (±4.00)	73.08
	(±51.2781)	6.000	(±1.7007)	(±310.0141)	(±653.0724)	15.35	(±20.34)
	140.000	(3.50-12.00)	3.003	1647.577	1628.558	(7.56-21.59)	76.58 (45.08-97.79)
	(100.00-268.00)		(2.07-7.32)	(1140.19-2134.69)	(1157.81-3306.31)		
30 mg Day 1 (n=9)	249.667	5.333 (±1.9365)	5.526	2189.149	2633.976	13.37 (±4.97)	80.99
	(±169.3148)	6.000	(±6.9703)	(±628.1884)	(±1295.2758)	13.98	(±51.04)
	198.000	(3.00-8.00)	3.973	1997.259	2145.761	(5.36-21.36)	63.69 (21.05-183.9)
	(119.00-684.00)		(1.67-23.78)	(1359.27-3367.88)	(1404.39-5596.20)		
50 mg Day 1 (n=9)	456.333	3.889 (±1.6729)	3.326	4166.215	4526.310	11.54 (±2.48)	54.97
	(±96.5104)	4.000	(±1.0287)	(±864.6377)	(±1020.3379)	11.65 (8.24-15.01)	(±19.83)
	472.000	(2.50-8.00)	3.066	4077.550	4292.754		49.24 (34.02-82.28)
	(292.00-584.00)		(2.06-4.84)	(3271.81-5990.78)	(3331.32-6069.63)		
80 mg Day 1 (n=8)	562.125	6.500 (±3.6154)	5.405	5112.627	5707.111	14.38 (±2.59)	108.5
	(±355.0756)	6.000	(±4.9921)	(±1002.1169)	(±972.1869)	13.76	(±92.55)
	396.500	(3.00-12.00)	3.546	4858.870	5818.008	(11.25-18.65)	84.37 (29.98-271.92)
	(312.00-1210.00)		(1.84-14.57)	(3999.28-7104.71)	(4289.65-7108.49)		

CL0600-022 Teduglutide PK parameters (Cont'd)							
Arithmetic Mean (±SD)							
Median (Minimum-Maximum)							
Dose Level	C _{max} (ng/mL)	T _{max} (h)	t _½ (h)	AUC _{0-last} (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	CL/F (L/h)	Vd _{ss} (L)
10 mg Day 8 (n=8)	103.575	4.188 (±1.1934)	3.404	739.901	863.413	11.84 (±1.81)	57.77
	(±36.1655)	4.000	(±1.5347)	(±144.6908)	(±140.1112)	11.81	(±26.52)
	97.400	(3.00-6.00)	2.909	725.146	849.860	(8.84-14.2)	51.98 (25.25-93.55)
	(62.50-158.00)		(1.40-5.73)	(519.79-1001.81)	(704.26-1131.21)		
15 mg Day 8 (n=8)	186.256	2.569 (±1.5125)	2.985	1134.979	1288.512	11.12 (±3.58)	49.08
	(±105.4469)	2.750	(±1.1469)	(±565.7867)	(±663.0747)	10.65	(±22.92)
	178.500	(0.52-4.00)	2.552	1244.916	1403.423	(7.08-16.09)	49.02 (26.82-93.39)
	(5.05-332.00)		(1.89-5.26)	(14.60-1960.44)	(17.78-2118.16)		
20 mg Day 8 (n=9)	165.122	4.224 (±1.1198)	4.499	1418.048	1789.506	11.67 (±2.78)	71.87
	(±57.4438)	4.000	(±2.5128)	(±288.3659)	(±364.1459)	10.82	(±33.08)
	147.000	(2.50-6.00)	3.986	1250.694	1847.719	(9.26-16.4)	83.63 (20.55-115.33)
	(92.10-267.00)		(1.49-8.24)	(1178.99-2025.14)	(1219.34-2160.07)		
25 mg Day 8 (n=9)	150.489	4.450 (±2.2962)	4.631	1529.100	1923.626	14.84 (±4.73)	89.83
	(±47.8351)	4.000	(±2.6808)	(±290.2515)	(±928.6685)	14.49	(±38.55)
	162.000	(3.00-10.00)	3.478	1529.369	1725.869	(5.9-22.04)	78.69 (43.33-175.41)
	(87.40-217.00)		(2.50-10.76)	(1062.08-1937.14)	(1134.09-4235.55)		
30 mg Day 8 (n=8)	211.375	4.879 (±1.2507)	4.609	2265.971	2432.936	13.14 (±3.57)	92.42
	(±101.6365)	5.000	(±1.9295)	(±679.2636)	(±651.4382)	13.07	(±53.67)
	178.500	(3.00-6.02)	4.866	2106.034	2296.027	(8.65-19.19)	88.13 (24.75-160.56)
	(101.00-369.00)		(1.98-6.55)	(1434.17-3462.95)	(1562.99-3468.73)		
50 mg Day 8 (n=8)	454.000	3.758 (±1.0647)	3.249	4056.653	4315.967	12.07 (±2.75)	57.5 (±34.12)
	(±156.5722)	3.750	(±1.7532)	(±987.7647)	(±894.8361)	11.62	42.92 (26.04-119.58)
	418.500	(2.50-6.00)	2.639	4026.948	4306.343	(8.48-17.85)	
	(255.00-650.00)		(1.78-6.41)	(2765.04-5860.50)	(2800.85-5893.55)		
80 mg Day 8 (n=8)	554.500	4.500 (±1.6690)	4.494	5088.384	5377.456	15.23 (±2.43)	107.14
	(±329.7739)	4.000	(±3.3479)	(±1208.6102)	(±910.0106)	15.93 (11.79-18.47)	(±92.36) 81.6
	456.500	(3.00-8.00)	3.649	4832.400	5026.118		(28.62-286.71)
	(242.00-1220.00)		(1.66-10.76)	(3318.49-6783.20)	(4332.40-6786.45)		

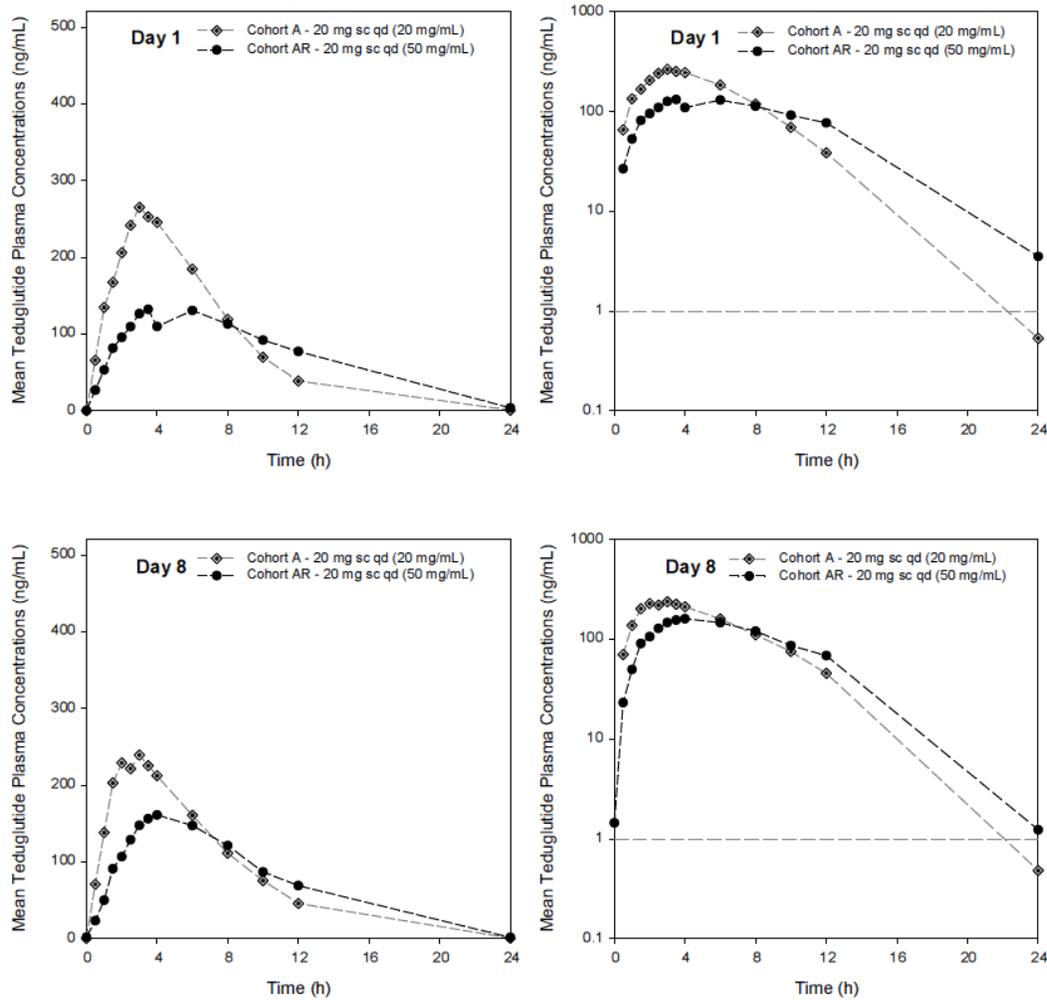
Peak plasma concentrations of teduglutide were observed at approximately 3~5 hours (2.75 to 6 hours) after SC administration on Days 1 and 8. Teduglutide was absorbed and then rapidly eliminated, declining in a mono-exponential manner with median $t_{1/2}$ values ranging from 2.6 to 4.9 hours. The mean AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} parameters of teduglutide were similar on Days 1 and 8 across dose ranges between 10 and 80 mg teduglutide. These findings suggest minimal accumulation of the drug following once daily SC injection for 8 consecutive days in healthy subjects.

The dose-proportionality in AUC_{0-t} and $AUC_{0-\infty}$ of teduglutide given once daily was confirmed over the 10 to 80 mg dose range. However, C_{max} values of teduglutide increased in a dose-proportional manner over the 10 to 50 dose range.

