

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203441Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 203441
Product Name: GATTEX (teduglutide [rDNA origin]) for injection,

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

PMR Schedule Milestones:	Final Protocol Submission:	<u>09/30/2013</u>
	Study/Trial Completion:	<u>12/30/2029</u>
	Final Report Submission:	<u>06/30/2031</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Based on the pharmacologic activity and findings in animals, GATTEX has the potential to cause hyperplastic changes including neoplasia.

Colorectal polyps were identified during the clinical trials.

Based on benign tumor findings in the rat carcinogenicity study, patients should be monitored clinically for small bowel neoplasia.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

X Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective, multi-center, long-term, observational, registry study, of short bowel syndrome patients treated with teduglutide in a routine clinical setting, to assess the long-term safety of teduglutide.

Required

- Observational pharmacoepidemiologic study
X Registry studies
X Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

Y Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
Y Are the objectives clear from the description of the PMR/PMC? Yes

- Y Has the applicant adequately justified the choice of schedule milestone dates? Yes
- Y Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes
-

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

RUYI HE
12/20/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	GATTEX (teduglutide [rDNA origin]), for injection for subcutaneous use
Applicant	NPS Pharmaceuticals, Inc.
Application/Supplement Number	NDA 203441
Type of Application	Original Submission (NME)
Indication(s)	For the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support
Established Pharmacologic Class ¹	None listed in Highlights
Office/Division	ODE III/DGIEP
Division Project Manager	Matthew Scherer
Date FDA Received Application	November 30, 2011
Goal Date	December 30, 2012
Date PI Received by SEALD	December 19, 2012
SEALD Review Date	December 19, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: *There is no white space between each major heading in HL.*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

NO

10. Product title in HL must be **bolded**.

Comment: *Product title is not bolded; also, route of administration (i.e., for subcutaneous use) is missing and required by regulation.*

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *This is a new molecular entity. There is no established pharmacological class(PC) listed in HL. DGIEP notified and to follow-up with pharm/tox reviewer. If there is an established PC, DGIEP must include it in HL.*

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES

Selected Requirements of Prescribing Information

23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Subsection headings 14.1, 14.2 and 17.1 listed in the TOC do not match the subsection headings 14.1, 14.2 and 17.1 listed in the FPI.*

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE

Selected Requirements of Prescribing Information

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *The Medication Guide and Instructions for use do not appear at the end of the PI. DGIEP notified and stated that all FDA-approved patient labeling will appear at the end of the PI upon approval.*

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: *In the cross reference, the numerical identifier should appear as (12.1), (13.1) respectively, and not “(12-1)” “(13-1)”. Delete the “dash” and replace with a “period.” This comment applies to Warnings and Precautions, subsection 5.1 and Patient Counseling Information, subsection 17.1.*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JEANNE M DELASKO
12/19/2012

ERIC R BRODSKY
12/20/2012
Eric Brodsky, SEALD labeling team leader, signing for Laurie Burke, SEALD Director

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: December 17, 2012

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Drug Name: Gattex (Teduglutide [rDNA origin]) for Injection
5 mg per vial

Application Type/Number: NDA 203441

Applicant: NPS Pharmaceuticals

OSE RCM #: 2011-4410-1

***** This document contains proprietary and confidential information that should not be released to the public.*****

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1 INTRODUCTION

This memorandum evaluates the revised packaging configuration, container labels, carton labeling, package insert, Medication Guide, and Instructions for Use for Gattex (Teduglutide [rDNA origin]) Injection submitted on November 9, 2012 (see Appendix A) and December 12, 2012. The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the packaging configuration, container labels, carton labeling, package insert, Medication Guide, and Instructions for Use under OSE Review 2011-4410, dated February 16, 2012.

2 MATERIALS REVIEWED

DMEPA evaluated the following labels and labeling.

- Revised container labels and carton labeling submitted on November 9, 2012
- Revised package insert, Medication Guide, and Instructions for Use submitted on December 12, 2012

Additionally, our recommendations in OSE Review 2011-4410, dated February 16, 2012 were reviewed to assess whether the revised labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSION AND RECOMMENDATIONS

Review of the revised documents show that the Applicant has implemented all of DMEPA's recommendations under OSE Review 2011-4410, dated February 16, 2012 and we find them acceptable. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact, Franklin Stephenson OSE Project Manager, at 301-796-3872.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MANIZHEH SIAHPOUSHAN
12/17/2012

ZACHARY A OLESZCZUK
12/17/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 6, 2012

TO: Matthew Scherer, Regulatory Project Manager
John Troiani, Clinical Reviewer

FROM: Khairy Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-441

APPLICANT: NPS Pharmaceuticals, Inc.
DRUG: Gattex™ (teduglutide)
NME: Yes
THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Treatment of adults with short bowel syndrome

CONSULTATION REQUEST DATE: January 30, 2012
PDUFA DATE: December 20, 2012

I. BACKGROUND:

Short Bowel Syndrome (SBS) results from inadequate anatomical or functional length of residual small intestine following surgical resection. As a consequence, there is significant reduction in the absorptive capacity of the intestine. Patients with SBS are highly prone to malnutrition, diarrhea, and dehydration due to reduced intestinal capacity to absorb macronutrients, water and electrolytes. Despite the adaptation that occurs generally two years after resection, a large proportion of SBS patients require the use of supplemental PN (parenteral nutrition). PN is associated with:

- High cost
- Potential life threatening complications including sepsis and liver damage
- Reduced quality of life.

Consequently, increasing the absorptive capacity of the remaining intestine is a rational therapeutic objective.

Teduglutide is a recombinant analog of human glucagon-like Peptide-2 (GLP-2). Clinical experience has shown that teduglutide is able to reduce PN volumes substantially; so that patients can be weaned off PN completely.

Anticipated adverse reactions are: injection site reactions; gastrointestinal pain and distention; constipation, nausea and vomiting; headache and increase in CRP (C reactive protein). The most frequent adverse events were headache and abdominal pain in up to 30% of subjects.

The following protocols were studied at the two sites inspected:

1. Protocol CL0600-004 “A Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome”.
2. Protocol CL0600-020 “A 24-Week Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome”

Sites were chosen on the basis of high enrollment, and, for Site 155, low number of adverse events reported for Protocol CL0600-020.

II. RESULTS (by Site):

Name of CI/ Sponsor and Location	Protocol # / # of Subjects/ Site #	Inspection Date	Final Classification
CI: Marek Pertkiewicz, M.D. Ul. Czerniakowska 231 Oddzisl Kliniczny Zywienia Warszawa, Poland	CL0600-004/9 Subjects CL0600-020/11 Subjects Site # 138	August 20-24 2012	NAI
CI: Marek Kunecki, M.D. Ul. Wolczanska 191/195 90-531 Lodz, Poland	CL0600-004/5 Subjects CL0600-020/8 Subjects Site # 155	August 27-30 2012	VAI
Sponsor: NPS Pharmaceuticals, Inc. 500 Hills Dr. Bedminster, NJ 07921	CL0600-004 CL0600-020 For Sites 0136, 0105 106 and 156	November 15- December 4, 2012	Pending (preliminary VAI)

During the Sponsor in section, the field investigator expanded the inspection and added two more sites.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Marek Pertkiewicz, M.D.**
Warszawa, Poland

- a. **What was inspected:** At this site, subjects were enrolled in both protocols; for Protocol 004, 12 subjects were screened. Nine subjects were randomized and completed the study. For Protocol 020, twelve subjects were screened and enrolled, and all 12 completed the study. The field investigator reviewed all the study records for the randomized subjects. The review included source documents, informed consent documents, inclusion/exclusion criteria, and drug accountability records.
- b. **General observations/commentary:** The inspection revealed no significant regulatory violations. Comparison of findings reported to the FDA and source documents revealed no discrepancies.

- c. **Assessment of data integrity:** The data generated from this site can be used in support of the NDA

2. **Marek, Kunecki, M.D.**
Lodz, Poland

- a. **What was inspected:** At this site both protocols were studied. For Protocol 004, seven subjects were screened. Five subjects were randomized and completed the study. For Protocol 020, eight subjects were screened, randomized, and completed the study. The field investigator reviewed all the records of the randomized subjects in the studies. The review included consent forms, source documents, eCRFs, lab results, drug accountability records and adverse reactions.
- b. **General observations/commentary:** The inspection revealed minor protocol violations in study 020 in that procedures required by the protocol for Visit 7 (safety evaluation), were not done for Subjects #001 and 002. Also the CI did not monitor the drug storage temperature required by the protocol (15-25⁰ C degrees).
- c. **Assessment of data integrity:** The review division should assess whether the failure to monitor temperature could potentially impact study drug. Otherwise, these violations would not affect the validity of the data. Data derived at this site can be used in support of the NDA.

3. **NPS Pharmaceuticals, Inc.**
Bedminster, NJ

Note: Observations noted for this inspection are based on communications with the FDA investigator and receipt of the Form FDA 483. The sponsor inspection was conducted because Gattex is a NME. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

- a. **What was inspected:** The field investigator reviewed the records of the two protocols for Sites 105, 106, 136 and 156.
- b. **General Observations/Commentary:** The inspection revealed that the sponsor maintained adequate oversight of the clinical trial. A Form FDA 483 was issued for three violations:
 1. Failure to ensure proper monitoring, for Protocol -004, Site 136, because many protocol violations were not added to the sponsor protocol violation list. In addition Monitoring Visit (MV) #20 was conducted 21 weeks after MV #19, and MV #22 was conducted 23 weeks after MV #21 instead of every 5-7 weeks;

For Site #105 there were 3 MVs that were conducted outside of the 5-7 week interval (MV # 6 was conducted 14 weeks after monitoring MV #5, MV #14 conducted 9 weeks after MV #13, and MV #15 was conducted about 13 months after MV #14.

2. Failure to assure the return or other disposition of all unused supplies of an investigational drug. For Protocol-004, Site 105, Subject 002 only returned the empty boxes without the unused vials for four study drug kits and did not return one unused vial. For Protocol-020, Subject 1002 did not return one unused vial.
 3. Failure to obtain financial disclosure form for sub-investigator (b) (4) at site 156.
 4. Transfer of obligations to a contract research organization (b) (4) upon initiation of Protocol-020 was done without a Service Agreement.
- c. **Assessment of data integrity:** These violations are not expected to alter the validity of the data. The data generated by this sponsor can be used in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The review division requested that 2 sites be inspected for this NDA approval. The sponsor inspection was conducted because Gattex is a NME. The data generated by the sites are reliable and can be used in support of the NDA. The inspection of the sponsor has a preliminary classification of VAI and an inspection summary addendum will be written if conclusions change on final review of the EIR.

{See appended electronic signature page}

Khairy Malek, M.D., PhD.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Susan D. Thompson, M.D.
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/s/

KHAIRY W MALEK
12/07/2012

SUSAN LEIBENHAUT
12/07/2012

SUSAN D THOMPSON
12/07/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 30, 2012

To: Matthew Scherer, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kendra Y. Jones, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

CC: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: NDA 203441
OPDP labeling comments for Gattex[®] (teduglutide [rDNA origin]) for injection

In response to DGEIP's January 20, 2012, consult request, OPDP has reviewed the draft Medication Guide and Instructions for Use for Gattex[®] (teduglutide [rDNA origin]) for injection (Gattex).

OPDP's comments on the proposed draft Medication Guide and Instructions for Use are based on the versions sent via email from Latonia Ford (PLT) on November 30, 2012, and are provided directly on the marked version below.

Comments on the proposed draft Prescribing Information (PI) were previously provided by OPDP on November 29, 2012, from Eunice Chung-Davies.

Thank you for the opportunity to comment on this label.

