CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

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

1. Introduction

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

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

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

2. Background

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

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

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

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

Overview of Regulatory Activity

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

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

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

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

3. CMC/Device

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

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

Drug Substance

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

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

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

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

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

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

4. Nonclinical Pharmacology/Toxicology

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

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

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