Reviewer's comments:

- *It is important to point out that the study dose range 10 to 80 mg is well above the proposed 0.05 mg/kg/day dose. Overall, the dose-proportionality was demonstrated in the dose range 0.05 to 0.4 mg/kg (see Section 2.2.5.8), therefore, the proposed therapeutic dose, 0.05 mg/kg, falls within the linear range.*
- *The formulation strength appears to have impact on the extent of exposure following SC injection. The total exposure and peak plasma concentration of teduglutide 20 mg following SC administration of 1.0 mL of a 20 mg/mL formulation of teduglutide (Cohort A) were approximately 15% and 78% higher than those observed following SC administration of 0.4 mL of a 50 mg/mL formulation of teduglutide (Cohort AR, Figure 4). The comparison between groups for C_{max} was statistically significant ($p < 0.0015$). As such, PK comparison among studies using different formulation strength should take this into account. To alleviate the concerns of PK variation due to formulation strength, the Phase 3 trials used the to-be-marketed formulation concentration (10 mg/mL).*

Figure 4. Mean Plasma Concentration Profiles of Teduglutide on Days 1 and 8 for Cohort A (20 mg/mL) and AR (50 mg/mL)



Multiple Dose PK in SBS Subjects (Study CL0600-004)

Study CL0600-004 was a Phase 3, randomized, double-blind, parallel-group, multicenter/multinational, 24-week study designed to evaluate the efficacy, safety, tolerability, and PK of 2 dose levels of teduglutide compared with placebo in subjects with PN/IV-dependent SBS. Teduglutide was administered by SC injection once daily into the abdomen or thigh for 24 weeks. A total of 83 subjects were randomized in a 2:2:1 ratio to 1 of 3 treatment arms: 0.05 mg/kg/day teduglutide (10 mg/mL), 0.10 mg/kg/day teduglutide (20 mg/mL), or placebo. A total of 63 subjects (of which 40 and 23 subjects, respectively, received teduglutide 0.05 and 0.10 mg/kg/day) were included in the PK substudy.

Subjects had blood samples taken for teduglutide PK analyses at baseline and at Weeks 8, 16, and 24 visit. Subjects not participating in the 72-hour nutrition absorption tests and randomized to Schedules 1-6, while subjects participating in the 72-hour nutrition absorption tests were randomized to Schedule 7 (Tables 6). Schedules 1-6 reflect a sparse sampling design where a full

PK profile is composed of three data points each of 4 sampling occasions; whereas Schedule 7 produced a full PK profile at each of two sampling occasions (Table 7).

PK data presented in this section are from subjects randomized to Schedule 7 as it contained intensive PK sampling scheme and resulted in two full PK profiles on Weeks 8 and 24.

Table 6. PK Sampling Randomization in Study CL0600-004

PK Randomization	Sampling Schedule			
	Baseline	Week 8	Week 16	Week 24
1	A	A	B	C
2	A	A	C	B
3	A	B	A	C
4	A	B	C	A
5	A	C	A	B
6	A	C	B	A
Participants in the 72-hour Nutrient Absorption Test:				
7	None	D	None	D

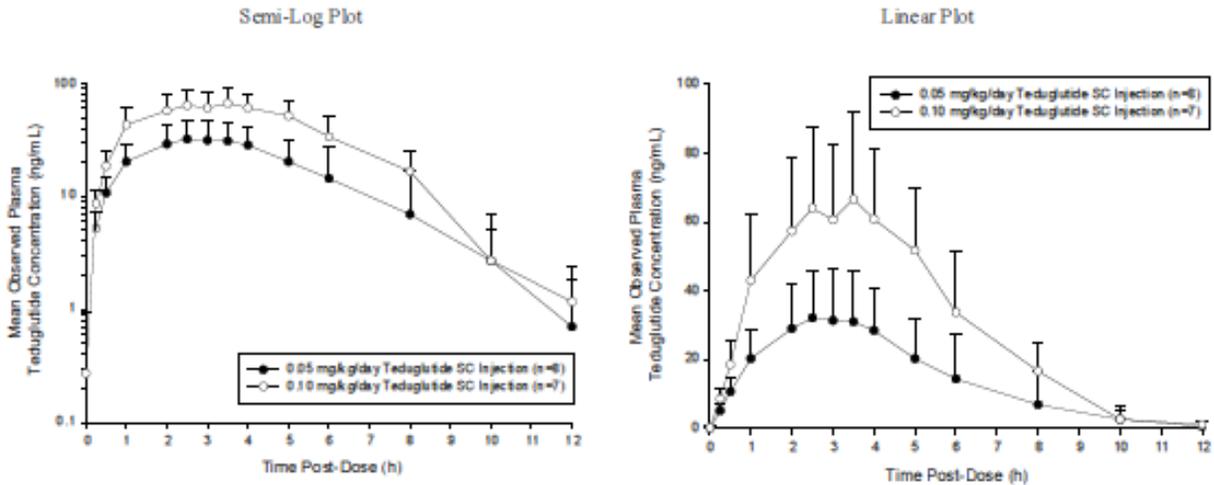
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Table 7. PK Sampling Windows in Study CL0600-004

Sampling Window	Collection Time Window (related to time of drug administration)	# of Samples
A ^{a, b}	1 hour pre-dose to 3 hours postdose	3
B ^b	3 to 6 hours post-dose	3
C ^b	6 to 9 hours post-dose	3
D ^c	Predose; 15, 30, 60 minutes, and 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours postdose	14
^a First sample must be drawn prior to drug administration. Subsequent samples should be drawn after dose administration. ^b Consecutive samples must be separated by at least 1 hour. ^c Samples from Window D must be drawn at the indicated times. No random sampling. Subjects with no peripheral venous access will provide 3 blood samples: at 60 minutes and at 2 and 3 hours postdose.		

The mean plasma concentration profiles at Week 24 of two dose levels are presented below (Figure 5).

Figure 5. Mean(\pm SD) Plasma Concentration vs. Time of Teduglutide for SBS Subjects Enrolled in the 72-hour Nutrition Absorption Tests (Study CL0600-004)



Peak plasma concentrations of teduglutide were observed at approximately 3 hours after SC administration. The median $t_{1/2}$ value was 1.3 hours. 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 ($AUC_{0-\tau}$) was 0.15 $\mu\text{g}\cdot\text{hr}/\text{mL}$. Additionally, teduglutide demonstrated a dose-proportional PK profile over the dose range of 0.05 to 0.10 mg/kg/day. The descriptive statistics of PK parameters was presented below (Table 8). One subject (0135-0002) out of 8 subjects who received daily 0.05 mg/kg teduglutide SC treatment developed ADA. As the PK parameters of this subject fell within the range of the PK parameters of the reminding 7 subjects receiving daily 0.05 mg/kg teduglutide treatment, this subject was included in the summary (Table 8 and Figure 5).

Table 8. Descriptive Statistics of PK Parameters of Teduglutide on Week 24 for Subjects Enrolled in 72-hour Nutrition Absorption Tests (CL0600-004)

(A) 0.05 mg/kg/day Teduglutide SC Injection

	AUC _{τ,ss} (mcg•h/mL)	C _{max,ss} (ng/mL)	T _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)
N	8	8	8	8	8	8
Mean	0.17	34.2	2.8	1.3	19.8	39.1
SD	0.09	14.0	0.8	0.3	7.4	18.8
CV%	50.9	40.9	28.2	19.	37.2	48.1
Median	0.15	36.8	2.8	1.3	19.7	37.1
Min	0.08	14.8	2.0	1.0	10.9	19.2
Max	0.35	50.4	4.0	1.7	28.9	67.2

(B) 0.10 mg/kg/day Teduglutide SC Injection

	AUC _{τ,ss} (mcg•h/mL)	C _{max,ss} (ng/mL)	T _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)
N	5	7	7	5	5	5
Mean	0.37	70.8	2.8	1.0	16.9	25.5
SD	0.12	21.9	1.0	0.2	4.3	8.0
CV%	31.6	30.9	34.6	21.	25.3	31.3
Median	0.30	67.2	3.5	1.0	17.5	20.6
Min	0.28	43.7	1.1	0.8	11.6	19.1
Max	0.52	103	3.6	1.4	22.9	36.6

2.2.5.2 How do the pharmacokinetics in healthy volunteers compare to those in patients?

To assess whether there is a PK difference between healthy subjects and SBS subjects, this reviewer compared the PK parameters from multiple-dose PK study in SBS patients (CL0600-004) with the PK parameters from single-dose PK study in healthy subjects (Study C09-001). This comparison is supported by no accumulation of teduglutide after repeated daily SC administration and both studies used the same to-be-market formulation strength (10 mg/mL).

As teduglutide demonstrated linear PK over the dose range 0.05 to 0.4 mg/kg, the individual PK parameters (including C_{max}, AUC, T_{max}, and T_{1/2}) at 0.05 mg/kg dose group were normalized to 5 mg, so the parameters can be compared to those at 5 mg dose level from Study C09-001. The PK parameter comparison is shown in below Table 9.

Table 9. Pharmacokinetic Parameter Comparison between Healthy and SBS Subjects at 5 mg Dose Level

PK Parameters		C09-001 (HS)	CL0600-004 (SBS)
		5 mg (N=70)	Normalized to 5 mg (N=8)
C _{max} (ng/mL)	Median (range)	61.0 (30.3-189)	59.0 (32.3-100.8)
	Mean (±SD)	64.2 (±23.4)	58.1 (±24.1)
AUC _{0-τ} or AUC _{0-∞} (ng*h/mL)	Median (range)	448.4 (268.2-742.1)	254.7 (173.3-458)
	Mean (±SD)	447.6 (±90.13)	289.6 (±116)
T _{max} (h)	Median (range)	4.2 (2.1-8.1)	2.8 (2.0-4.0)
	Mean (±SD)	4.5 (±1.0)	2.8 (±0.8)
T _{1/2} (h)	Median (range)	1.8 (0.9-4.8)	1.3 (1.0-1.7)
	Mean (±SD)	2.0 (±0.8)	1.3 (±0.3)

As shown in the above Table 9, the median or mean exposures (AUC) of teduglutide were generally lower in SBS subjects (median 254.7 ng*h/mL) compared to healthy subjects (448.4 ng*h/mL) at the same dose although the maximal peak concentrations (C_{max}) were similar. This is consistent with the observed shorter half lives in the SBS patients (median 1.33 hours) compared to healthy subjects (median 1.8 hours).

2.2.5.3 What are the characteristics of drug absorption?

Bioavailability

Teduglutide had a mean absolute bioavailability of 88% after SC administration in the abdomen (Study CL0600-006).

Study CL0600-006 was a Phase 1, randomized, 2-way crossover study designed primarily to evaluate the bioavailability, safety, and tolerability of 0.12 mg/kg teduglutide administered as a single SC injection (in 10 mg/mL formulation) and as a 1-hour IV infusion in fasted, healthy subjects. Fourteen male and female subjects between 20 and 41 years of age were randomized. Blood samples for PK analysis of teduglutide were collected during each study period as follows: immediately before teduglutide administration (0 hour), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 hours after the start of the 1-hour IV infusion or after SC injection. Additional blood samples were collected at 5, 10, and 20 minutes after the end of the IV infusion. Plasma concentrations of teduglutide were determined using a validated enzyme-linked immunosorbent assay (ELISA) method with a calibration range of 0.2 to 200 ng/mL (LLOQ of 0.05 ng/mL). As there were apparent detectable levels in some subjects prior to dosing, most likely due to endogenous GLP-2 related peptides cross-reacting with the teduglutide ELISA assay, the data were analyzed with correction for these background levels.