If you have any questions regarding this proposed draft Medication Guide or Instructions for Use please contact Kendra Jones at 301-796-3917 or Kendra.Jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
11/30/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: November 30, 2012

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)
and Instructions for Use (IFU)

Drug Name (established name): GATTEX (teduglutide [rDNA origin])

Dosage Form and Route: for injection

Application Type/Number: 203441

Applicant: NPS Pharmaceuticals Inc.

1 INTRODUCTION

On November 30, 2011, NPS Pharmaceuticals Inc. submitted Original New Drug Application (NDA) 203441 for GATTEX (teduglutide [rDNA origin]) for injection. The Applicant's proposed indication for GATTEX (teduglutide [rDNA origin]) for injection is for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent parental support.

On January 5, 2012, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for GATTEX (teduglutide [rDNA origin]) for injection.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for GATTEX (teduglutide [rDNA origin]) for injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review was completed on February 16, 2012.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to (DGIEP) under separate cover.

2 MATERIAL REVIEWED

- Draft GATTEX (teduglutide [rDNA origin]) for injection Medication Guide (MG) and Instruction for Use (IFU) received on November 30, 2011 and received by DMPP on November 20, 2012.
- Draft GATTEX (teduglutide [rDNA origin]) for injection Prescribing Information (PI) received on November 30, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on November 19, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
11/30/2012

BARBARA A FULLER
11/30/2012

LASHAWN M GRIFFITHS
11/30/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 29, 2012

To: Matt Scherer
Senior Regulatory Project Manager
Division Gastroenterology, Inborn Error Products (DGIEP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

CC: Kendra Jones, Pharm.D., Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 203441
OPDP labeling comments for Gattex® (teduglutide [rDNA origin]) for injection

In response to DGIEP's January 20, 2012, consult request, DPDP has reviewed the draft Prescribing Information (PI) for Gattex® (teduglutide [rDNA origin]) for injection.

Comments on the proposed are based on version 10, entitled "From NPS GATTEX_PI_Draft_16Nov2012_Word_Tracked1.doc" accessed via the DGIEP eroom on November 27, 2012. Please note that DPDP's comments on the proposed PI are provided directly on the marked version below.

OPDP's comments on the Medication Guide will follow under separate cover from Kendra Jones.

If you have any questions regarding the PI, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov.

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/s/

EUNICE H CHUNG-DAVIES
11/29/2012



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Shan Pradhan, MD; Medical Officer, DOP2/OHOP
THROUGH: Steven Lemery, MD, MHS; Team Leader, DOP2/OHOP
THROUGH: Patricia Keegan, MD, Division Director, DOP2/OHOP
SUBJECT: NDA 203441; consult regarding risk of malignancy
PRODUCT: Gattex (teduglutide)
SPONSOR: NPS Pharmaceuticals
DATE: Initial review 5/24/2012; finalized 11/16/2012 upon review of Sponsor's response to IR)

EXECUTIVE SUMMARY

- Gattex (teduglutide) is a glucagon-like peptide-2 (GLP-2) analog and new molecular entity under review in DGIEP. The proposed indication is for the treatment of adult patients with short bowel syndrome.
- The mechanism of action involves regulation of the proliferation of intestinal epithelium. In nonclinical carcinogenicity and toxicology studies, animals showed a hyperplastic response including benign adenomas in epithelial tissues in the pancreas, gallbladder, bile ducts, and small intestine.
- Gastrointestinal polyps occurred with similar incidence with teduglutide as compared to placebo in the controlled clinical trials included in the NDA. However, with regard to the number of such events with teduglutide in the development program overall, there are insufficient data to be able to quantify or otherwise draw further conclusions regarding potential risk of carcinogenesis at this time. In addition, any baseline risk of polyp that may be associated with either the intended condition or intended patient population (i.e., short bowel syndrome) lies outside DOP2's areas of expertise.
- As previously communicated, DOP2 cannot make determinations regarding whether a REMS is necessary or whether additional data are necessary in order to approve the drug. Decisions regarding approval or regarding whether a REMS is necessary must take into account the indicated population, the potential benefits of the therapy in the intended population, and other risks of the drug. DOP2 cannot determine whether the benefits of this drug in the treatment of short bowel syndrome would outweigh its risks.
- Whether or not a REMS that includes colonoscopies would reduce any risk of malignancy with teduglutide is not known (i.e., if there is a risk of malignancy, it

may or may not follow the typical pattern of oncogenesis observed in patients with spontaneously occurring colon cancer).

BACKGROUND

Teduglutide is a glucagon-like peptide-2 analog (GLP-2 analog) and new molecular entity under review in DGIEP. The proposed indication is "Gattex is indicated for the treatment of adult patients with short bowel syndrome (SBS). Gattex is used to improve intestinal absorption of fluid and nutrients." Gattex is to be administered by subcutaneous injection once daily, alternating sites, into 1 of the 4 quadrants of the abdomen or into alternating thighs or arms, at the recommended dose of 0.05 mg/kg.

The mechanism of action of teduglutide involves the proliferation of intestinal epithelium. Teduglutide is an analog of human GLP-2, a peptide purported to accelerate growth of crypts and microvilli and to inhibit apoptosis through a paracrine mechanism.

Nonclinical data showed a hyperplastic response in GI tissues. NPS Pharmaceuticals reported that in a carcinogenicity rat study, statistically significant treatment-related neoplastic changes included benign tumors of the bile duct epithelium observed in male rats treated at 35 mg/kg/day (at an incidence of 5/50) and adenomas of the jejunal mucosa observed in 5/50 male rats treated at 35 mg/kg/day. NPS Pharmaceuticals stated that no treatment-related malignant tumors were observed following treatment with teduglutide in the study. NPS Pharmaceuticals further reported that epithelial hyperplasia of the gall bladder and biliary ducts was seen in mice and monkeys but did not lead to obstruction, and that these changes often resolved partially if not completely following a recovery period. In addition, NPS Pharmaceuticals reported that epithelial hyperplasia in the pancreatic ducts occurred in both subchronic and chronic toxicity studies in monkeys but did not lead to obstruction. Finally, NPS Pharmaceuticals cited non-clinical studies in the literature in which growth of pre-existing polyps of the colon were described.

As a precaution, in clinical studies all patients underwent a full colonoscopy with removal of all polyps prior to teduglutide therapy. Patients with a history of cancer within the last 5 years before the start of the studies were excluded from the clinical development program.

The Listing of Clinical Studies below is copied from Module 2 of the NDA. Across all studies, 566 patients were exposed to teduglutide: 368 for less than 3 months and 198 for 3 months or longer. Of 566 teduglutide-treated patients, 140 were exposed to teduglutide for at least 6 months and 97 were exposed for at least 12 months. Across the SBS Efficacy and Safety studies (Studies 004, 005, 020, and 021), a total of 173 patients were exposed to teduglutide: 134 treated with 0.05 mg/kg/day and 39 treated with 0.10 mg/kg/day. Fifty-nine patients in these 4 studies received placebo. Of the 173 patients exposed to teduglutide, 140 were treated for at least 6 months and 97 were treated for at least 12 months.

LISTING OF CLINICAL STUDIES

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
Bioavailability	CL0600-006	Evaluate the bioavailability, safety, and tolerability of an SC injection relative to a 1-hour infusion of 0.12 mg/kg teduglutide in fasted normal healthy subjects	Phase 1 Single-center, randomized, open-label, 2-way crossover	teduglutide 0.12 mg/kg SC, injected into the abdomen or 1-hour I.V. infusion	14	Healthy male and female subjects	Single 1-hour I.V. infusion or single SC injection
Relative Bioavailability	CL0600-015	Determine relative bioavailability and safety of teduglutide 10 mg SC injected into the thigh and arm vs the abdomen	Phase 1 Single-center, randomized, open-label, 3-way crossover	teduglutide 10 mg SC, injected into the thigh, arm, or abdomen	18	Healthy male and female subjects	3 single doses, each separated by 3 days
Safety, Tolerability, and PK	1621/13	Evaluate safety, tolerability, and PK of ascending SC doses of teduglutide	Phase 1 Single-center, single-blind, placebo-control, single dose	teduglutide 2.5, 5, 7, or 10 mg SC and placebo. SC, injected into the abdomen	32	Healthy male subjects	Single dose
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
Safety, Tolerability, and PK	CL0600-022	Evaluate safety, tolerability, and PK of teduglutide, following once daily SC administration	Phase 1 Single-center, randomized, double-blind, placebo-control, ascending multi-dose	teduglutide 10, 15, 20, 25, 30, 50, or 80 mg SC or placebo SC once daily, injected into the abdomen	95	Healthy male and female subjects	8 days
Intrinsic Factor PK	CL0600-017	Evaluate the effect of moderate hepatic impairment on teduglutide pharmacokinetics following SC administration of teduglutide	Phase 1 Single-center, open-label, parallel group, prospective, normal control	teduglutide 20 mg SC, injected into the abdomen	24	Hepatically impaired male and female subjects and healthy matched control subjects	Single dose
Intrinsic Factor PK	CL0600-018	Evaluate the effect of renal impairment on teduglutide pharmacokinetics following SC administration of teduglutide	Phase 1 Single-center, open-label, parallel group, prospective, normal control	teduglutide 10 mg SC, injected into the abdomen	36	Male and female subjects with moderate or severe renal impairment or end stage renal disease and healthy matched control subjects	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
Cardiac Safety, PD and PK	C09-001	Evaluate the effect of a single SC dose of teduglutide on cardiac repolarization (QT, QTc interval)	Phase 1 Single-center, randomized, double-blind (teduglutide doses) single dose, placebo and positive control, 4-period, change-over	teduglutide 5 and 20 mg SC or placebo SC or moxifloxacin 400 mg po (positive control), injected into the abdomen	72	Healthy male or female subjects	4 single doses administered of each treatment, administered 7 days to 4 weeks apart.
PK and PD	C10-003	Assess the effects of teduglutide as compared with placebo on gastric emptying as assessed by acetaminophen absorption	Phase 1 Single-center, randomized, double-blind, placebo-control, multidose, parallel group	teduglutide 4 mg SC, injected once daily into the abdomen	36	Healthy male or female subjects	10 days
PD and PK	ALX-0600-92001	Evaluate safety, tolerability, and PK of a 21-day, dose regimen of teduglutide in SBS subjects	Phase 2 Multicenter, open-label, ascending dose-ranging pilot	teduglutide 0.03 mg/kg SC qd or teduglutide 0.10 or 0.15 mg/kg SC qd or bid, injected into the abdomen	17	Male or female SBS subjects	21 days

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
Other Controlled Clinical Study	CL0600-008	To evaluate efficacy of different doses of teduglutide in subjects with moderately active Crohn's disease compared with placebo	Phase 2 Multicenter, randomized, double-blind, placebo control, pilot	teduglutide 0.05, 0.10, or 0.20 mg/kg SC or placebo SC, injected 1 or 2 times daily into the abdomen or thigh	100	Male or female subjects with moderately active Crohn's disease.	8 weeks
Other Uncontrolled Clinical Study	CL0600-009	An open labelled extension study of the safety and efficacy of teduglutide in subjects with Crohn's Disease, who completed the study protocol CL0600-008	Phase 2 Multicenter, open-label extension of Study CL0600-008	teduglutide 0.10 mg/kg SC, injected once daily into the abdomen or thigh	67	Male or female subjects with Crohn's disease, who completed Study CL0600-008	12 weeks
Controlled Clinical Study	CL0600-004	Evaluate the efficacy, safety, tolerability and PK of teduglutide compared with placebo in subjects with parenteral nutrition-dependent SBS	Phase 3 Multicenter, double-blind, randomized, parallel-group, placebo control	teduglutide 0.05 or 0.10 mg/kg SC or placebo SC, injected once daily into the abdomen or thigh	83	Male and female subjects with parenteral nutrition-dependent SBS	24 weeks
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
Uncontrolled Clinical Study	CL0600-005	Evaluate safety and efficacy of teduglutide in subjects with parenteral nutrition-dependent SBS, who completed Protocol CL0600-004	Phase 3 Multicenter, randomized, double-blind extension of Study CL0600-004	teduglutide 0.05 or 0.10 mg/kg SC injected once daily into the abdomen or thigh	65	Male or female subjects with parenteral nutrition-dependent SBS, who completed Study CL0600-004	28 weeks
Controlled Clinical Studies	CL0600-020	To evaluate safety, efficacy, tolerability, and PK of teduglutide compared with placebo in subjects with parenteral nutrition-dependent SBS	Phase 3 Multicenter, double-blind, randomized, parallel-group, placebo control	teduglutide 0.05 mg/kg SC or placebo SC injected once daily into the abdomen, thigh, or arm.	86	Male or female subjects with parenteral nutrition-dependent SBS	24 weeks
Uncontrolled Clinical Study (ongoing)	CL0600-021	To evaluate safety and efficacy of teduglutide in subjects with parenteral nutrition-dependent SBS who completed CL0600-020	Phase 3 Multicenter, open-label extension of Study CL0600-020	teduglutide 0.05 mg/kg SC injected once daily into the abdomen, thigh, or arm.	88	Male or female subjects with parenteral nutrition-dependent SBS, who completed Study CL0600-020	2 years

bid = twice a day; I.V. = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; po = per os (by mouth); qd = once a day; SBS = short bowel syndrome; SC = subcutaneous

*Study CL0600-022 was amended to include bid dosing, however, the final amendment (3) eliminated this regimen.

REVIEW

The following is a review from the SBS (short bowel syndrome) Efficacy and Safety studies of cases involving malignancies and cases involving GI polyps.

Three malignancies were reported in the SBS extension study 021. No patients in the placebo-controlled trials developed cancer. One patient with a history of Hodgkin's disease developed metastatic adenocarcinoma involving the liver and experienced a fatal outcome, and 2 patients with a history of smoking developed lung neoplasms.

The first patient was a 48-year old man with a history of Hodgkin's disease (diagnosed in 1988 and treated with chemotherapy and radiotherapy) and cecal necrosis due to radiation. He was diagnosed with metastatic adenocarcinoma 11 months after initiating treatment. Six months prior to initiating teduglutide treatment, the patient had a CT of the abdomen, which showed an enlarged liver with no focal lesions. Subsequent review by 2 independent radiologists revealed a focal liver lesion of unclear significance, present prior to exposure with teduglutide. A biopsy revealed metastatic adenocarcinoma; metastases were also observed in the spine. The patient died 10 days later. An autopsy was performed but was inconclusive as to the primary site of the cancer.

The second case involved a 64 year old man with a history of smoking (30 cigarettes/day for approximately 30 years) and exposure to asbestos. The patient was diagnosed with non-small cell lung cancer after 85 days of teduglutide treatment, with the stage reported as T2BN2M0. Teduglutide was discontinued and the patient received chemotherapy with vinorelbine and carboplatin. A CT of the lumbar spine suggested tumor metastasis and soon afterward, bone scan revealed multifocal metastases. The patient died one month later; an autopsy was not performed.

The third case was a 74 year old patient with a history of smoking 10 cigarettes a day for about 5 years, who then stopped 25 years ago. The patient was diagnosed with squamous cell carcinoma of the lung, stage unspecified. The patient's medical history included embolectomy of the superior mesenteric artery, intestinal anastomosis, small intestinal resection, coronary artery disease and MI, and viral hepatitis.

All three patients who developed cancer were enrolled at study sites in Poland. Patients developing cancer had additional risk factors in each case, including smoking and prior radiation. Overall, there are insufficient data to conclude (or exclude) from the three cases that there is an increased risk of malignancy associated with teduglutide treatment.

Gastrointestinal polyps including a colonic polyp, a duodenal polyp, an intestinal polyp, a colorectal polyp, and a rectal polyp were observed in teduglutide-treated patients in the SBS Efficacy and Safety studies. In the SBS placebo controlled trials, teduglutide-treated patients experienced a treatment-emergent adverse event (TEAE) of this type at a frequency of 1.8% (2/109 patients), compared to 1.7% (1/59 patients) in the placebo group. Gastrointestinal polyps were reported as TEAEs in 7 patients enrolled in one or more teduglutide efficacy and safety studies (Studies 004, 005, 020, and 021). The table below, copied from the ISS in the NDA, summarizes these cases. Note that in the third case, the TEAE polyps were identified on treatment Day 1 and therefore were highly unlikely to be teduglutide treatment-related.

Histopathology reports for the cases listed in the ISS table below were requested and reports (both originals and translations) were received for all but the third case (the case identified on Day 1). All reports were reviewed and are summarized in Table 1 below. Two reports described hyperplastic polyps, generally associated with rare if any malignant potential.

Within the placebo-controlled SBS trials, the incidence of GI polyp events was similar between arms (see above; 1.8% with teduglutide compared to 1.7% with placebo); however, with regard to the number of such events in the development program overall (with short duration of follow-up), there was insufficient data to be able to quantify or otherwise draw further conclusions regarding potential risk of carcinogenesis at this time.

TABLE 90 GASTROINTESTINAL POLYP RELATED ADVERSE EVENTS

BEST AVAILABLE COPY

AE Preferred Term	AE Verbatim Term	Subject Number/ Country/ Treatment (mg/kg)	Severity/ Onset Day	Age/ Sex	Comments
Colonic polyp	Small polyp in sigmoidum	004-0138-0008/ Poland/ Teduglutide 0.05	Mild/ 155	22/F	22-year-old female with verbatim term "small polyp in sigmoidum" occurring on treatment day 155 (3/2/06). There are 2 AE reports for this subject, the second of which was "GI tract adenoma" with verbatim term "large bowel adenoma" reported on 3/28/06 (005 treatment day 9). The pathology was reclassified to "hyperplastic colon polyp" in August 2008.
Intestinal polyp	Polyp growths (external peri-stomal area)	020-0109-1005/ USA/ Placebo	Severe/ 79	48/F	47-year-old female with verbatim term "polyp growths (external peri-stomal area)" occurring on treatment day 79 (3/9/10). There are 2 "Intestinal polyp" AE reports for this subject, the second of which was reported on treatment day 87 on 3/17/10. Subject discontinued participation on 5/4 due to an AE (peri-stomal polyp growths).
Intestinal polyp ^a	Polipi at 20 and 40 cm from anus evidenced at colonoscopy	020-0207-1004/ Italy/ Teduglutide 0.05	Mild/ 1	45/F	45-year-old female with verbatim term "polipi at 20 and 40 cm from anus evidenced at colonoscopy" occurring on treatment day 1 (4/9/10).
Rectal polyp	Rectal polyp	005-0103-0007/ USA/ Placebo/ Teduglutide 0.10	Mild/ 189	58/F	50-year-old female with verbatim term "rectal polyp" occurring on treatment day 189 (5/24/07). Medical history of Crohn's disease.
Rectal polyp	Polyp in rectum	005-0145-0004/ Poland/ Placebo/ Teduglutide 0.10	Mild/ 190	55/M	55-year-old male with verbatim term "polyp in rectum" occurring on treatment day 190 (10/26/07). Medical history of intestinal diverticulum. This subject had a non-treatment emergent polyp during the PN stabilization phase of study 004.
Colorectal polyp ^b	3 Minipolips in colon and rectum	021-0208-1001/ Italy/ Teduglutide 0.05	Mild/230	49/F	49-year-old female with verbatim term "3 minipolips in colon and rectum" occurring after 230 days on teduglutide when the patient discontinued because of weight loss.
Duodenal polyp	Duodenal polyp	021-0138-1011/ Poland/ Teduglutide 0.05	Mild/87	64/M	64-year-old male with diagnosed lung cancer underwent upper GI endoscopy which revealed a small duodenal polyp. Subsequently the subject died from lung cancer.

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

^aSubject 020-0207-1004, a 45-year-old female, enrolled in study 020 in the teduglutide 0.05 mg/kg/day treatment group had an AE of "Intestinal polyp" reported on treatment Day 1 (09 April 2010). This was the result of the baseline colonoscopy and reported on the baseline day. Therefore, this subject is not included in the treatment emergent GI polyp related adverse event tables.

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

Table 1

Subject number	Arm	Dose	Polyp histopathology (summarized from reports)
0138-0008	Teduglutide	0.05	Hyperplastic
0109-1005	Placebo	-	Inflammatory
0207-1004	Teduglutide	0.05	-
0103-0007	Placebo/teduglutide	0.10	Hyperplastic
0145-0004	Placebo/teduglutide	0.10	Tubulovillous adenoma with low grade dysplasia
0208-1001	Teduglutide	0.05	Tubulovillous adenoma with low grade dysplasia
0138-1011	Teduglutide	0.05	Tubular adenoma with low grade dysplasia

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CONCLUSIONS

In the context of the nonclinical data (showing a hyperplastic response in gastrointestinal mucosa) and teduglutide’s mechanism of action (involving proliferation of intestinal epithelium), the number of events of GI polyp in the teduglutide development program overall may represent a potential risk of carcinogenesis. However, in the placebo-controlled trials, the incidence was nearly identical between arms. Regardless, there was insufficient data based on the length and size of the trials to be able to quantify, exclude, or otherwise draw further conclusions regarding the potential risk at this time. This division cannot determine the clinical importance of the benefits of teduglutide in regards to the treatment of patients with short bowel syndrome. Therefore, as communicated in our email dated March 7, 2012, we are unable to advise on the need for a REMS or whether additional safety data should be obtained to further evaluate the risk:benefit ratio prior to making a determination of whether to approve the drug. Whether a REMS that includes serial colonoscopy would mitigate the possible increased risk of malignancy with teduglutide is not known, since, if there is a risk of malignancy, this may not follow the typical pattern of oncogenesis observed in patients with spontaneously-occurring colon cancer.

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/s/

SHAN PRADHAN
11/19/2012

STEVEN J LEMERY
11/19/2012

PATRICIA KEEGAN
11/20/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 23, 2012

TO: Donna Griebel, M.D.
Director,
Division of Gastroenterology and Inborn Errors
Products, Office of New Drugs

FROM: Young Moon Choi, Ph.D., Pharmacologist and
Michael F. Skelly, Ph.D., Pharmacologist
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D., DABT
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 203-441, Teduglutide (rDNA
origin) powder for subcutaneous injection, sponsored by
NPS Pharmaceuticals

At the request of the Division of Gastroenterology and Inborn Errors Products (DGIEP), the Division of Bioequivalence and GLP Compliance (DBGC), conducted audits of the pharmacokinetic-bioanalytical portions of the following safety-efficacy study and its extension:

Study Number: CL0600-004
Study Title: "A Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome. A 24-week double-blind, randomized, parallel group study comparing two doses of teduglutide (0.05 mg/kg/day and 0.10 mg/kg/day) and placebo"

Study Number: CL0600-005
Study Title: "A Study of the Safety and Efficacy of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome Who Completed Protocol CL0600-004"

The audit of clinical portions of the study was conducted under the GCP inspection program, and the inspectional outcomes will be reported separately, in combination with the safety/efficacy inspections.

Bioanalytical measurements of teduglutide concentrations in plasma, for pharmacokinetic evaluations, were conducted at

(b) (4)
Measurements of antibodies to teduglutide and *E. coli* protein, for immunologic evaluations, were conducted at (b) (4)

(b) (4) However, Matthew Scherer of DGIEP confirmed with NPS that after (b) (4) (b) (4), no original records of this study or its method validations are available for inspection. (b) (4) conducted measurements of antibodies to teduglutide and *E. coli* protein for samples from study CL0600-005, as reported in (b) (4) report TNJR07-368, which was submitted in the NDA. (b) (4) conducted measurements of antibodies to teduglutide and native GLP-2, and neutralizing antibodies to teduglutide activity, for samples from study CL0600-004, as summarized by NPS in the Integrated Summary of Immunogenicity -- 4-Month Safety Update, which was submitted in eCTD Module 5.3.5.3 of the NDA.