After termination of the IV infusion, teduglutide levels steadily declined, with mean (standard deviation [SD]) t_{1/2} values of 3.2 (± 1.67) hours. The mean (SD) volume of distribution at steady state (V_{dss}) was 103 (± 23) mL/kg. The mean (SD) clearance (CL) was 127 (± 19) mL/hr/kg. After SC injection in the abdomen, teduglutide was absorbed and rapidly eliminated from plasma with mean (SD) t_{1/2} values of 1.65 (± 0.39) hours. The results demonstrated that teduglutide is

highly bioavailable after SC administration, with a mean (\pm SD) bioavailability of 88% (\pm 14%) based on the mean AUC_{0-t} (Table 10).

Table 10. Descriptive Statistics of PK parameters Following IV or SC Administration of a Single 0.12 mg/kg Teduglutide (Corrected by Baseline, Study CL0600-006).

Dose Route	Mean (\pm SD)		Median		(Min – Max)		Vd _{ss} (mL/kg)
	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)	AUC _{0-t} (ng•hr/mL)	CL (mL/hr/kg)	F (%)	
IV (n=14)	840 (\pm 123)	1.0 (\pm 0.1)	3.2 (\pm 1.7)	979 (\pm 152)	127 (\pm 19)	---	103 (\pm 23)
	863	1.0	3.1	999	122		95.8
	(602-988)	(0.9-1.3)	(0.5-6.8)	(707-1249)	(102.3-169)		(71.3-139)
SC (n=14)	111 (\pm 18)	4.4 (\pm 2)	1.6 (\pm 0.4)	856 (\pm 189)	10.5 (\pm 2.2)	88 (\pm 14)	24.7 (\pm 8.0)
	107	4.0	1.7	862	10.8	94	23.1
	(87.7-156)	(1.5-8.0)	(1.0-2.6)	(608-1242)	(6.2-14.4)	(61-102)	(16.3-47.4)

Relative Bioavailability

The relative bioavailability of teduglutide was 89% and 92% for the thigh and arm, respectively, relative to the abdomen (based on AUC_{0-∞} [ANCOVA analysis]). The 90% CI for the AUC_{0-t} or AUC_{0-∞} was within the 80% to 125% range, indicating that total exposure was similar after SC injection (in 20 mg/mL formulation) at the 3 sites. A summary of statistical analysis results of PK parameter of 3 injection sites to determine relative bioavailability is shown in the following Table 11.

Table 11. Summary of Statistical Results of Relative Bioavailability for Teduglutide following SC Administration at Thigh or Arm Relative to Abdomen.

Parameter	Units	Mean ^a			Comparison	Ratio	90% Confidence Interval ^b
		Thigh	Arm	Abdomen			
C _{max}	ng/mL	118	NA	143	Thigh vs Abdomen	82.7	(74.0 , 92.4)
		NA	114	143	Arm vs Abdomen	79.7	(71.4 , 89.1)
AUC _{0-t}	ng•hr/mL	745	NA	851	Thigh vs Abdomen	87.5	(82.6 , 92.8)
		NA	768	851	Arm vs Abdomen	90.3	(85.1 , 95.7)
AUC _{0-∞}	ng•hr/mL	836	NA	943	Thigh vs Abdomen	88.6	(82.2 , 95.5)
		NA	869	941	Arm vs Abdomen	92.4	(85.3 , 100)

^a Geometric least squares mean from ANCOVA.
^b 90% confidence interval of geometric least squares mean ratio from ANCOVA.

It is noted that the lower bound of the 90% CI of relative C_{max} of teduglutide for the thigh and the arm, relative to the abdomen, was outside the 80% to 125% range. The point estimates for relative C_{max} was 83% for the thigh and 80% for the arm administrations relative to the abdomen administration, suggesting that C_{max} of teduglutide was lower after SC injection in thigh and arm. However, the sponsor has allowed all three injection sites in Phase 3 studies and the treatment efficacy was demonstrated.

2.2.5.4 What are the characteristics of drug distribution?

Following IV administration in healthy subjects, teduglutide had a mean volume of distribution at steady state of about 103 mL/kg (Study CL0600-006), similar to blood volume.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance study was not conducted with teduglutide. It is considered acceptable for a therapeutic peptide product.

2.2.5.6 What are the characteristics of drug 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.

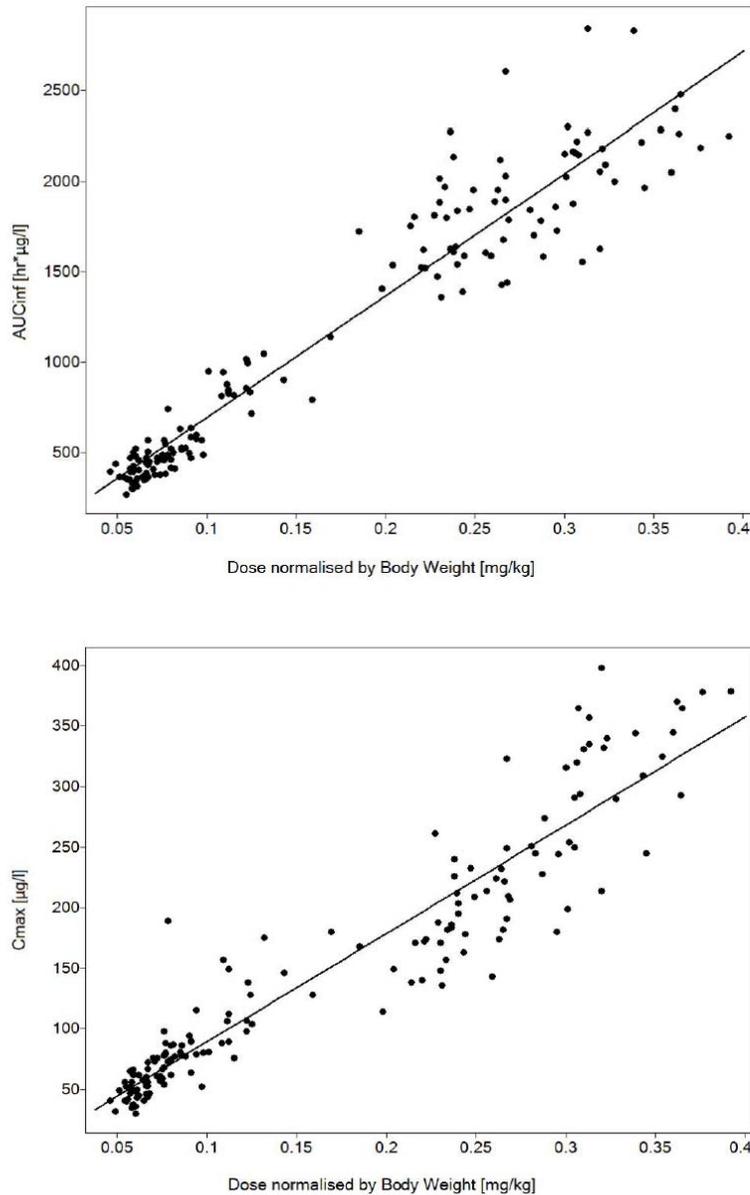
2.2.5.7 What are the characteristics of drug excretion?

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 kidneys (Study CL0600-006).

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

For the proposed commercial concentration of 10 mg/mL investigated in studies CL0600-018 and C09-001, dose proportionality was demonstrated over the dose range 0.05 to 0.4 mg/kg in healthy subjects (Figure 6).

Figure 6. Extent of Absorption (AUC and C_{max}) versus Teduglutide Doses (5, 10, and 20 mg) Normalized by Body Weight in Healthy Subjects in Pooled Studies C09-001 and CL-0600-018



2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

The mean PK parameters of teduglutide were similar on Days 1 and 8 (Study CL0600-022). These findings suggest minimal accumulation following daily administration of teduglutide (see Section 2.2.5.1).

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

Based on conventional PK analysis, inter-subject variability for AUC and C_{max} were 40% and 41%, respectively, for SBS subjects while 21% and 50%, respectively for healthy subjects (Table 9).

The major cause of variability was not investigated.

2.2.6 What are the pharmacodynamic characteristics of the drug? (Include PD parameters that are not addressed in 2.2.4 but important to understand the clinical pharmacology of the drug)

- Parameters of gastrointestinal absorption (from Study ALX-0600-92001)

Fluid absorption: A highly significantly increase in gastrointestinal fluid absorption (approximately 1000 mL/day, corresponding to a relative increase of 30%) at the end of the 21-day treatment for teduglutide doses of 0.10 and 0.15 mg/kg once daily ($p \leq 0.01$), but not for the dose of 0.03 mg/kg once daily.

Fat absorption: Statistically significant increases in fat absorption were observed at the end of treatment for teduglutide dose of 0.10 mg/kg once daily (24.3 g/day; $p = 0.028$) and 0.05 or 0.075 mg/kg twice daily (17.9 g/day; $p = 0.041$); whereas a clinically meaningful, but not statistically significant, increase was observed following dosing with 0.03 mg/day.

Nitrogen absorption: Significant increases in nitrogen were observed following dosing with 0.15 mg/kg/day (2.9 g/day; $p = 0.027$); the increase following dosing with 0.10 mg/kg/day was clinically meaningful but not statistically significant.

Calorie absorption: The increase in calorie absorption was significant at the 0.05 or 0.075 mg/kg twice daily teduglutide dose (247.4 kcal/day; $p = 0.009$), and clinically meaningful at the 0.10 mg/kg/day dose level.

- Structural/histological mucosal changes of small and large intestine (from Study CL0600-004)

Analyses of mucosal biopsies showed that teduglutide administration (0.05 mg/kg and 0.10 mg/kg doses) in SBS subjects resulted in targeted intestinal effect in the absorptive surface area within the small and large intestine with the greatest changes in mucosal-crypt architecture observed in the small intestine.

The results of the exploratory analyses of the crypt-villus architecture and cellular composition within the small and large intestine at Week 24 demonstrated that teduglutide administration induced significant structural adaptations in the intestinal mucosa of adult subjects with SBS. Both teduglutide doses induced expansion of the absorptive epithelium by increasing villus height in the small intestine (teduglutide 0.05 mg/kg/day [$p = 0.0065$] and teduglutide 0.10 mg/kg/day [$p = 0.0024$]).

The composition of the mucosa did not differ between teduglutide treated subjects and placebo treated subjects when expressed on a mucosal mass basis, indicating that these structural adaptations involved the production of additional tissue that did not differ in cellular size or composition from what was originally present. Histopathological evaluation of the intestinal tissue samples demonstrated normal tissue.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

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.

The intrinsic factor which had the most pronounced effect on teduglutide exposure was creatinine clearance (CL_{Cr}): renal dysfunction characterized by a reduced CL_{Cr} led to a clinically relevant increase in teduglutide exposure. The Phase 3 programs did not assess the impact of exposure difference caused by renal dysfunction on efficacy and safety as patients with renal impairments were not enrolled.

Renal Impairment

Study CL0600-018 was a Phase 1, open-label, prospective study designed to evaluate the effect of renal impairment on the PK parameters of teduglutide following SC administration of teduglutide 10 mg. A total of 36 subjects were enrolled in the study: 6 subjects in each of 3 groups of renal impaired subjects (moderate renal impairment [CL_{Cr} 30 to 50 mL/min], severe renal impairment [CL_{Cr} < 30 mL/min], and ESRD [requiring dialysis]), and 6 subjects with CL_{Cr} ≥80 mL/min in each matched control group with respect to gender, BMI, and age, with at least 2 elderly subjects (≥65 years) in each group.

AUC_{0-∞} and C_{max}, are higher in subjects with renal impairments (Table 12) with 90% CI not including 100%. In subjects with moderate and severe renal impairment, the ratios (renal impaired/healthy subjects) of AUC_{0-∞} and C_{max} were 141% to 172%. In ESRD subjects, the primary PK parameters of teduglutide were higher by a factor of 2.6 (AUC_{0-∞}) and 2.1 (C_{max}) compared to healthy subjects.

Table 12. Statistical Comparison of AUC_{0-∞} and C_{max} after 10 mg SC Teduglutide (Study CL0600-018)

Test Group ^a	1	3	5			
Reference Group ^a	2	4	6			
	Ratio [%]	90% CI [%]	Ratio [%]	90% CI [%]	Ratio [%]	90% CI [%]
AUC _{0-∞} (μg•h/l)	152	127-182	172	137-216	259	205-327
C _{max} (μg/l)	158	118-212	141	94-211	208	134-323

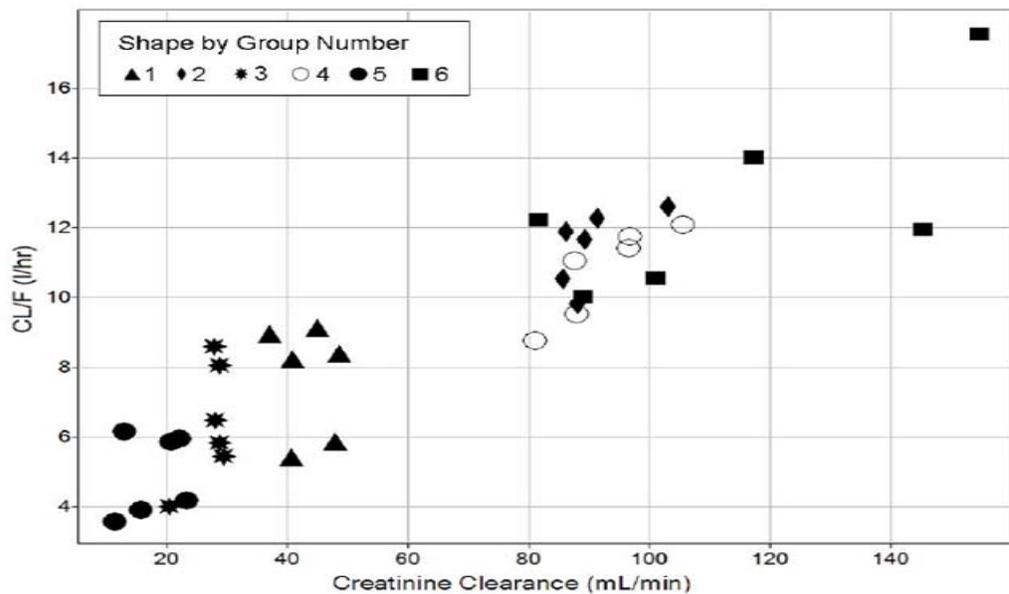
AUC_{0-∞} = Area under the concentration-time curve extrapolated to infinity; CI = Confidence interval;
C_{max} = Maximum (peak) plasma concentration; SC = Subcutaneous

^aGroup 1: Moderate renal impairment; Group 2 (Control group healthy subjects to Group 1); Group 3: Severe renal impairment; Group 4 (Control group healthy subjects to Group 3); Group 5: End stage renal disease (requiring dialysis); Group 6: (Control group healthy subjects to Group 5).

Source: Table 2-3 in CL0600-018 CSR

Generally, the apparent clearance (CL/F) of teduglutide decreased with increasing degree of renal impairment as illustrated in Figure 7, therefore, the systemic exposure to teduglutide increased with increasing degree of renal impairment.

Figure 7. Correlation of Teduglutide Clearance (CL/F) versus Creatinine Clearance in Individual Healthy Subjects and Subjects with Moderate to Severe Renal Impairment and ESRD (Study CL0600-018)



CL/F = Apparent total body clearance

Group 1: Moderate renal impairment; Group 2 (Control group healthy subjects to Group 1); Group 3: Severe renal impairment; Group 4 (Control group healthy subjects to Group 3); Group 5: End stage renal disease (requiring dialysis); Group 6: (Control group healthy subjects to Group 5).

Source: Listings 16.2.4.1, 14.2.2.1.5, 14.2.2.2.5, 14.2.2.3.5, 14.2.2.4.5, 14.2.2.5.5, and 14.2.2.6.5 CL0600-018 CSR

Hepatic Impairment

Study CL0600-017 was a Phase 1, open-label study conducted to evaluate the effect of moderate hepatic impairment on teduglutide PK following SC administration of a 20-mg dose. Twelve subjects with moderate hepatic impairment (Child-Pugh Classification, Grade B) were matched with 12 healthy subjects with a similar distribution of gender, age, renal function, and BMI. The dose of 20 mg teduglutide was used to characterize the potential impact of moderate hepatic impairment on the PK of teduglutide at the upper end of the dose range for the clinical indication. Results showed that the peak mean teduglutide concentration was lower and occurred earlier in the hepatically-impaired subjects compared to healthy matched control subjects. The arithmetic means and SD of the plasma teduglutide PK parameters from a single 20 mg SC injection administered to subjects with moderate hepatic impairment and healthy matched control subjects are summarized in the following Table 13.

Table 13. Summary of the Pharmacokinetic Parameters of Teduglutide Following Single 20 mg SC Administration to Healthy Subject and Subjects with Moderate Hepatic Impairment

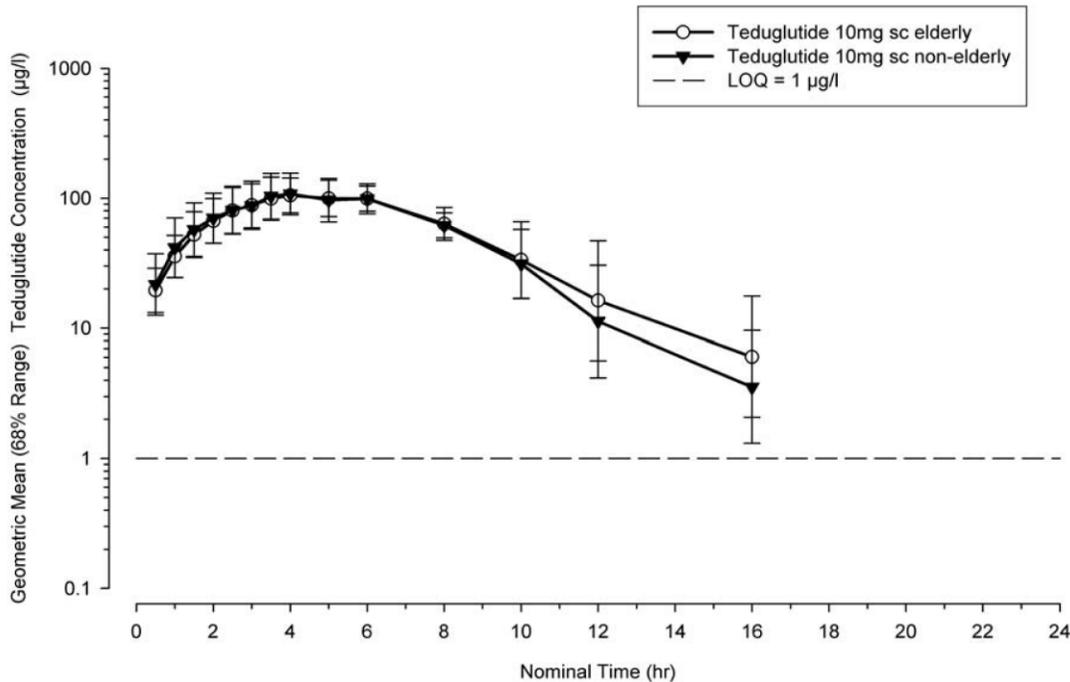
PK Parameters	Impaired Mean ± SD (N)	Normal Mean ± SD (N)	%GMR (90% CI)
C _{max} (ng/mL)	215 ± 95.6 (12)	244 ± 76.7 (12)	90.46 (75.93 – 107.77)
AUC _{0-t} (ng*hr/mL)	1676.8 ± 705.6 (12)	1993.6 ± 554.2 (12)	85.12 (70.58 – 102.67)
AUC _{0-∞} (ng*hr/mL)	1948.9 ± 854.6 (11)	2177 ± 639.3 (12)	89.40 (75.08 – 106.45)

Based on geometric mean ratios, plasma teduglutide C_{max}, AUC_(0-inf) and AUC_(0-t) values were about 10%, 10% and 15% lower, respectively, in subjects with moderate hepatic impairment compared to healthy matched control subjects. The results from this study indicate that overdose safety concern is unlikely in subjects with mild to moderate hepatic impairment. Additionally, as efficacy reached plateau at 0.05 mg/kg and 10 ~ 15% lower exposures are unlikely to be associated with significant loss of efficacy.

Elderly

Age appeared to have no effect on the PK of teduglutide in healthy subjects. As a secondary objective of Study CL0600-018, the sponsor assessed the PK profiles of teduglutide in elderly (≥ 65 years) healthy subjects. The concentration-time profiles of teduglutide plasma concentrations were similar for healthy non-elderly and healthy elderly subjects (Figure 8). Furthermore, no difference in AUC or C max of teduglutide could be detected between healthy subjects younger than 65 years (non-elderly) versus subjects older than 65 years (elderly).