Analytical portions of the studies were audited (b) (4) (b) (4) (conducted 5/7 to 5/11/2012 by ORA Investigator Jessica L. Peterson and OSI Scientist Young Moon Choi) and at (b) (4) (conducted 6/11 to 6/12/2012 by ORA Investigator Michael Serrano and OSI Scientist Michael Skelly). The audits included a thorough examination of study records, facilities, and equipment, and interviews and discussions with the firms' management and staff.

Following the inspection at (b) (4), no significant objectionable conditions were observed and Form FDA 483 was not issued. However, the inspection discussed that the demonstration of teduglutide stability in whole blood was generated in a study with failing quality control samples. Therefore, (b) (4) committed to repeating the whole blood stability experiments, and provided the new data on 6/11/2012 to FDA in post-inspectional correspondence. New data appropriately demonstrated teduglutide stability in whole blood up to 90 min.

Because FDA regulations do not address immunologic measurements for drug studies, following the inspection at (b) (4), only verbal observations were made at the closeout meeting, and Form FDA 483 was not issued. These verbal observations, the response from (b) (4) (attached), and our evaluations follow.

Analytical Portion - Study CL0600-004

1. The sponsor submitted a draft tabulation of (b) (4) data for CL0600-004 without a separate (b) (4) final report.

These data were intended in part to repeat earlier measurements by (b) (4) using the identical samples. The data tables were presented in the NDA without any discussion by (b) (4) of possible limits to interpretation, such as using materials and solutions from (b) (4) documentation or beyond expiration, and the partial method validations.

(b) (4) responds that the tabulated data were verified as being the same as their original data by their QC process, and subsequently by their QA process. (b) (4) indicates that a report designated TNJR11-135 will be completed before July 13, 2012.

2. Another CRO, (b) (4), performed method validations for NPS clinical study CL0600-004. (b) (4). FDA has no access to (b) (4) raw data or facility records, and thus cannot verify the validations and reagent or solution preparations conducted at (b) (4).

The planned inspection at (b) (4) was cancelled, after Matthew Scherer of DGIEP confirmed with sponsor NPS that no original records (b) (4) for this study or its method validations are available for inspection.

(b) (4) confirms that they do not have original preparation records for the materials and solutions (including Quality Control samples, QCs), used in studies CL0600-004 and CL0600-005. They maintain that their (b) (4) methodology, developed for analysis of samples for study CL0600-005, successfully assayed (b) (4) QCs by reference to calibrators prepared at (b) (4) from teduglutide reference material. The original teduglutide reference material, provided by sponsor to (b) (4) and then to (b) (4), has been recertified by NPS. [See item #5]

- 3. In the partial method validation for (b) (4) study number TNJS07-365, accuracy and precision run 14 had failed and data from that run were not reported.**

During the inspection, (b) (4) recalculated the summary table to include all valid data. The outcome was that accuracy and precision results remained within specifications.

- 4. No long term stability for the antibody concentrations was performed. The (b) (4) report cited a literature reference only for antibody stability.**

(b) (4) responds that long term stability is currently being evaluated. A date for anticipated delivery was not provided.

- 5. Certificates of analysis were not available for all reference materials with expiration dates recertifications.**

(b) (4) responds that certificates of analysis have been received from the sponsor, and that newly certified references will be used in the long term stability experiments.

Conclusions:

Following the above inspections, the reviewers recommend that pharmacokinetic portions of study CL0600-004 be accepted for agency review. The reviewers recommend that the immunologic assessments from (b) (4) for studies CL0600-004 and CL0600-005 be accepted for agency review, pending receipt of report TNJR11-135 and the certificates of analysis.

The immunologic assessments at (b) (4) partly rely on (b) (4) operations (including storage of samples and preparation of reagents and solutions), and thus are not entirely verifiable. However, the supplementary information expected in report TNJR11-135 and the amendment for long term stability should enable confidence in the (b) (4) operations.

Page 5 - NDA 203-441, Teduglutide [rDNA origin] powder for
subcutaneous injection

Final Classifications:

NAI:  (b) (4)

VAI:

OOB/Canc:

CC:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Haidar/Dejernett/Choi/Skelly/CF

OSI/Malek/File PDUFA 1701

DGIEP/Scherer

OCP/DCP-3/Bashaw/Fang

ORA/HFR-SW350/Bromley/Stevens/Peterson

ORA/HFR-CE250/Smith/Harris

ORA/HFR-CE350/Rolli/Harlan/Serrano

Draft: MFS 7/20/2012

Edit: YMC

File BE6307

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FACTS:  (b) (4)

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/s/

YOUNG M CHOI
07/24/2012

MICHAEL F SKELLY
07/24/2012

SAM H HAIDAR
07/24/2012

WILLIAM H TAYLOR
07/24/2012



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1790

Memorandum

Date: 06/29/12
Subject: Immunogenicity Assessments (Review on IR responses)
From: Faruk Sheikh, Ph.D., Staff Fellow, Laboratory of Immunology
Susan Kirshner, Ph.D., Associate Chief, Laboratory of Immunology
NDA: 203441
Route: Subcutaneous injection
Phase: Phase III
Product: Gattex[®] (teduglutide [rDNA origin]) powder, ALX-0600,
recombinant analog of human Glucagon like Peptide-2(GLP-2).
Sponsor: NPS Pharmaceutical
550 Hills Dr, Bedminster, NJ 07921
Indication: For the treatment of Short Bowel Syndrome (SBS).

Recommendation:

*The anti-teduglutide antibody screening assay and a cell-based neutralizing antibody assay were initially reviewed for validation in **IND-58213** ([Review is available in DARRTS](#)). The information supplied for validation for the assays was deemed inadequate at that time. The Agency requested that the Applicant submit additional information to complete the assay validation on June 13, 2012. The Applicant responded on July 16, 2012. The responses were reviewed (see [Appendix I](#)) and found adequate. Therefore, the validation of the antibody screening assay and the neutralizing antibody assay were completed and accepted to use in clinical sample analysis.*

The manufacturer analyzed the clinical samples obtained from phase III trials for the presence of anti-teduglutide antibodies using (b) (4) validated assays (reviewed in [Appendix II](#)). In one study (CL0600-004), 21% (14/66) of patients' sera and in another study (CL0600-020), 17.6% (6/34) of patients' sera screened positive for the presence of anti-teduglutide antibodies. These studies were conducted for 24 weeks in subjects with parenteral nutrition (PN) dependent short bowel syndrome (SBS). The manufacturer stated that all these antibody positive patients responded to teduglutide treatment in spite of the presence of antibodies to teduglutide.

An extension trial (CL0600-021) was also conducted for up to two years at a dose of 0.05mg/kg/day of teduglutide in subjects with PN-dependent SBS. Twenty-seven of 80 patients (33%) developed antibodies to teduglutide. None of these antibody positive patient's sera were neutralizing in nature as tested by a cell-based validated neutralizing

antibody assay (Method validation review can be found in DARRTS). The timing of sample collection relative to Gattex dosing is not known. Since on board drug can interfere in the NAb assay there may be false negative results. This can be addressed in the package insert.

Teduglutide is a recombinant analog of human GLP-2 that harbors one amino acid difference from native GLP-2. Due to high homology between teduglutide and GLP-2 amino acid sequence, the manufacturer developed an assay to test if the plasma from antibody positive subjects contained antibodies that could crossreact with native GLP-2. Six subjects in Study CL0600-020 who were antibody positive to teduglutide, were assessed for cross reactivity with endogenous GLP-2. Five out of 6 (83%) cross reacted against the native GLP-2 protein. The Agency requested cross-reactivity information from additional patients ([Appendix I](#)) from study CL0600-021. The manufacturer did not provide additional data because they believe that any observed antibody responses to ALX-0600 would likely show cross-reactivity to native GLP-2 due to high protein sequence homology. We concur with the Applicant because the protein sequence differs by only one amino acid between two peptides.

Many of these patients 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. In fact, the manufacturer stated that all these patients who developed antibodies from 24 week study or extended trial responded to teduglutide treatment indicating that the presence of anti-teduglutide antibody did not impact drug efficacy. Since, these 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 we do not recommend additional studies at this time. However patients in on-going clinical studies should continue to be tested to provide as much longitudinal data as possible, since this will likely be a life long therapy. In addition the Applicant should be prepared to test samples from any patient who loses efficacy to Gattex treatment. An appropriate mechanism to achieve this should be discussed with the Applicant.

Immunogenicity Labeling Language:

As with all therapeutic proteins, patients have developed IgG anti-drug antibodies (ADA) to GATTEX. In study 1 (CL0600-020), six of 34 subjects with parenteral nutrition (PN) dependent SBS patients (6/34, 17.6%) who were administered GATTEX for 24 weeks developed ADA at week 24. In another 24 weeks study (CL060-004) in subjects with SBS, who were administered GATTEX developed ADAs in 14 out of 66 (14/66, 21%) patients. In an extension trial study (CL0600-021), 27 out of 80 patients (27/80, 33.7%) who were administered GATTEX at 0.05mg/kg/day for up to 2 years developed ADA. Three out of the 27 subjects who tested positive for antibodies to GATTEX experienced an injection site reaction, without evidence of any other hypersensitivity reactions. None of the subjects were positive for the presence of neutralizing antibody in a cell based assay. However on-board drug may have resulted in false negative results in the NAb assay. Five out of 6 subjects (5/6, 83%) from study CL0600-020, who were tested

positive for antibodies to GATTEX cross reacted with native GLP-2 protein. All six ADA positive patients responded to GATTEX treatment and did not show any immune-related pathology.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to GATTEX with the incidence of antibodies to other products may be misleading.

[Appendix I: Review of IR responses received on 7/16/2012](#)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1790

Memorandum

Date: 06/29/12
Subject: Immunogenicity Assessments (Review on IR response)
From: Faruk Sheikh, Ph.D., Staff Fellow, Laboratory of Immunology
Susan Kirshner, Ph.D., Associate Chief, Laboratory of Immunology
NDA: 203441
Route: Subcutaneous injection
Phase: Phase III
Product: Gattex[®] (teduglutide [rDNA origin]) powder, ALX-0600,
recombinant analog of human Glucagon like Peptide-2(GLP-2).
Sponsor: NPS Pharmaceutical
550 Hills Dr, Bedminister, NJ 07921
Indication: For the treatment of Short Bowel Syndrome (SBS).

Recommendations:

The Applicant submitted additional supporting information/data requested for the validation of an anti-GLP-2 antibody (anti-drug antibody; ADA) screening assay and a cell-based neutralizing antibody assay. The responses to agency questions are adequate. Therefore both antibody screening assay and neutralizing antibody assay are ready to use in clinical sample analysis. Regarding cross-reactivity, the Applicant did not provide requested data. The Applicant anticipated that any observed ADA responses to ALX-0600 would likely show cross-reactivity to GLP-2. In spite of cross-reactivity, the Applicant stated that the treated subjects under the study continued to respond to treatment and did

not show any evidence of clinical pathologies associated with immune-mediated reactions. Therefore, we do not recommend additional studies at this time.

1. In your antibody screening assay, you used 500 ng/ml ALX-0600 to assess percent inhibition in establishing the confirmatory assay. Provide data showing 500 ng/ml ALX-0600 is optimum in your assay.

NPS Response:

Although there is no widely accepted approach for determining the optimal level of drug to use for a confirmatory assay two general aspects seem relevant. First, the amount of drug should be sufficient to abrogate the specific response of the assay to ADA. Second, huge excess of drug should be avoided as it may cause the possibility of non-specific interactions. During the validation of the ALX-0600 confirmatory assay, samples were incubated with drug and conjugate. In the incubation of samples with conjugate, the conjugate and drug concentrations per well were 25 ng/mL and 200 ng/mL, respectively. It can be expected that this excess of drug is sufficient to give a percent inhibition reliably greater than the cut point for immunodepletion, which was set at approximately 15% inhibition. Given an 8-fold excess of drug over conjugate, one would anticipate a decrease in the response from antibody in the sample, regardless of the amount of antibody that is present. The results summarized below from the [Validation Report TNJS09-259](#) confirm that expectation (Tables 1-4).