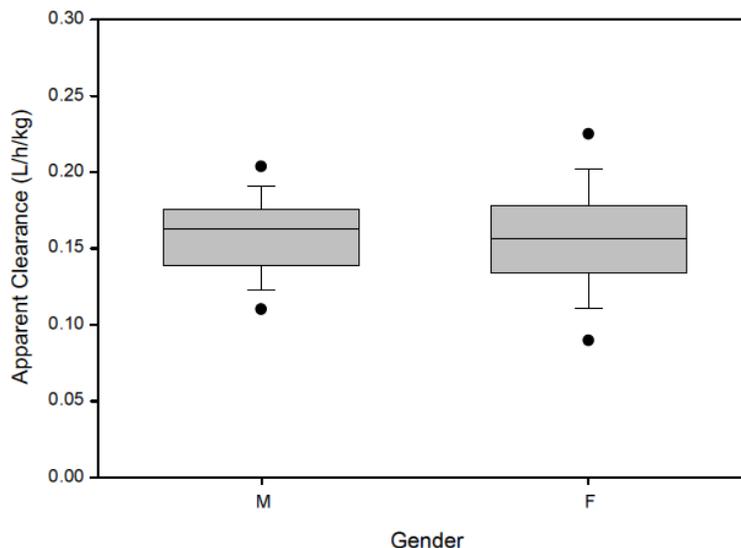
Figure 8. Comparison of Teduglutide Concentration versus Time in Healthy Elderly Subjects (≥ 65 years, $n=8$) and Non-elderly (<65 years, $n=10$)



Gender

No apparent gender differences were observed in exposure (as measure by CL/F) in healthy subjects (Study CL0600-022). The CL/F values in males and females were pooled across cohorts to assess any gender-related trends. Individual apparent clearance (CL/F) values of teduglutide were calculated and adjusted for body weight for male and female subjects. A comparison of CL/F between males and females is presented below (Figure 9). Mean CL/F values were 0.155 L/h/kg for males and 0.159 L/h/kg for females. Overall, no gender-related difference in CL/F values was observed and data distribution among males and females was similar. Therefore, gender had no apparent impact on the exposure of teduglutide based on 71 subjects who received teduglutide treatment in Study CL0600-022.

Figure 9. Comparison of CL/F in Male and Female Subjects (Study CL0600-022)



Note: Median and 5th/95th percentile are represented in the above Whisker Plot.

Race

The impact of race on PK is unknown.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

No dose adjustment is necessary in patients above the age of 65 years based on the results from Study CL0600-018.

2.3.2.2 Pediatric Patients

No pediatric patients were enrolled in the clinical studies conducted for this application as the product is intended only for adult patients. According to the Pediatric Research Equity Act of 2007, products with orphan designation are exempt from the requirements of a pediatric study.

2.3.2.3 Gender

No dose adjustment is necessary based on the results from Study CL0600-022.

2.3.2.4 Race

No dose adjustment can be recommended as the impact of race on PK is unknown.

2.3.2.5 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.

2.3.2.6 Hepatic impairment

No dose adjustment is necessary for subjects with mild and moderate hepatic impairment according to the study results from Study CL0600-017. Teduglutide has not been formally studied in subjects with severe hepatic impairment.

2.3.2.7 What pregnancy and lactation use information is there in the application?

Pregnancy Class B: Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

It is unknown whether this drug is excreted in human milk. In rats, mean teduglutide concentration in milk was less than 3% of the plasma concentration following a single SC injection of 25 mg/kg. A risk to the breastfed child cannot be excluded. The use of this drug during nursing should be avoided.

2.3.3 Immunogenicity

2.3.3.1 What is the incidence of the formation of the anti-product antibodies, including the rate of pre-existing antibodies, the rate of anti-product antibodies formation during and after the treatment, time profiles and adequacy of the sampling schedule if possible?

Overall, the immunogenicity incidence was 18% at Week 24 following once daily administration of teduglutide at 0.05 mg/kg (Study CL0600-020) and 32% in the ongoing open-label extension study (CL0600-021) where subjects have been treated with the same dose for up to 18 months.

Anti-teduglutide IgG antibody incidence – Pivotal study CL0600-020

Using a validated ECL ^{(b) (4)} assay, the incidence of anti-teduglutide IgG antibody following 24 weeks of daily SC administration of 0.05 mg/kg teduglutide was evaluated in the pivotal Phase 3 study (CL0600-020) in subjects with parenteral nutrition (PN) dependent SBS.

Thirty-four subjects were tested at Week 24, and six subjects (6/34, 18%) were positive for anti-drug antibody (ADA). Two out of these 6 ADA positive subjects were also tested for ADA at Week 12 and the ADA status was negative, indicating ADA developed between Weeks 12 and 24; whereas the remaining 4 ADA positive subjects were not tested at Week 12. At Week 12, a total of 16 subjects were tested for immunogenicity and none developed a positive ADA.

The immunogenicity incidence rate appears to increase with the duration of treatment based on two pieces of evidence (1) 0/16 ADA positive at Week 12 and 6/34 ADA positive at Week 24, and (2) among all 6 ADA positive subjects at Week 24, 2 were negative at week 12 and became positive between Week 12 and Week 24.

Of note, one subject (Patient 0136-1002) had positive ADA at baseline; however, this subject remained negative post-baseline for Study CL-0600-020.

Anti-teduglutide IgG antibody incidence – Extension study CL0600-021

In the Phase 3 open label extension study (CL0600-021) where subjects had the option to continue taking teduglutide 0.05 mg/kg/day for up to 2 years. Twenty-seven out of 85 subjects (27/85, 32%) was ADA positive at one or more time points post baseline up to the approximate 1-year cut (currently ongoing). Among 34 subjects who were treated with teduglutide in both the pivotal study and the extension study, 6 subjects tested ADA+ at baseline (of which 5 continued to be ADA+) in the extension study and 8 additional subjects became ADA+ post-baseline. The incidence rate was 38% (13/34) for subjects who received teduglutide treatment for the duration of 18 months. Among 51 subjects who initiated teduglutide treatment in the extension study, 14 subjects were ADA+ (14/51, 27%) during the extension study after teduglutide treatment of 12 months.

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

Of note, the immunogenicity assessment was based on a validated (b) (4) electrochemiluminescent (ECL) assay which has a drug tolerance significantly higher than the observed mean C_{max} at the clinical dose, 0.05 mg/kg. The same method was used in the pivotal Phase 3 study.

Again, Subject 0109-1001 had positive ADA in CL0600-020 at baseline and was negative throughout CL0600-021.

Cross-reactivity of ADA to GLP-2

The sponsor assessed the potential cross-reactivity of teduglutide-specific antibodies to endogenous GLP-2 protein. It was found that out of the six subjects who were anti-teduglutide specific antibodies positive in Study CL0600-020, 5 had evidence of cross reactivity against the native GLP-2 protein.

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Impact on Pharmacokinetics

The effect of ADA on teduglutide PK is not known as it has not been adequately assessed.

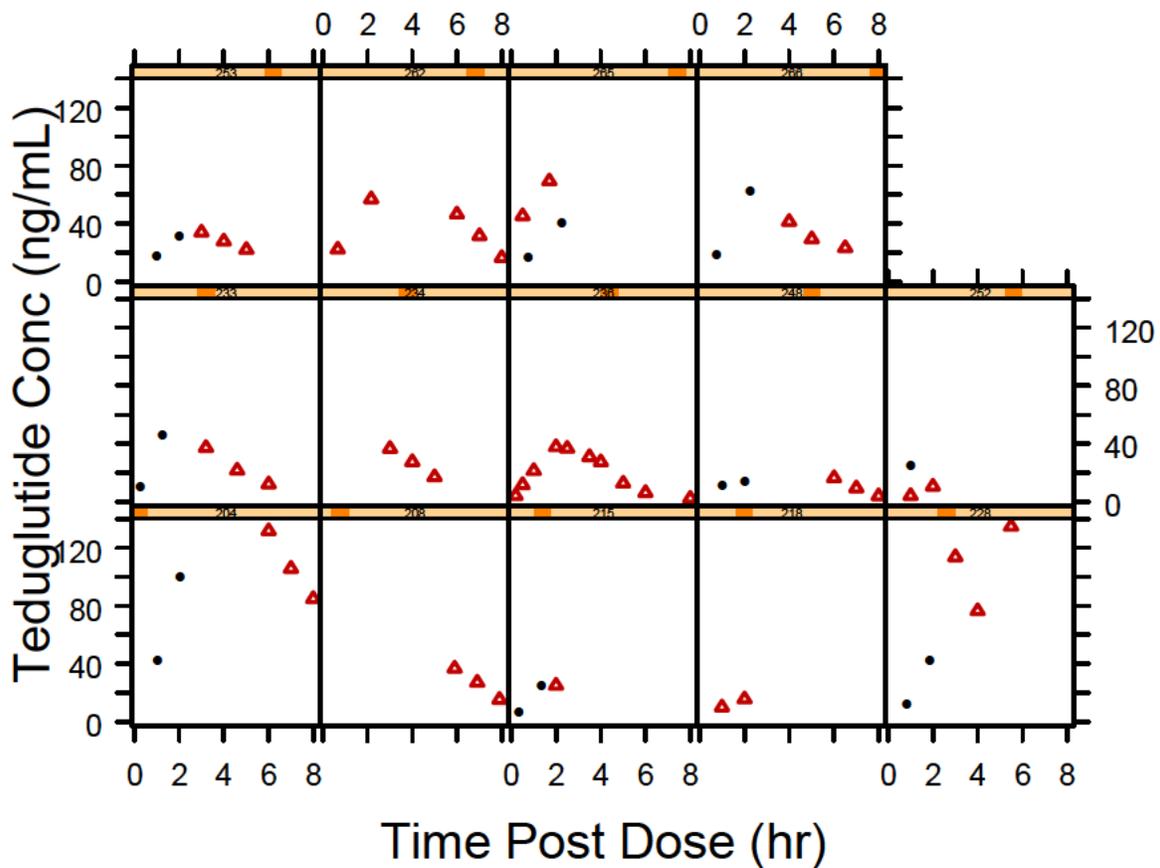
In Study CL0600-004 the sponsor collected sparse PK samples from each subject (three samples each at Weeks 0, 8, 16 and 24) and immunogenicity samples at Weeks 0 and 24 to assess the impact of ADA on PK. Given the post-treatment ADA data are only available on Week 24, PK data from Week 24 are required to evaluate the impact of ADA on teduglutide PK.

Unfortunately, the Week 24 sparse PK samples were collected at different time point post-dose in different subjects; as a result, direct comparison of PK data between ADA positive subjects and ADA negative subjects is not feasibility.

The effect of antibody titer on teduglutide PK could not be assessed from the sponsor's population PK analysis (Figure 10). The PK sampling scheme was not sufficient for evaluating the impact of ADA on PK. The primary issue was that for most individuals who developed ADA at Week 24, their PK samples collected prior to ADA development (i.e., at Week 0) only

included the absorption phase while their PK samples collected after ADA development (i.e., at Week 24) only included the elimination phase of teduglutide PK. The estimate of CL is only informed from the elimination phase, thus the PK data prior to ADA development are insufficient to estimate CL prior to ADA development for the ADA+ subjects. Given the additional complexity of the population PK model containing other confounding covariates, it would be difficult to rule out the impact of those factors in order to assess the impact of ADA on PK alone. Therefore, the impact of ADA on PK is unknown.

Figure 10. Concentration-Time Course of Teduglutide for ADA+ Subjects Who Had PK Measurements at Week 0 (black circles) and at Week 24 (open red triangles)



Impact on Pharmacodynamics

The impact of immunogenicity on pharmacodynamics of teduglutide was not assessed in this application.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

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

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

ADA appears to have no impact on short term (up to 1.5 years) clinical efficacy and the long term impact is unknown.

In the pivotal Phase 3 study (CL0600-020), all 6 ADA positive subjects were responders. In the extension study (CL0600-021), 26 out of 27 ADA positive subjects had a reduced PN/IV volume at the time of last dosing visit when compared to the baseline PN/IV volume. Altogether, the results from Studies CL0600-020 and CL0600-021 suggest that ADA appeared to have no impact on short term clinical efficacy.

2.3.3.5 What is the impact of anti-product antibodies on clinical safety (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

ADA appears to have no impact on short term (up to 1.5 years) clinical safety and the long term impact is unknown.

None of the 6 subjects who developed positive ADA in CL0600-020 had evidence of hypersensitivity adverse event (AE) or immune related clinical symptoms in the CL0600-020 study. For the open-label extension CL0600-021 study, 3 subjects (0111-1002, 0135-1001, 0203-1003) out of the 27 ADA positive subjects experienced an injection site reaction without evidence of any other hypersensitivity reactions. These results seem to suggest that ADA had no impact on short term clinical safety.

However, as mentioned previously in Section 2.3.3.1, data from both studies CL0600-020 and CL0600-021 suggested that immunogenicity incidence rate increased with treatment duration. Furthermore, 5 out of the 6 subjects who were anti-teduglutide specific antibodies positive had evidence of cross reactivity against the native GLP-2 protein in Study CL0600-020. The long term safety impact of this cross-reactivity with endogenous GLP-2 is unknown. As such, the sponsor should assess the long term safety impact of ADA in the post-marketing studies if approved.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

The sponsor did not conduct *in vivo* drug-drug interaction studies to evaluate the effect of the extrinsic factors on the clinical pharmacology of teduglutide.

2.4.2.1 What are the results of *in vitro* drug-drug interaction studies?

No *in vivo* DDI studies were conducted based on the results from *in vitro* studies in which significant inhibition or induction on tested cytochrome P450 isozymes was not observed at 2000 ng/mL teduglutide which is 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.

- Cytochrome P450 proteins (CYPs) Induction or Inhibition

Pooled human liver microsomes were used to investigate the possible effect (inhibition and induction) of teduglutide on human CYPs. Teduglutide did not inhibit the activity of any of the tested isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [10HMDZ and 6βT]) to a significant degree (> 50%) at 2000 ng/mL which is significantly greater (55-fold) than the median peak concentration (36 ng/mL) following administration of a clinical dose of 0.05 mg/kg (P10-001). Further results show that teduglutide at concentrations up to 2000 ng/mL did not induce CYP1A2, CYP2B6 and CYP3A4 *in vitro* in human hepatocytes (P10-002).

- P-glycoprotein (P-gp) Substrate and Inhibition

Determination of the P-gp substrate and inhibition potential of teduglutide was carried out using Caco-2 cell monolayers. The sponsor tested *in vitro* teduglutide concentration up to 1 μM (i.e., 3759 ng/mL) and the results showed that teduglutide did not permeate through the cell monolayers thus the efflux ratio of teduglutide could not be determined. Additionally, at a concentration of 0.75 μM (i.e., 2819 ng/mL), the percentage inhibition of teduglutide on digoxin transport was 0%. Considering the mean C_{max} of 36 ng/mL following the proposed marketing dose (S.C. 0.05 mg/kg), [I]_i/IC₅₀ for teduglutide would be significantly less than 0.1. Thus, teduglutide is not likely to be a substrate or inhibitor of P-gp at the tested concentrations based on the *in vitro* results.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

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.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Teduglutide is a monotherapy for SBS and not likely to be used with other approved therapies for SBS. Of note, the FDA approved NutreStore™ [L-glutamine for oral solution] as a cotherapy with Zorbtive™ [somatropin (rDNA origin) for injection] together with a specialized oral diet.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Yes. Teduglutide demonstrated that it increased intestinal absorption of fluids and many nutrients through increasing the gastrointestinal absorption area, thus there does exist the potential for indirect drug-drug interactions resulting from a subsequent increase in intestinal absorption of concomitant medications.

2.4.3 What issues related to dose, dosing regimens, or administration, are unresolved and represent significant omissions?

No.

2.5 General Biopharmaceutics

2.5.1 What is the pharmacokinetic and/or pharmacodynamic comparability of the proposed to-be-marketed formulation to the pivotal clinical trial? (Applicable to Biologics only)

Not applicable to this application. The pivotal Phase 3 study (CL0600-020) and the extension study (CL0600-021) were conducted using the to-be-marketed formulation.

Drug products from two manufactures, the proposed commercial manufacturing site (Hospira) and the previous manufacturing site (b)(4), were used during the clinical developed. No *in vivo* bioequivalence study has been performed comparing the products manufactured at (b)(4) and Hospira sites. This is considered acceptable because extensive *in vitro* characterizations have demonstrated comparability between teduglutide drug products manufactured at (b)(4) and Hospira sites. Please refer to CMC review by Dr. Yichun Sun for more details.

2.6 Analytical

This section should address issues related to the analytical and bioanalytical methods used to support the CPB studies.

2.6.1 What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

Three different assays were used to measure teduglutide plasma concentrations, the active moiety; an enzyme-linked immunosorbent assay (ELISA) and two assays based on liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). One LC-MS/MS assay

was developed for studies conducted in USA and the other for studies conducted in European Union based on the method for USA. .

ELISA assay

The ELISA method was developed by (b) (4) and used in 4 clinical studies (1621/13, CL0600-006, CL0600-015 and ALX-0600-92001) for the quantification of teduglutide concentration in human plasma samples. The validation results are summarized in Table 14.

The ELISA method allows measurement of intact ALX-0600 in the nanogram range with the use of ALX-0600 in-house reference standard. The procedure will measure both native glucagon-lime peptide-2 (GLP-2) and ALX-0600 (which modifies GLP-2 with a change in the amino acid in position 2).

Table 14. Validation Report for ELISA Assay

Parameter	
Analyte	Teduglutide
Matrix	Human plasma
Assay method	ELISA
Calibration range in assay	0.02 to 20 ng/mL
Calibration range in plasma	0.2 to 200 ng/mL
Linearity	$r^2 \geq 0.997$ (correlation coefficient of 4-parameter fit standard curve)
LLOQ in assay	0.05 ng/mL (Amendment 2 of report)
LLOQ in plasma	0.05 ng/mL (Amendment 2 of report)
Limit of detection in assay	0.038 ng/mL
Limit of detection in plasma	0.38 ng/mL
Inter-assay precision and accuracy	QCH: CV = 7.5%; Recovery = 99.2% QCL: CV = 3.9%; Recovery = 112.6%
Intra-assay precision and accuracy	QCH: CV = 7.8%; Recovery = 106.5% QCL: CV = 6.5%; Recovery = 120.8%
QCH/QCL stability	Human plasma samples spiked with teduglutide show acceptable recovery when stored at temperatures of -60°C to -80°C for a period of up to 2 years. (Amendment 1 of report)
Specificity	No interference from blank plasma
Signal stability	Assay plate can be read up to 72 hours after the assay has been completed. (Amendment 1 of report)
Analyte stability in thawed plasma	Stable at room temperature for at least 2 hours
Analyte stability in frozen plasma	Stable at -60°C to -80°C for at least 2 weeks
Analyte freeze-thaw stability in plasma	Stable after each of 4 freeze-thaw cycles
Standard stock solution stability	Teduglutide standard stock solution verified for 2 weeks stored at -60°C to -80°C
Stability of coated plates	Plates pre-coated with the capture antibody cannot be stored; they should be used immediately after they are prepared

CV = Coefficient of variation; ELISA = Enzyme-linked immunosorbent assay; LLOQ = Lower limit of quantitation; QCH = Quality control high-concentration; QCL = Quality control low-concentration

Reviewer's Comment:

The performance of the assay was considered acceptable based on the acceptance criteria recommended in the *Guidance for Industry: Bioanalytical Method Validation* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>).

Of note, this ELISA assay can be interfered by the endogenous or native GLP-2. In healthy subjects (Study CL0600-006), the mean (range) predose systemic native GLP-2 levels was 0.8 ng/mL (range 0-7.8 ng/mL, n=28). Most subjects (25/28) had baseline native GLP-2 levels below 1 ng/mL. As LC-MS/MS assay does not detect native GLP-2, the PK analysis was performed on the corrected data for baseline in Study CL0600-006.

LC-MS/MS assay (used in US studies)

The LC-MS/MS method developed by (b) (4) was used in 5 clinical studies: CL0600-004, CL0600-008, CL0600-015, CL0600-017, and CL0600-022.

Briefly, an aliquot of human plasma (K₃EDTA) containing the analyte and internal standard was extracted using an automated protein precipitation procedure. The extracted samples were analyzed using an (b) (4) API 4000 mass spectrometer. Multiple-charged positive ions (4+) were monitored in the multiple reaction monitoring (MRM) mode. Quantification was by peak area ratio. A summary of the in-process validation results is presented in Table 15 below.

Table 15. Validation Report for LC-MS/MS assay (used in US studies)

Parameter		
Analyte	Teduglutide	
Matrix	Human plasma (with K ₃ EDTA)	
Assay method	LC-MS/MS	
Instrumentation	(b) (4) API 4000	
Assay sample volume required	0.100 mL	
Standard curve range	1.00 to 120 ng/mL	
Regression type	Linear (1/concentration ²)	
Quantitation method	Peak Area Ratio	
LLOQ	1.00 ng/mL	
	Precision (%)	Accuracy (%)
LLOQ validation samples		
Inter-batch	12.8	96.0
Intra-batch	8.5	90.9

Quality control samples			
Inter-batch	Low (3.00 ng/mL)	5.0	107.7
	Medium (30.0 ng/mL)	4.0	107.3
	High (90.0 ng/mL)	4.9	97.8
Intra-batch	Low (3.00 ng/mL)	3.0	111.0
	Medium (30.0 ng/mL)	4.4	109.0
	High (90.0 ng/mL)	3.9	102.0
Recovery		Recovery (%)	
Analyte	Low	68	
	High	76	
Internal standard ^a		74	
Dilution integrity		Up to 500 ng/mL	
Long-term stability		6 months at -20°C; 26 months at -80°C (Addendum I of report)	
Short-term stability		23 hours at ambient temperature under non-ultraviolet-shielded light	
Freeze-thaw stability		6 cycles at -80°C	
Stock solution stability		103 days in NANOpure [®] water at -80°C	
Substock solution stability		52 days in 30% acetonitrile at -80°C	
Processed sample integrity		362 hours at 5°C	
Batch size (intra-batch)		96 injections	

K₃EDTA = Tripotassium ethylenediaminetetraacetic acid; LC-MS/MS = Liquid chromatography tandem mass spectrometry; LLOQ = Lower limit of quantitation

^aTeduglutide (b) (4) lot Log 662; purity/potency: 81.7%.