Table 1. Results of ALX-0600 (Drug) Tolerance Experiment in the Presence of Anti-ALX-0600 (Anti-ALE0303) or Anti-GLP-2 Antibodies.

Table 11: Drug Interference (Drug Tolerance)

Run 16 Anti-ALE0303

Drug, ng/mL	Low (25 ng/mL)			Mid (1000 ng/mL)			High (5000 ng/mL)		
	Mean ECLU	%CV	Result	Mean ECLU	%CV	Result	Mean ECLU	%CV	Result
500	68.0	4.2	Negative	788.0	9.0	Positive	4959.0	7.3	Positive
200	80.0	5.3	Positive	1464.0	7.9	Positive	9667.5	4.0	Positive
100	97.0	1.5	Positive	1829.5	1.8	Positive	12940.0	4.4	Positive
50	104.0	1.4	Positive	2507.0	0.9	Positive	15386.5	9.8	Positive
25	104.5	4.7	Positive	2405.0	2.8	Positive	18360.0	5.8	Positive
10	109.5	7.1	Positive	3298.5	0.2	Positive	26194.0	0.4	Positive
5	120.0	7.1	Positive	3400.5	9.2	Positive	21891.0	0.1	Positive
1	129.5	2.7	Positive	4081.0	2.5	Positive	30642.0	2.6	Positive
*0	162.2	8.5	Positive	6090.8	1.9	Positive	39493.5	2.0	Positive

Cut Point Value = 73.79

Interpolated Drug Tolerance level = 355.3

Run 17 Anti-GLP-2

Drug, ng/mL	Low 100 ng/mL			Mid (1000 ng/mL)			High (5000 ng/mL)		
	Mean	%CV	Result	Mean ECLU	%CV	Result	Mean ECLU	%CV	Result
500	67.0	2.1	Negative	226.5	3.4	Positive	910.5	0.1	Positive
200	75.0	1.9	Positive	339.0	0.8	Positive	1566.0	5.1	Positive
100	84.5	2.5	Positive	386.5	6.8	Positive	1948.5	4.9	Positive
50	95.5	0.7	Positive	429.0	3.6	Positive	2370.0	1.4	Positive
25	99.5	0.7	Positive	444.5	18.3	Positive	2268.5	3.6	Positive
10	111.0	6.4	Positive	510.5	12.6	Positive	2845.0	3.8	Positive
5	107.0	2.6	Positive	577.0	3.7	Positive	3072.5	2.9	Positive
1	117.0	1.2	Positive	586.0	6.0	Positive	3433.0	5.1	Positive
*0	110.3	7.1	Positive	642.2	2.0	Positive	3652.2	1.4	Positive

Cut Point Value = 70.31

Interpolated Drug Tolerance level = 375.9

*The 0 ng/mL values were taken from the quality control samples used for plate acceptance

Table 2: Results from Drug Tolerance with Anti-ALX-0600-Antibody Recalculated as Percent Inhibition

Calculated % Inhibition			
ALX-0600 (ng/mL)	Anti-ALX-0600 (25 ng/mL)	Anti-ALX-0600 (1000 ng/mL)	Anti-ALX-0600 (5000 ng/mL)
500	58	87	87
200	51	76	76
100	40	70	67
50	36	59	61
25	36	61	54
10	32	46	34
5	26	44	45
1	20	33	22
0	0	0	0

Table 3: Results from Drug Tolerance with Anti-GLP-2-Antibody Recalculated as Percent Inhibition

Calculated % Inhibition			
ALX-0600 (ng/mL)	Anti-GLP-2 (100 ng/mL)	Anti-GLP-2 (1000 ng/mL)	Anti-GLP-2 (5000 ng/mL)
500	39	65	75
200	32	47	57
100	23	40	46
50	13	33	35
25	10	31	38
10	-1	21	22
5	3	10	15
1	-6	9	5
0	0	0	0

Table 4: Results from the Confirmatory Assay

Tandem Lab:

Study No. TNJS09-259
Report No. TNJR09-259

Table 23: Confirmation of Positive Response by Drug Inhibition

Run Number	Samples without Drug					Samples: 500 ng/mL Drug					Percent Inhibition
	Sample ID	Mean ECLU	%CV	S/N	P/N	Sample ID	Mean ECLU	%CV	S/N	P/N	
20	Lowl-1	173.5	2.0	2.7	P	Low1Con-1	59.5	1.2	0.9	N	65.7
	Lowl-2	163.0	0.9	2.5	P	Low1Con-2	63.0	4.5	1.0	N	61.3
	Lowl-3	170.0	1.7	2.6	P	Low1Con-3	63.5	3.3	1.0	N	62.6
NC=60.0 CP=65.4	Mid1-1	7383.5	1.6	112.9	P	Mid1Con-1	449.0	1.3	6.9	P	93.9
	Mid1-2	8010.0	2.0	122.5	P	Mid1Con-2	457.5	0.2	7.0	P	94.3
	Mid1-3	7021.5	2.0	107.4	P	Mid1Con-3	446.0	2.5	6.8	P	93.6
	High1-1	51429.0	0.8	786.4	P	High1Con-1	2602.5	0.5	39.3	P	94.9
	High1-2	46386.0	1.5	712.3	P	High1Con-2	2594.0	1.6	39.7	P	94.4
	High1-3	48367.0	1.6	739.5	P	High1Con-3	2658.5	1.0	40.6	P	94.5
	NC-1	57.0	5.0	0.9	N	NCCon1	58.0	2.4	0.9	N	-1.8
	NC-2	63.5	10.0	1.0	N	NCCon2	61.5	5.7	0.9	N	3.1
	NC-3	59.5	8.3	0.9	N	NCCon3	54.5	14.3	0.8	N	8.4

In conclusion, the fairly modest choice of an 8-fold excess of drug over drug conjugate is confirmed by the more than adequate percent inhibition versus confirmation cut point, for all levels of sample antibody.

Reviewer's Comment: The confirmation cut-point was determined as 14.07%, which is good. The rationale of using 500ng/ml drug was presented with supporting documents. The drug inhibition assay indicated that 500ng/ml drug was able to inhibit 25ng/ml anti ALE0303 antibody present in LQC up to 65%. In presence of higher amount of antibody (MQC and HQC) the activity could be inhibited to 95%. With 14.07% confirmatory cut-point, the Applicant justified the use of 500ng/ml drug in confirmatory inhibition assay that could adequately detect all levels of antibody tested. Therefore, the response to this question was satisfied.

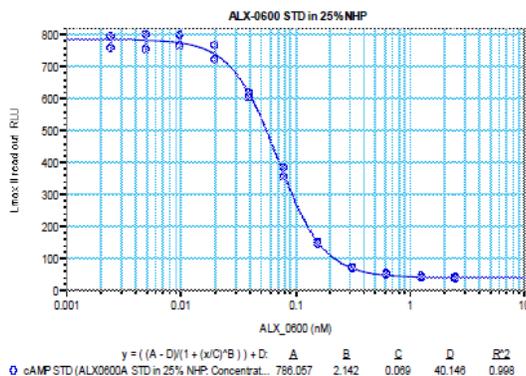
2. In your neutralizing antibody assay, you did not provide data to support that the engineered cell line was well characterized to ensure responsiveness to the drug product during continuous culture. Provide data ensuring that the length of time required to stimulate cells and the cell culture used in the assay development were optimum for the assay.

NPS Response: The neutralizing antibody assay is a cell-based bioassay that analyzes the capacity of ALX-0600 to activate recombinant rat Glucagon-Like Peptide-2 receptor (rGLP-2R), a G protein coupled receptor, expressed in human 293-EBNA cells. The binding of GLP-2 peptides and related analogs, 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 used for the neutralizing antibody assay 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.

Development experiments demonstrated that ALX-0600 in 25% normal human plasma (Figure 1) stimulated rGLP-2R expressing cells in the expected dose-dependent manner when incubated at 25 ± 5 minutes.

Figure 1. ALX-600 Dose Response in Normal Human Plasma



Representative graph of rGLP-2R expressing cells incubated with ALX-0600 in 25% normal human plasma.

The neutralizing antibody assay is similar to the potency bioassay used for Gattex release and stability (Module 3, 3.2.R.3.P, Section C). Validation experiments performed on the bioassay demonstrate that the cell line is responsive to the drug between 2-22 passages. Development experiments demonstrate that the curve shapes (Figure 2) are comparable between 30 and 60 minutes of sample incubation (stimulation).

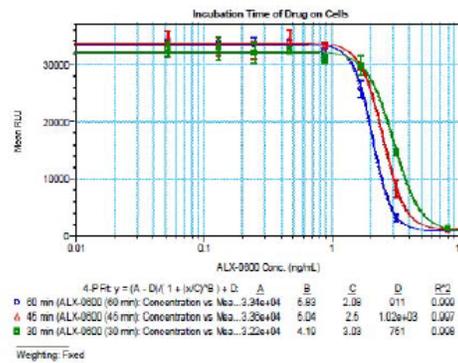
Figure 2. ALX-600 Dose Response in Potency Bioassay

Figure 11 - ALX-0600 titration ranged from 0.078 to 40 ng/mL ALX-0600. Cells are from NPS Pharmaceuticals. Luminescence was measured on a SpectraMax M5e plate reader. Figure is derived from 17215_04-28-11-124959.eda; two graphs from this file are shown on one axis.

Reviewer's comment: *The Applicant demonstrated that ALX-0600 stimulated the rGLP-2R expressing cells in a dose-dependent manner in 25% normal human plasma (Figure 1) and the responsiveness to the drug was good between cell passages 2-22. The Applicant also demonstrated that the incubation time for the stimulation was comparable between 30 and 60 minute simulation (Figure 2). Therefore, the Sponsor's response was adequate.*

3. In your cut-point analysis for neutralizing antibody assay, the mean nominal absorbance for unspiked samples were 310.5, 112.9 and 104.8 electrochemiluminescence units (ECLU) for run 7/8, run 11/12 and run 13/14 respectively (Table 2: cut point analysis). Explain the observed background differences of the study samples.

NPS Response: The following parameters were investigated as potential factors that may have influenced the background differences among the Runs of the 30 individual normal human K2EDTA plasma samples: rabbit anti-serum to ALX-0600, neat normal human plasma, induction buffer (including DMEM/F-12, BMI, IBMX), ALX-0600, trypsin/EDTA, trypan blue, media lot, protein kinase kit, cAMP-Glo reaction buffer. The same lots were used for all of the above listed reagents between runs 7 and 14. There were no deviations noted during the execution of these experiments. Three qualified analysts performed the 6 runs (Analyst 1 for Runs 7/8, Analyst 2 for Runs 9/10/11/12, and Analyst 3 Runs 13/14). The only difference noted was the cell lots used in the assay. Lot G3-050510 was used for Runs 7- 10 and Lot G3-050610 was used for Runs 11-14. Therefore it is possible that the specific cell lot may have contributed to the differences observed in the background/unspiked samples. Of note, Runs 9/10, which failed due to incorrect plating of the controls (HPC/LPC and NC positions were switched) demonstrated a background unspiked average ECLU of 164 which used the same lot as 7/8. This assay has been validated by various analysts and various reagents and the observed change in the background have no impact in the integrity of the assay.

Reviewer's Comment: *The Applicant stated that they have investigated the potential cause that influenced the observed background differences between assay runs. Although the reagents were used from same lot, the Applicant stated that the use of different cell*

lines between runs may have caused the observed differences in the background/unspiked of samples. Since the change in background differences does not have any effect on the integrity of the assay, this justification is acceptable.