Reviewer's Comment:

The performance of the assay was considered acceptable based on the acceptance criteria recommended in the Guidance for Industry: Bioanalytical Method Validation

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>).

Compared to ELISA assay, settings of the LC-MS/MS mass analyzer assured a selective quantification of both molecules (i.e., teduglutide and native GLP-2), as their signals did not overlap. Thus, LC-MS/MS assay is more selective compared to ELISA assay. It is also noted that ELISA is slightly more sensitive than LC-MS/MS assay based on lower limit of quantification (LLOQ, 0.05 and 1 ng/mL for ELISA and LC-MS/MS, respectively).

The sponsor compared the teduglutide concentrations measured with ELISA or LC-MS/MS assays in Study CL0600-015. It was noted that the differences of teduglutide concentrations measured by these two assays were not statistically significant for blood samples collected from 30 minutes through 10 hours post dose. But a consistent trend was observed overall, with LC-MS/MS producing slightly greater teduglutide concentrations (14% greater overall [mean across all time points]) than those obtained with ELISA, particularly at the lower teduglutide plasma concentrations. Considering the PK variability are generally greater than 20% for C_{max} and AUC, these two assays are considered comparable.

LC-MS/MS assay (used in EU studies)

The LC-MS/MS method developed and validated by (b) (4) was used for the quantification of teduglutide in human plasma collected from 2 clinical studies (CL0600-018

and C09-001) that were conducted in the EU. Of note, this method was based on the method for US studies.

Briefly, the plasma sample work-up procedure was performed using protein precipitation. Stable labeled teduglutide was used as internal standard in combination with semi-automated protein precipitation. Mass spectrometry was performed on an API 4000 (b) (4) triple quadrupole mass spectrometer in the MRM mode (multiple reaction monitoring) with the Turbo Ion SprayR interface. The chromatographic run-times were 6 minutes per sample. The selected precursor- and product-ions for teduglutide were at m/z 939.7 and m/z 235.1, respectively. The selected precursor- and product-ions for the internal standard were at m/z 944.1 and m/z 235.1. The validation results are presented in Table 16 below.

Table 16. Validation Report for LC-MS/MS assay (used in EU studies)

Parameter		
Analyte	Teduglutide	
Matrix	Human plasma (with potassium-EDTA)	
Assay method	LC-MS/MS	
Instrumentation	API 4000 (b) (4)	
Assay sample volume required	100 µL	
Standard curve range	1.00 to 500 µg/L	
Regression type	Linear (weighting 1/concentration ²)	
LLOQ	1.00 µg/L	
	Precision (%)	Accuracy (%)
LLOQ validation samples		
Inter-day	0.85 to 12.11	96.6 to 101.4
Intra-day	NC	87.1 to 108.6
Quality control samples		
Inter-day	4.03 to 13.03	90.0 to 97.4
Intra-day	1.59 to 17.07	87.2 to 102.0
Recovery for analyte	51%	
Long-term stability	No long-term stability was assessed	
Freeze-thaw stability	24 hours at room temperature and after 3 freeze-thaw cycles The compound was stable in reconstituted samples for 24 hours under auto-sampler conditions (10°C) and when frozen (-20°C).	
Matrix effects	Enhancement of ionization = 325%	
Influence of anti-GLP-2 antibody	No influence was found	
Selectivity and LLOQ	No significant interference by the plasma matrix was observed. Interference from the internal standard could be detected in blank plasma from 6 different individuals for teduglutide. Values ranged between 21.4% and 30.0% compared with the signal at LLOQ.	

EDTA = Ethylenediaminetetraacetic acid; LC-MS/MS = Liquid chromatography tandem mass spectrometry; LLOQ = Lower limit of quantitation; NC = Not calculated

The performance of the assay was considered acceptable

2.6.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

For assessing the formation of binding ADA, the sponsor used three methods: ELISA, electrochemiluminescent (ECL), and (b) (4) ECL. Only (b) (4)-ECL assay performance was reviewed in depth and summarized below because it was used to analyze immunogenicity samples from the pivotal trial CL0600-020 and extension trial CL-0600-021.

For assessing the formation of neutralizing antibodies, an *in vitro* cell-based bioassay was developed and used in Phase 3 Studies CL0600-020 and CL0600-021.

For more information about the above mentioned immunogenicity assays, please refer to CMC review by Dr. Faruk Sheikh.

(1) Anti-teduglutide antibody (b) (4)-ECL assay:

In this method anti-drug (ALX-0600) antibodies were sandwiched between Biotinylated Drug (ALX-0600) and Ruthenylated (b) (4) Drug (ALX-0600). Positive controls (High1, Med1 and Low1) were prepared by spiking human K3EDTA plasma with rabbit anti-ALF0303 at 5000, 1000 and 25ng/ml respectively.

A second set of Positive controls (High2, Med2, Low2) were prepared by spiking human K3EDTA plasma with anti GLP-2 antibody at 5000, 1000 and 100ng/ml respectively. Negative Control in the assay was normal human plasma pool. The plasma samples were diluted 1:5 in assay diluent. Following overnight incubation with Biotinylated and Ruthenylated ALX0600 to allow the formation of molecular complex, the samples were loaded into the wells of a blocked (b) (4) plate. After unbound material was washed, (b) (4) read buffer was added and the bound complexes were detected by chemiluminescence in the (b) (4) instrument. The amounts of anti-drug antibodies in the samples were determined from the chemiluminescence data.

According to Dr. Faruk Sheikh's review, this assay is validated and acceptable. A summary of the validation results is presented in Table 17 below. It is noted that this assay had acceptable drug tolerance (up to 376 ng/mL) compared to the mean C_{max} following the proposed daily SC administration of 0.05 mg/kg teduglutide dose.

Table 17. Validation Report of ^{(b) (4)}-ECL Assay

Parameter	High QC	Mid QC	Low QC
Precision (CV)			
Anti-ALE-0303	5000 ng/mL	1000 ng/mL	25 ng/mL
Inter-assay	2.6%	3.4%	3.3%
Intra-assay	0.0% to 14.8%	0.0% to 6.1%	0.0% to 14.8%
Anti-GLP-2	5000 ng/mL	1000 ng/mL	100 ng/mL
Inter-assay	3.1%	2.1%	3.2%
Intra-assay	0.0% to 3.9%	0.0% to 4.0%	0.0% to 7.9%
Negative control			
Inter-assay	4.3%		
Intra-assay	0.0% to 20.5%		
Method sensitivity			
Anti-ALE-0303	1.11 ng/mL		
Anti-GLP-2	19.5 ng/mL		
Percent inhibition confirmation cutpoint	14.07		
Drug tolerance/interference			
Anti-ALE-0303	100 ng/mL of anti-teduglutide will be detected in the presence of up to 355.3 ng/mL of teduglutide		
Anti-GLP-2	100 ng/mL of anti-GLP-2 will be detected in the presence of up to 375.9 ng/mL of teduglutide		
Storage stability in matrix (for both anti-ALE-0303 and anti-GLP-2)			
Bench top	Up to 20 hours 10 minutes at room temperature		
At 5°C	Up to 7 days 12 minutes		
Freeze/thaw	Up to 6 cycles		

CV = Coefficient of variation; ECL = Electrochemiluminescent; ECLU = Electrochemiluminescence Units; GLP-2 = Glucagon-like peptide-2; K₂EDTA = Dipotassium ethylenediaminetetraacetic acid; NC = Negative control; QC = Quality control; SD = Standard deviation

(2) *In vitro* cell-based bioassay for neutralizing antibodies:

This cell-based bioassay analyzes the capacity of ALX-0600 to activate a G protein coupled receptor, a recombinant rat Glucagon-Like Peptide-2 receptor (rGLP-2R) expressed in human 293-EBNA cells. The binding of GLP-2 peptides and related analogues, such as ALX-0600, to the rGLP-2R stimulates the cellular Gas protein pathway, which in turn activates adenylate cyclase enzyme and increases intracellular cAMP levels.

The method is based on the use of Promega's cAMP-Glo™ Assay kit, which supplies a homogeneous, bioluminescent and high throughput assay to measure cAMP levels in cells. The cAMP-Glo™ Assay monitors cAMP production in cells in response to the effects of an agonist or test compound on G protein-coupled receptors (GPCRs). GPCRs that couple with adenylate cyclase will increase or decrease intracellular cAMP. The assay is based on the principle that cyclic AMP (cAMP) stimulates protein kinase A (PKA) holoenzyme activity, decreasing available ATP and leading to decreased light production in a coupled luciferase reaction. Therefore, in this method, as ALX-0600 stimulates cell production of cAMP, the luminescence signal will decrease. A sample containing anti-drug antibody will generate a greater signal than the assay negative control. Samples that are found positive in binding ADA will be analyzed in

this method. Evidence of neutralizing antibodies will be based on RLU values exceeding a method specific cut point.

According to Dr. Faruk Sheikh's review, this assay is validated and acceptable. A summary of the validation results is presented in Table 18 below. It is noted that this assay had low drug tolerance (1.5 ng/mL above). The sponsor didn't record the immunogenicity sample collection time, thus elapse time of immunogenicity sampling since the previous dose is unknown. Therefore, the results based on this neutralizing antibody assay should be interpreted with caution as circulating drug concentration could interfere with the assay for neutralizing antibodies detection.

Table 18 Validation Report of Neutralizing Antibody Assay

Parameter	
Analyte	Anti-teduglutide neutralizing antibodies
Matrix	Normal human plasma (with K ₂ EDTA or K ₃ EDTA)
Assay method	<i>In vitro</i> cell-based bioassay with a luminometer detection platform
Additional data analysis and calculations	Watson [®] LIMS version 7.2
Cutpoint analysis	30 individual normal human plasma samples analyzed across a total of 6 plates
Cutpoint factor ratio	1.3 (if the ratio of positive control / negative control or post-dose / pre-dose is ≥ 1.3 , then the sample is positive; < 1.3 is negative)
Minimum required dilution	No dilution
Negative control	6 replicates with %CV ranging from 3.79% to 19.52%
High positive control	1.0% rabbit anti-teduglutide serum spiked into 100% pooled normal human plasma
Low positive control	0.1% rabbit anti-teduglutide serum spiked into 100% pooled normal human plasma
Positive Control	
Precision (K ₂ EDTA)	Validation Sample (VS)
	VS-1 VS-2 VS-3 VS-4 VS-5
	3% 1% 0.1% 0.01% 0.001%
Inter-assay precision (CV)	$\leq 14.7%$ $\leq 13.9%$ $\leq 21.3%$ $\leq 35.3%$ $\leq 36.6%$
Intra-assay precision (CV)	$\leq 12.2%$ $\leq 12.1%$ $\leq 35.2%$ $\leq 20.1%$ $\leq 17.1%$
Positive Control	
	VS-1 VS-2 VS-3 VS-4 VS-5
	3% 1% 0.1% 0.01% 0.001%
Inter-assay precision (CV)	$\leq 20.8%$ $\leq 21.3%$ $\leq 19.8%$ $\leq 41.8%$ $\leq 39.5%$
Intra-assay precision (CV)	$\leq 16.5%$ $\leq 16.2%$ $\leq 31.1%$ $\leq 20.2%$ $\leq 20.2%$
Method sensitivity	Rabbit anti-teduglutide anti-serum (positive control) (Raw neutralizing antibody): Up to 100% Affinity purified rabbit anti-teduglutide antibody (AP neutralizing antibody): Up to 0.1 $\mu\text{g/mL}$
Method selectivity	Selectivity samples (Unspiked plasma samples): 80% classified as Negative
(matrix effect)	Selectivity samples (Spiked at a concentration of 0.5 $\mu\text{g/mL}$ of positive control): 100% classified as Positive
Specificity	In presence of 4 nM Glucagon-37 and GLP-1(7-36) 10 μM
Negative control	100% of the samples were classified as Negative
High positive control (1%)	100% of the samples were classified as Positive
Low positive control (0.1%)	100% of the samples were classified as Positive
Drug tolerance/interference	Positive control at 0.5 $\mu\text{g/mL}$: Drug tolerance was demonstrated up to 1.5 ng/mL teduglutide Positive control at 1.0 $\mu\text{g/mL}$: Drug tolerance was demonstrated up to 25 ng/mL teduglutide
Storage stability in matrix	
Bench top	Up to 22 hours 25 minutes at room temperature
At 1°C to 8°C	Up to 7 days 23 hours 39 minutes
Freeze/thaw	Up to 6 cycles
Long-term	199 days at -70°C
Drug storage stability after reconstitution	
Teduglutide	353 days
Freeze/thaw	Up to 6 cycles

CV = Coefficient of variation; GLP-1 = Glucagon-like peptide-1; K₂EDTA = Dipotassium ethylenediaminetetraacetic acid; K₃EDTA = Tripotassium ethylenediaminetetraacetic acid; LIMS = Laboratory Information Management System

3 APPENDIX

NO APPENDIX WAS ATTACHED AFTER THIS REVIEW PAGE.

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

/s/

LANYAN FANG
09/19/2012

JUSTIN C EARP
09/19/2012

YOW-MING C WANG
09/19/2012

EDWARD D BASHAW
09/19/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203441	Brand Name	Gattex
OCP Division (I, II, III, IV, V)	DCP III	Generic Name	teduglutide
Medical Division	DGIEP	Drug Class	Recombinant human glucagan-like peptide-2 (GLP-2)
OCP Reviewer	Lanyan Fang, Ph.D.	Indication(s)	Short Bowel Syndrome
OCP Team Leader	Yow-Ming Wang, Ph.D.	Dosage Form	Lyophilized powder
Pharmacometrics Reviewer Secondary Reviewer		Dosing Regimen	subcutaneous (SC) injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. The recommended daily dose of GATTEX is 0.05mg/kg BW.
Date of Submission	11/30/11	Route of Administration	S.C.
Estimated Due Date of OCP Review	7/30/12	Sponsor	NPS
Medical Division Due Date	8/30/12	Priority Classification	Priority
PDUFA Due Date	9/30/12	Dosing Strength	Single-use 3 mL vial contains a dose of 5 mg GATTEX that upon reconstitution with the 0.5 mL sterile water for injection (sWFI) provided in the prefilled syringe delivers a maximum of 0.38 mL of the reconstituted solution.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	1		
Reference Bioanalytical and Analytical Methods	X	18		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		
multiple dose:	X	2		
Patients-				
single dose:				
multiple dose:	X	4		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting multiple dose:	X	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	5		
Subpopulation studies -				
ethnicity:				
gender:				
Age:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		
hepatic impairment:	X	1		
Immunogenicity:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:	X	4		
Population Analyses -				
Data rich:	X	9		
Data sparse:	X	2		
Immunogenicity	X	7		CL0600-004 in SBS CL0600-008 in CD ALX-0600-92001, CL0600-004, CL0600-005 (004 extension), CL0600-008, CL0600-009 (008 extension), CL0600-020, CL0600-021 (020 extension)
II. Biopharmaceutics				
Absolute bioavailability	X	1		
Relative bioavailability -	X	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
PK and PD comparability:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		35		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			Covariate analysis in the popPK analysis
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Orphan designation and PREA does not apply
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Orphan designation and PREA does not apply
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		
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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

This submission is fileable from a clinical pharmacology's perspective.

Lanyan Fang, Ph.D.

Clinical Pharmacology Reviewer Date

Yow-Ming Wang, Ph.D.

Team Leader Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Review Summary

GATTEX® (teduglutide [rDNA origin]) powder for subcutaneous injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS). It is a 33–amino acid recombinant analog of the human glucagon-like peptide-2 (GLP-2), a peptide that is secreted primarily from the lower gastrointestinal tract. Teduglutide is used to improve intestinal permeability and thus absorption of fluid and nutrients. This indication was granted Orphan Designation (OD) on June 29, 2000.

On 11/30/2011, NPS pharmaceuticals submitted this NDA (203441, NME) for GATTEX® (teduglutide [rDNA origin]). The sponsor indicated that there is no obligation under PREA for sponsors of drugs or biologics with Orphan designation to provide pediatric data, as defined by PREA, at the time of submitting an initial marketing application.

The proposed indication is based on data from four Phase 3 efficacy and safety studies: The pivotal double blind, placebo-controlled study CL0600-020 that compared a single 0.05 mg/kg/day dose of teduglutide to placebo and its ongoing, open-label extension study CL0600-021; and the supportive double-blind, placebo-controlled study CL0600-004 that compared single daily doses of 0.05 mg/kg/day and 0.10 mg/kg/day of teduglutide to placebo and its randomized extension study CL0600-005 that studied the long term safety of randomized 0.05 mg/kg/day and 0.10 mg/kg/day daily doses of teduglutide. Based on these studies, it is proposed that the recommended daily dose of teduglutide be 0.05mg/kg body weight for the proposed indication for the treatment of adults with SBS.

The current submission contains a total of 14 completed clinical trials and an interim report of an ongoing SBS, open-label, extension study (CL0600-021). A total of 623 unique subjects received at least one dose of teduglutide throughout the clinical program (one subjects participated in two studies 92001 and CL0600-004). There have been 198 subjects treated with placebo across the clinical program.

Outline of the overall clinical pharmacology program is attached.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table 1 Outline of clinical pharmacology studies and studies with PK and/or PD components

Study Type	Study Identifier	Study Population	Number of Treated Subjects		
			Placebo	Teduglutide	Total
Human Biomaterial Studies (<i>in vitro</i>)					
CYP450 inhibition (exploratory)	PK0600-E-011	-	-	-	-
CYP450 inhibition (confirmatory)	P10-001	-	-	-	-
CYP450 induction	P10-002	-	-	-	-
P-gp inhibition	P10-005	-	-	-	-
Teduglutide stability in human hepatocytes	P10-007	-	-	-	-
Clinical Pharmacology Single Dose Studies^a					
Bioavailability (SC vs I.V.)	CL0600-006	Healthy	0	14	14
Bioavailability (SC abdomen vs thigh, arm)	CL0600-015	Healthy	0	18	18
PK and initial tolerability	1621/13	Healthy	8	24	32
Intrinsic Factor PK – Hepatic	CL0600-017	Hepatic-impaired		12	
		Healthy	0	12	24
Intrinsic Factor PK – Renal	CL0600-018	Renal-impaired		18	
		Healthy	0	18	36
PD Cardiac Repolarization	C09-001	Healthy	69 ^b	72 ^b	72 ^b
Clinical Pharmacology Multiple Dose Studies^a					
PK and tolerability	CL0600-022	Healthy	24	71	95
PD Gastric Emptying and PK/PD	C10-003	Healthy	13	23	36
PD Intestinal Absorption and PK/PD	ALX-0600-92001	SBS	0	17 (1) ^c	17 (1) ^c
Efficacy and Safety Studies					
Placebo-controlled, 24-week ^d	CL0600-020	SBS	43	42 (1) ^c	85 (1) ^c
Uncontrolled, open-label, up to 2-years ^d	CL0600-021	SBS	0	88 (37) ^e	88 (37) ^e
Placebo-controlled, 24-week ^{a,f}	CL0600-004	SBS	16	67 (1) ^c	83 (1) ^c
Uncontrolled, 28-week extension ^d	CL0600-005	SBS	0	65 (52) ^e	65 (65) ^e
Other Studies					
Placebo-controlled, 8-week ^{a,g}	CL0600-008	Crohn's	25	75	100
Uncontrolled, 12-week extension ^d	CL0600-009	Crohn's	0	67 (48) ^e	67 (67) ^e

CYP = Cytochrome P; I.V. = Intravenous; PD = Pharmacodynamic; P-gp = P-glycoprotein; PK = Pharmacokinetic; SBS = Short bowel syndrome; SC = Subcutaneous

^aIncluded in overall population PK analysis.

^bSubjects who received both teduglutide and placebo in this crossover study are counted once in each column. Seventy of the 72 subjects received a single oral dose of 400 mg moxifloxacin as positive control.

^cNumbers in parentheses refer to the number of subjects randomized but not dosed.

^dIncluded measurements of plasma citrulline as a PD parameter; PK was not examined.

^eNumbers in parentheses refer to the number of subjects exposed to the drug in a previous study.

^fData derived from this study included in population PK analysis (SBS) and in PK analysis to assess the effect of antibodies on teduglutide. Also included as part of this study were PK/PD assessments for plasma citrulline and biopsy sampling for histological evaluation of intestinal mucosa.

^gData derived from this study included in population PK analysis (Crohn's disease). Also included as part of this study were PK/PD assessments for CDAI and plasma citrulline.

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/s/

LANYAN FANG
01/11/2012

YOW-MING C WANG
01/11/2012