4. You provide data for study 020 on cross-reactivity between antibodies to ALX-0600 and native glucagon-like peptide -2 (GLP-2) by the native cross reactivity assay (Table 10: 5/6 AD+patients).

a) Provide information where the validation report for this assay is located in your NDA.

b) Provide data on cross -reactivity rates for clinical studies 04 and 021.

NPS Response: **4a)** To confirm the expected cross-reactivity in the immunogenicity method for the detection of antibodies to ALX-0600 with GLP-2, the validation was performed and reported in Module 5, Bioanalytical and Analytical Methods for Human Studies, Section 5.3.1.4. The assay results are summarized in Report Addendum 1 to the Validation Report entitled, “Validation of an ^{(b) (4)} Immunogenicity Method for Detection of Antibodies to ALX-0600 and Native GLP-2 in Human EDTA Plasma”.

4b) ALX-0600 is a linear protein that differs only in a single, conservative, amino acid substitution in the second position to the native GLP-2 (see [Figure 3](#)). Data generated during ALX-0600 immunogenicity method development and validation ([TNJR09-259 Addendum 1](#), re-plotted below) suggests that the method is capable of detecting polyclonal antibodies as positive controls, rabbit anti-ALX-0600 (Drug Product) and a commercially available rabbit anti-GLP-2 (1-34). Because ALX-0600 is a close analog of GLP-2 and because both antibodies react with the ALX-0600 conjugates used in the immunogenicity method, it would be expected that both ALX-0600 and GLP-2 would cross-react with both antibodies.

In the experiment shown in [Figure 4](#), the middle level Quality Control Sample (“mid-QC”) for either Anti-GLP-2 or Anti-ALX-0600 was incubated with increasing amounts of either ALX-0600 or GLP-2 protein (i.e. all 4 combinations were assessed) thereby competing for signal as the protein concentration increases ([TNJR09-259 Addendum 1](#)). As shown in [Figure 4](#) both proteins are able to compete with anti-GLP-2 antibodies or anti-ALX-0600 antibodies. The slopes generated were comparable, suggesting that affinities and avidities of both antibodies to the two proteins are likely to be similar. Given the linear nature of both ALX-0600 and GLP-2 this result is not unanticipated and thus supports further extrapolation of these data.

Data on cross-reactivity rates for clinical studies CL0600-004 were not generated due to limitations in sample volume. However, samples from clinical study CL0600-020 were assessed for cross-reactivity using this same competition method ([TNJR09-259 Addendum 1](#)). Five of the six samples that were found to be ADA positive to ALX-0600 were also positive to GLP-2. This result further confirms the observations made above during method development and validation and suggests that in general, ADA

generated against ALX-0600 will likely be cross-reactive against GLP-2. Therefore, ADA samples to ALX-0600 that were measured in clinical trial CL0600-021 were not assessed specifically for cross-reactivity to GLP-2 as it was anticipated that these samples would have a high likelihood of being cross-reactive to GLP-2.

NPS proposes that additional testing of clinical samples from trial CL0600-021 for cross-reactivity is not warranted they anticipate that any observed ADA responses to ALX-0600 will likely show cross-reactivity to GLP-2 based on both method validation data as well as prior clinical trial experience, and accordingly, these additional requested data for study CL0600-021 are not provided.

Figure 3 Comparison of ALX-0600 and GLP-2

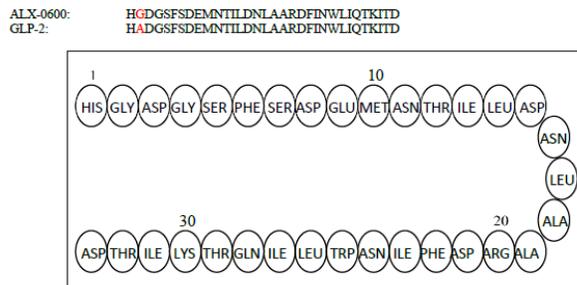


Figure 4 Cross-reactivity of Anti-GLP2 and Anti-ALX0600 Antibodies



Reviewer's Comment: NPS did not provide additional requested data for study CL0600-021 for cross-reactivity. The Applicant believes that any observed ADA responses to ALX-0600 would likely show cross-reactivity to GLP-2. The Applicant evaluated cross-reactivity of Teduglutide-Specific Antibodies and GLP-2 in 6 subjects from Study CL0600-020 who were positive for anti-teduglutide antibody, 5 cross reacted with the native GLP-2 protein (83%). All those subjects responded to teduglutide treatment according to the Applicant (*CTD module 5.3.5.3 Integrated Summary of Immunogenicity, 23rd Feb 2012, page 19*). Many of these patients have part of their intestine removed and therefore produce very low amount of GLP-2. Since, these 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 therefore we do not recommend additional studies at this time..

Appendix II:

Immunogenicity data analysis from Phase III Clinical samples:

Background and Overview:

GATTEX (Teduglutide, ALX-0600) is a novel recombinant analog of human glucagon-like peptide-2 (GLP-2). It is manufactured in *E. coli* using recombinant technology. Because it is protein therapeutic in nature, there is potential for formation of antibodies to this compound. The manufacturer assessed the formation of antibodies in studies designed to evaluate the efficacy and safety of tGATTEX in patients with short bowel syndrome (SBS) or Crohn's disease. Three assays have been developed in accordance with the principles of the Industrial guidance. One of the assays used (b) (4) methods was subsequently validated to determine the presence of binding antibodies to GATTEX.

The manufacturer also conducted a study to assess whether plasma from ADA positive subjects contained antibodies to ALX-0600 that could cross react with native GLP-2 by (b) (4) Immunogenicity Method. This review summarized the immunogenicity data obtained from studies that was conducted by validated (b) (4) method.

(b) (4) was used in Studies CL0600-020, CL0600-021 and for Study CL0600-004 samples. Initially ECL method was used to assess antibodies specific to GATTEX in study CL0600-004. The manufacturer repeated to perform the binding assay by validated (b) (4) assay because they already had PK data on samples from these subjects. The overview of the antibody analysis is provided in the following table (reproduced from the original).

Summary (major findings):

1. *Study CL0600-004 and CL0600-20 were conducted for 24 weeks and the extension study, CL0600-021 was carried out for up to 2 years.*
2. *In study CL0600-004, 14/66 (21%) patients were positive for the presence of anti-teduglutide antibodies.*
3. *In study CL0600-020, 6/34 (17.6%) patients were positive for the presence of anti-teduglutide antibodies.*
4. *In study CL0600-021, 27/80 (33%) patients were positive for the presence of anti-teduglutide antibodies.*
5. *Six patients' plasma samples who were positive for antibody to teduglutide from study CL0600-020, were tested crossreactivity with endogenous GLP-2. Five of them (83%) were crossreactive.*

Table 1 Overview of Studies with Antibody Analyses

Study	Dose/s [number of subjects enrolled]	Duration of treatment	Follow-up	Anti- teduglutide [neutralizing antibodies] Assays	anti- <i>E. Coll</i> protein Assay	Method and laboratory	Sample times
ALX-0600- 92001	0.03 mg/kg/day [3] 0.10 mg/kg/day [10] 0.15 mg/kg/day [4] Rechallenge - dose split and given as two daily doses: 0.10 mg/kg/day, 0.15 mg/kg/day [5]	21 days	Days 39 to 42	Yes [no]	Yes	ELISA (b) (4) NPS	Screening, days 21 and 42
CL0600-004	Placebo [16], 0.05 mg/kg/day [33] 0.1 mg/kg/day [31]	24 weeks	4 weeks (for subjects not entering CL0600-005)	Yes [yes]	Yes	ECL (b) (4) cAMP accumulation method for NAB	Screening, week 24 (or early termination), and week 28 (if not continuing to CL0600-005)
CL0600-005 ^b	0.05 mg/kg/day [31] 0.1 mg/kg/day [34]	28 weeks	4 weeks	Yes [no]	Yes	ECL (b) (4)	Baseline (week 24 of CL0600-004), week 28 (or early termination) and at follow-up
CL0600-008, CL0600-009 ^b	Placebo [25], 0.05 mg/kg/day [24], 0.10 mg/kg/day [26], 0.20 mg/kg/day [25]	8 weeks (008), 12 weeks (009)	4 weeks (for subjects not in CL0600-009)	Yes [yes]	No	ECL (b) (4) cAMP accumulation method for NAB [009]	Screening, weeks 4 and 8, and at follow- up (if not continuing to CL0600-009)
CL0600-020	Placebo [43] 0.05 mg/kg/day [42]	24 weeks		Yes [yes]	Yes	(b) (4) cAMP accumulation method for NAB	Baseline, week 12, 24 [or early termination]
CL0600-021 ^b	0.05 mg/kg/day [88 to-date]	Up to 2 years		Yes [yes]	Yes ^{cd}	(b) (4) cAMP accumulation method for NAB	1 st visit [last visit 020], month 3, 6, 9, 12, 24 [or early termination]

cAMP = cyclic AMP; ECL = electrochemiluminescence; ELISA = enzyme linked immunosorbent assay; NPS = NPS Pharmaceuticals
^a Samples were assayed beyond the stability data in the validation report but were stored at -80° C.
^b Studies CL0600-005, -009, and -021 were long term extensions of studies CL0600-004, -008, and -020, respectively.
^c Assays (b) (4) are ongoing and any safety issues will be reported in the Safety Update.
^d To be done at study completion
 Source: CSRs for ALX0600-92001, CL0600-004, CL0600-005, CL0600-008, CL0600-009, CL0600-020, CL-0600-021

Reviewer’s Comment: Study CL0600-004 and CL0600-20 were conducted for 24 weeks and the extension study CL0600-021 was carried out for up to 2 years. The table contains antibody analysis using ECL or ELISA methods which are not validated and are not acknowledged for review purpose. The binding assay developed by using (b) (4) method was validated and therefore, the data obtained by using validated (b) (4) method was only reviewed in this memorandum.

Study CL0600-004:

This was a double blind, randomized, parallel group, placebo controlled study to evaluate the efficacy and safety of teduglutide in subjects with SBS for 24 weeks. The incidence of antibody reactions to teduglutide is summarized as analyzed by (b) (4) in Table 3C below.

Results: The manufacturer used ECL method to analyze the antibody positive samples but no antibody reactions specific to teduglutide were observed by the ECL method (data reviewed but not shown here). However, 14 specific antibody reactions (6 in the 0.10 mg/kg/day dose group and 8 in the 0.05 mg/kg/day dose group) were detected when samples were repeated using the (b) (4) method. Of these 14 subjects, 5 (2 in the 0.10

mg/kg/day dose group and 3 in the 0.05 mg/kg/day dose group) were responders to treatment with teduglutide.

None of these ADA positive samples for teduglutide exhibited neutralizing activity in a validated cell based assay.

Table 3C Number of Subjects Who Developed Antibodies to Teduglutide in Study CL0600-004 (Method: (b) (4))

Variable	Parameter	Teduglutide (N=66)	Placebo (N=16)
Detectable at baseline	Anti-teduglutide	1	NA
Detectable at week 24	Anti-teduglutide	14	NA
Neutralizing antibody development	Anti-teduglutide	0	NA

(b) (4) process-specific impurities

Source: Appendix 2, Pharmacokinetic Report of Module 5.3.5.3

Reviewer's Comment: Fourteen out of 66 patients (14/66, 21%) were identified as positive for anti-teduglutide antibodies in 24 week study trial. None of these antibody positive samples were positive for neutralizing antibodies.

Study CL0600-020/CL0600-021:

The study CL0600-020 was a double blind, placebo controlled, parallel group study to evaluate the efficacy, safety, and tolerability of teduglutide in subjects with parenteral nutrition (PN) dependent SBS over 24 weeks.

Six out of 34 subjects (6/34, 17.6%) who received teduglutide, developed antibodies to teduglutide at Week 24 (**Table 8**). The manufacturer stated that these 6 subjects were all responders and there was no evidence of immune related clinical pathologies in these subjects.

The study CL0600-021 was an extension study and was conducted for up to 2 years at dose of 0.05 mg/kg/day of teduglutide. All subjects who completed the CL0600-020 study had the option to continue taking extension study.

Results: Twenty-seven of 85 subjects in the extension trial CL0600-021 have developed teduglutide antibodies (**Table 9**). The manufacturer stated that 3/27 subjects who tested positive for antibodies to teduglutide experienced an injection site reaction without the evidence of any other hypersensitivity reactions.

Six subjects (0109-1004, 0138-1007, 0203-1003, 0207-1003, 0208-1003, and 0214-1003) developed low titer antibodies to teduglutide during CL0600-021 (data reviewed but not presented in this memo).

One subject (0109-1001) developed antibodies to teduglutide in CL0600-020, however was negative in CL0600-021 (data not presented in this memo).

Four subjects (0132-1001, 0138-1004, 0138-1009 and 0211-1001) developed antibodies to teduglutide for both CL0600-020 and CL0600-021 (data not presented in this memo).

One subject (0136-1002) who developed baseline antibodies to teduglutide, remained negative post-baseline for CL0600-020 and CL0600-021 (this subject was a participant in a previous non-sponsored GLP-2 study more than six months prior to being enrolled in CL0600-020).

No neutralizing antibodies were detected in any subjects and no subject was discontinued due to hypersensitivity or injection site reactions in both CL0600-020 and CL0600-021 studies, the Applicant stated.

Table 8 Number of Subjects Who Developed Antibodies to Teduglutide and (b) (4) in Study CL0600-020

Variable	Parameter	Teduglutide (N=42)	Placebo (N=43)
Detectable at baseline	Anti-teduglutide ^a	0/39	0/41
	Anti-(b) (4)	19/62	4/61
Antibody development	Anti-teduglutide ^a	6/34	0/38
	Anti-(b) (4)	16/42	4/41
Neutralizing antibody development	Anti-teduglutide	0	0

(b) (4) process specific impurities

^aNumber of subjects with antibodies specific to teduglutide / number of subjects evaluated.

^bNumber of samples classified as positive / number of samples with postdose / predose *E. Coli* protein.

^cSubjects with at least one value classified as positive.

Source: CSR for CL0600-020, End of Text Table 14.3.4.1

Reviewer's Comment: Six out of 34 patients (6/34, 17.6%) were identified as positive for the presence of anti-teduglutide antibodies in 24 week study trial. None of these antibody positive samples were positive for neutralizing antibodies. In an extension study for 2 years, 27/80 (33%) patients were positive for the presence of antibodies, indicating a tendency to become more immunogenic when teduglutide is treated for longer period of time. However, the manufacturer stated that all of the antibody positive patients had completed treatment up to 2 years and all of them responded to teduglutide.

Table 9 Number of Subjects Who Developed Antibodies to Teduglutide and ECP in Study CL0600-021

Variable	Parameter	Teduglutide (N=85)
Antibody development	Anti-teduglutide ^a	27
	Anti-ECP ^b	48 ^c
Neutralizing antibody development	Anti-teduglutide	0

^aNumber of subjects with antibodies specific to teduglutide.

^bSubjects with at least one value classified as positive

^cN = 80

Evaluation of the Potential Cross Reactivity of Teduglutide-Specific antibodies and GLP-2:

The manufacturer assessed by a modified (b) (4) immunogenicity method whether plasma from antibody positive subjects contained antibodies that could cross react with native GLP-2.

Briefly, in this method, native GLP-2 was pre-incubated with antibody positive test samples or left untreated. Both samples were subsequently assayed by the validated immunogenicity method. Samples pre-incubated with GLP-2 that had a greater than 14.1% (1) reduction in signal compared to untreated samples were considered to have evidence of potentially cross reactive antibodies to GLP-2.

Six subjects in Study CL0600-020 who were antibody positive to teduglutide, were assessed for cross reactivity with endogenous GLP-2. The result indicated the 5/6 had evidence of cross reactivity against the native GLP-2 protein.

Table 10 Summary of Anti-Teduglutide, Antibody-Positive Subjects Assessed in the GLP-2 Native Cross Reactivity Assay

Subject Sample ID Visit	"No Drug" Samples Mean ECL Counts	"Plus Drug (GLP-2)" Samples Mean ECL Counts	% Immuno-depletion ^a	Pos/Neg ^b
1 0132-1001 039410000745 Visit 10 EOS A	464.0	404.5	12.82	Negative
1 0138-1004 039410001051 Visit 10 EOS A	85.0	73.0	14.12	Positive
1 0109-1001 039410002060 Visit 10 EOS ^c	116.5	86.0	26.18	Positive
1 0138-1009 039410001136 Visit 10 EOS A	152.0	88.0	42.11	Positive
1 0211-1001 039410001697 Visit 10 EOS A	168.0	64.0	61.90	Positive
1 0135-1007 039410000813 Visit 10 EOS A	309.0	103.0	66.67	Positive

ECL = electrochemiluminescence; EOS = end of study

^aImmunodepletion was tested in a confirmation assay for specific antibodies. See Method TLIAM-0186.

^bCutpoint = 14.1% immunodepletion.

^cInitial results were negative. The samples that were determined to be specific in the confirmation assay (immunodepletion) were further tested by incubating them with GLP-2 to determine if the antibodies were specific against GLP-2.

Source: Results from GLP-2 Cross Reactivity on file.

The manufacturer stated that the 2/6 subjects (0109-1001 and 0132-1001) did not show positive for the antibodies to teduglutide at subsequent time points. The other 4/6 subjects had antibodies at various time points, ie, 3, 6, 9, or 12 months. All these subjects with persistent antibodies continued to respond to treatment and had no evidence of clinical sequelae associated with hypersensitivity or immune mediated pathologies.

Reviewer's Comment: *The Agency requested for more information (reviewed in IR response review memo) from CL0600-021 study on cross-reactivity but the manufacturer did not provide any data for cross-reactivity because the Applicant believes that any observed antibody responses to ALX-0600 would likely show cross-reactivity to GLP-2. Many of these patients have part of their intestine removed and therefore may produce very low amount of GLP-2. Therefore the impact of cross reactivity may not be overcome*

¹ Confirmation cut point was validated to 14.07%.

the efficacy of the drug during treatment. In fact, the manufacturer stated that all these patients responded to the teduglutide treatment indicating that the drug efficacy was not impacted on those patients. Since, these subjects with persistent antibodies to teduglutide continued to respond to treatment and did not show any evidence of clinical pathologies associated with immune-mediated reactions therefore we do not recommend additional studies at this time.

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/s/

FARUK G SHEIKH
10/24/2012

SUSAN L KIRSHNER
10/24/2012

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	203441
Brand Name	Gattex
Generic Name	Teduglutide
Sponsor	NPS Pharmaceuticals, Inc.
Indication	Treatment of adults with short bowel syndrome (SBS)
Dosage Form	Subcutaneous injection
Drug Class	GLP-2 agonist
Therapeutic Dosing Regimen	0.05 mg/kg/day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	20 mg
Submission Number and Date	SDN 002 / 30 Nov 2011
Review Division	DGIEP

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of teduglutide (5 mg and 20 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between teduglutide (5 mg and 20 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, indicating that the magnitude of moxifloxacin can be detected in this study. However, the rising phase of moxifloxacin is missing. We would like to evaluate the $\Delta\Delta\text{QTc}$ for moxifloxacin at hour 0.25 or hour 0.5 post-dose of moxifloxacin.

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. Overall summary of findings is presented in Table 1.

Table 1: 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.

The suprathreshold dose (a single 20-mg dose) produces mean C_{max} values of 3.8-fold the mean C_{max} for the therapeutic dose (a single 5-mg dose). These concentrations are above those for the predicted high exposure scenario (end stage renal disease (ESRD)). At these concentrations there are no detectable prolongations of the QT-interval. It is important to note that sponsor proposes 50% dose reduction for moderate, severe renal impaired and ESRD patients.

2 PROPOSED LABEL

2.1 SPONSOR PROPOSED LABEL

Sponsor proposes the following text in section 12.2 in the package insert:



2.2 QT-IRT RECOMMENDED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

The effect of single subcutaneous dose of teduglutide 5 mg and 20 mg on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 70 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 20 mg is expected to cover the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Teduglutide (2-glycine-1-33-glucagon-like peptide II (human); [gly2]-hGLP-2; ALX-0600) is a novel recombinant analogue of the human glucagon-like peptide-2 (GLP-2). Teduglutide is a 33 amino acid peptide (molecular weight: 3752 d) that differs from GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. Teduglutide mediates its biological activity via the endogenous GLP-2R, a receptor whose expression within the gastrointestinal tract is restricted to a few non-epithelial cell types. The proposed indication for teduglutide is for the treatment of adult patients with Short Bowel Syndrome (SBS) to improve intestinal absorption of fluid and nutrients.

3.2 MARKET APPROVAL STATUS

Teduglutide is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.4

“No prolongation of cardiac action potential, action potential duration or any of the additional action potential parameters such as rate of depolarization, overshoot, or resting membrane potential were observed in Canine Purkinje fibers in vitro at perfusion concentrations up to 5.8 µg/mL teduglutide.”

“With regard to cardiovascular effects, intravenous doses of up to 10 mg/kg did not result in teduglutide-related abnormalities in dogs, and concentrations up to 300 µg/mL did not affect the human Ether-à-go-go-Related Gene (hERG) channel current.”

3.4 PREVIOUS CLINICAL EXPERIENCE

From 2.7.4 and ISS

“ECG assessments consisted of a dedicated thorough QT study (Study C09-001), a retrospective, exploratory analysis of ECG data from Multiple Dose Clinical Pharmacology Study CL0600- 022, centrally read ECG data from Multiple Dose Clinical Pharmacology Study C10-003, and assessment of baseline and Endpoint routine 12-lead ECGs across all 15 clinical studies.”

Table 2: Summary of Electrocardiogram Interpretation Shifts from Baseline to Endpoint Which Suggested a Possible Worsening - Safety Population - Study Group: All Studies

Parameter	Statistic	Teduglutide			
		Clinical Pharmacology Studies (N=299)	SBS Efficacy and Safety Studies (N=173)	Other Studies - Crohn's Disease (N=94)	All Studies (N=566)
Subjects with both a Baseline and Endpoint Interpretation	n	299	164	68	531
Shift from Normal/Abnormal, CSINC/Abnormal, NCS to Abnormal CS	n (%)	0	1 (0.6%)	0	1 (0.2%)
Shift from Normal/Abnormal, NCS to Abnormal, CSINC/Abnormal CS	n (%)	4 (1.3%)	1 (0.6%)	0	5 (0.9%)

Studies included: CL0600-006, CL0600-015, 1621/13, CL0600-017, CL0600-018, C09-001, CL0600-021, C10-002, ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), CL0600-008 (core study), CL0600-009 (extension study).
 CS = Clinically Significant; CSINC = Clinical Significance Indicator Not Captured; NCS = Not Clinically Significant.
 Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment which is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).
 Note: Electrocardiogram findings are based on the investigator's interpretation.

Source: [S:\SAS\NFS\Teduglutide\JIA24434\BIOSTATISTICS\PRODUCTION\TABLES\FDA\ISS] T_ECG_SHFT_ALL.SAS, (b) (4) (US)
 09-AUG-2011 09:45

Source: ISS, Table 12.2.6

Table 3: Summary of Electrocardiogram Interpretation Shifts from Baseline to Endpoint Which Suggested a Possible Worsening - Safety Population - Study Group: All Studies

Parameter	Statistic	Placebo			
		Clinical Pharmacology Studies (N=114)	SBS Efficacy and Safety Studies (N=59)	Other Studies - Crohn's Disease (N=25)	All Studies (N=198)
Subjects with both a Baseline and Endpoint Interpretation	n	114	57	22	193
Shift from Normal/Abnormal, CSINC/Abnormal, NCS to Abnormal CS	n (%)	0	0	0	0
Shift from Normal/Abnormal, NCS to Abnormal, CSINC/Abnormal CS	n (%)	1 (0.9%)	0	0	1 (0.5%)

Studies included: CL0600-006, CL0600-015, 1621/13, CL0600-017, CL0600-018, C09-001, CL0600-021, C10-002, ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), CL0600-008 (core study), CL0600-009 (extension study).
 CS = Clinically Significant; CSINC = Clinical Significance Indicator Not Captured; NCS = Not Clinically Significant.
 Note: Baseline is defined as the last assessment prior to the start of study drug. Endpoint is defined as the last assessment after the start of treatment which is no more than seven days after study drug discontinuation (excluding a scheduled follow-up visit).
 Note: Electrocardiogram findings are based on the investigator's interpretation.

Source: [S:\SAS\NFS\Teduglutide\JIA24434\BIOSTATISTICS\PRODUCTION\TABLES\FDA\ISS] T_ECG_SHFT_ALL.SAS, (b) (4) (US)
 09-AUG-2011 09:45

Source: ISS, Table 12.2.6

Reviewers' comments: The percentage of clinically relevant ECGs was estimated in pooled data from >600 subjects revealed. No meaningful difference between placebo and treated arms was observed in the percentage of clinically meaningful ECGs.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of teduglutide's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 58,213. The sponsor submitted the study report TE-1777-102-EC for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, 4-Period, Placebo and Active-Controlled, Single-Dose, Change-Over Trial to Evaluate the Effects of Teduglutide on Cardiac Repolarisation and Conduction in Healthy Male and Female Volunteers.

4.2.2 Protocol Number

TE-1777-102-EC

4.2.3 Study Dates

First subject enrolled: 19 May 2011

Last subject completed: 02 August 2011

4.2.4 Objectives

Primary objective:

- To determine the effect of a single dose of teduglutide on cardiac repolarisation (QT, QTc interval).

Secondary objectives:

- To determine the effect of a single dose of a positive control, moxifloxacin, on cardiac repolarisation, heart rate, and conduction;
- To determine the effect of a single dose of teduglutide on heart rate and cardiac conduction (RR and PR intervals, QRS duration);
- To investigate pharmacokinetics of teduglutide in plasma;
- To explore the concentration effect relationship on QT/QTc intervals;
- Safety and tolerability of teduglutide.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, partially blinded, placebo- and moxifloxacin-controlled, single dose, four-way, crossover study to assess the cardiac conduction effects of a therapeutic and suprathreshold dose of teduglutide compared to placebo in eligible healthy male and female subjects.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Moxifloxacin treatment is an open-label. Investigators and subjects were blinded regarding placebo and teduglutide (5 mg and 20 mg).

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Treatments consisted of:

- Treatment A: 5 mg teduglutide subcutaneous injection (SC).
- Treatment B: 20 mg teduglutide subcutaneous injection (SC).
- Treatment C: Placebo to teduglutide subcutaneous injection (SC).
- Treatment D: Moxifloxacin 400 mg oral (p.o.).

4.2.6.2 Sponsor's Justification for Doses

The proposed therapeutic dose is 0.05 mg/kg/day. The maximal tolerated dose tested in clinical trials was 80 mg/day for 8 days. In this TQT study, a single 5-mg and 20-mg dose was chosen as the therapeutic dose and suprathreshold dose, respectively.

Reviewer's Comments:

The 20-mg single dose in this TQT study (3.8-fold the C_{max} and 4.3-fold the AUC compared with a single 5-mg dose) is sufficient to address the high exposure clinical scenario for the following reasons:

- *0.05 mg/kg/day is the proposed therapeutic dose for Teduglutide which corresponds to a dose of 3.5 mg for a 70-kg patient. Therefore, it is reasonable to use 5 mg as the therapeutic dose in this TQT study.*
- *Teduglutide has an elimination half-life of approximately 2 hours. No accumulation was observed following once or twice daily s.c. injection of 0.03 to 0.15 mg/kg for 21 days of dosing. PK is dose-proportional from 5 to 20 mg single dose. Therefore, a single dose is sufficient to characterize the exposure profile by repeated daily dosing of 5- and 20-mg teduglutide.*
- *As shown in the clinical pharmacology highlights provided by sponsor (section 6.1), intrinsic factors, including hepatic impairment, age, sex, and race, have no pronounced effect on teduglutide exposure. In addition, teduglutide is not expected to involve drug-drug interactions related to CYP activity. The food effects were not studied and should not have effect on exposure as teduglutide is*

administered subcutaneously. Teduglutide is mainly renally cleared. Therefore, renal impairment is the primary factor for potentially higher exposure. Patients with end stage renal disease have 2-fold C_{max} and AUC_{inf} of normal subjects. To address the higher exposure in patients with renal impairment, sponsor proposes 50% dosage reduction for moderate, severe renal impaired and ESRD patients.

4.2.6.3 Instructions with Regard to Meals

Subjects were fasted for at least 10 h before administration of the trial medications. They received standardized meals on Day 1.

Reviewer's Comment: As teduglutide is administered subcutaneously, the food is not expected to have effect on exposure.

4.2.6.4 ECG and PK Assessments

ECGs were recorded in triplicate at pre-dose (within 60 min before dosing), and at 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h post-dose. Blood samples to measure plasma teduglutide concentrations were drawn within 60 min before dosing (0 h), and at 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 h post-dose in each period (11 samples per period).

Reviewer's Comment: The proposed PK and ECG sampling times are appropriate to describe peak teduglutide concentration ($T_{max} \sim 3$ h) and time course. The day of assessments for each dose group at day 1 is also appropriate as no accumulation has been observed.

4.2.6.5 Baseline

The sponsor used same day pre-dose as baseline values.

4.2.7 ECG Collection

“Standard 12-lead ECGs were recorded for 10 s using Philips TRIM III (b) (4). The same equipment was used throughout the trial. ECGs were recorded in triplicate.

“All ECGs were recorded digitally and sent to a central ECG laboratory (b) (4) for an independent evaluation (measurement and interpretation) (except those from screening, Day -1 and end of trial examination).

“The personnel involved in central electrocardiogram (ECG) assessment was blinded regarding treatment and time point of ECG recording.

“ECGs of this trial were reviewed by a single technician. For quality assurance and control of the measurements, all ECGs of a subject were compared with respect to the overall variance of the measured intervals, in order to detect accidentally switching of leads and/or false subject assignments of the ECGs.

“Interval measurements (RR, QT, QRS, PR) were performed in four complexes in lead II. If this lead showed a flat T wave or was immeasurable for any reason, lead V2 was used, or, if that lead was immeasurable, then lead I was used. All interval measurements in one subject were performed on the same lead.”

Source: CSR, page 45.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Altogether, 72 subjects were included into the treatment phase. Five subjects discontinued prematurely, 67 subjects completed the entire trial.

Demographic data are summarized in Table 4.

Table 4: Demographic data (Safety Set)

		All	Female	Male
Age (years)	n	72	32	40
	Mean ± SD	35.4 ± 7.73	35.3 ± 6.64	35.5 ± 8.59
	Min - Max	18 - 45	24 - 45	18 - 45
Body height	n	72	32	40
	Mean ± SD	172.0 ± 9.57	163.7 ± 5.68	178.7 ± 6.27
	Min - Max	152 - 194	152 - 174	168 - 194
Body weight (kg)	n	72	32	40
	Mean ± SD	73.9 ± 12.82	63.3 ± 7.00	82.4 ± 9.69
	Min - Max	51.0 - 108.4	51.0 - 76.5	62.5 - 108.4
BMI (kg/m ²)	n	72	32	40
	Mean ± SD	24.8 ± 2.54	23.6 ± 2.30	25.8 ± 2.32
	Min - Max	19.0 - 28.9	19.0 - 28.9	21.4 - 28.9

Source: [Table 14.1.1](#)

Source: CSR, Table 11.2.1

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean differences between teduglutide (5 mg and 20 mg) and placebo in QTcF. The sponsor used an analysis of covariance (ANCOVA) and the result is presented in Table 5. This model included period, time, treatment, time-by-period interaction and time-by-treatment interaction as fixed effect terms. Baseline QTcF for each period was included as a covariate, and subject and subject by period as random effects. The upper limits of the 2-sided 90% CI for the teduglutide (5 mg and 20 mg) were below 10 ms.

Table 5: Sponsor Results $\Delta \Delta$ QTcF for Teduglutide (5 and 20 mg) and Moxifloxacin

Time [h] after administration	Low dose teduglutide (5 mg)		High dose teduglutide (20 mg)		Moxifloxacin (400 mg)	
	Estimate	95% UCL	Estimate	95% UCL	Estimate	95% LCL
	0.7	2.4	2.0	3.7	11.2	9.5
2	-1.2	0.5	-0.6	1.1	13.0	11.3
3	-0.8	0.9	-0.2	1.5	13.0	11.3
4	0.4	2.1	0.7	2.4	13.8	12.1
5	0.3	2.0	2.8	4.5	12.9	11.2
6	0.4	2.1	0.6	2.2	13.1	11.4
8	-1.0	0.7	-0.5	1.2	11.3	9.7
12	-1.3	0.4	-1.1	0.6	9.5	7.8
16	0.5	2.2	0.8	2.5	9.8	8.1
24	1.3	3.0	1.5	3.2	7.3	5.6

UCL: upper confidence limit (one-sided)
LCL: lower confidence limit

Source: Clinical Study Report No. TE-1777-102-EC, Section 11.5.2, Table 11.5.3, Pg 88/1781

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our analyses results are similar as those provided by the sponsor.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the Δ QTcF effect for moxifloxacin. The analysis results were presented in Table 5. The lower bound of the 2-sided 90% CI was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our analyses results are similar as those provided by the sponsor.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 480 ms and Δ QTc $>$ 60 ms.

4.2.8.3 Safety Analysis

No adverse events occurred during the screening phase. After administration of the trial medication, altogether 99 adverse events occurred in 40 subjects:

- 37 adverse events in 21 of 70 subjects (30%) under Treatment A (5 mg teduglutide)
- 35 adverse events in 26 of 70 subjects (37.1%) under Treatment B (20 mg teduglutide)
- 13 adverse events in 12 of 69 subjects (17.4%) under Treatment C (placebo)
- 14 adverse events in 13 of 70 subjects (18.6%) under Treatment D (400 mg moxifloxacin)

No deaths and serious adverse events occurred during the trial.

One AE (moderate nasopharyngitis, assessed as unlikely related to IMP) occurred during the trial that led to trial discontinuation of the subject (Subject No. 047).

In four subjects, increased CRP values were reported as AEs (3 teduglutide, related; 1 placebo, not related).

Table 6: Summary of Treatment-emergent Adverse Events during the Trial

MedDRA Version 12.1 System Organ Class	Preferred Term	5 mg Teduglutide (N = 70)		20 mg Teduglutide (N = 70)		Placebo (N = 69)		400 mg Moxifloxacin (N = 70)	
		n	% E	n	% E	n	% E	n	% E
Gastrointestinal disorders	Abdominal pain upper	7	10.0	7	8	11.4	9		
	Nausea	7	10.0	7	4	5.7	4		
	Flatulence	2	2.9	2	1	1.4	1		
	Vomiting	3	4.3	3					
	Abdominal discomfort	1	1.4	1	1	1.4	1		
	Dianthoia	1	1.4	1	1	1.4	1		
	Abdominal pain lower				1	1.4	1		
	Dry mouth							1	1.4
	Dyspepsia				1	1.4	1		
	Gastro disorder						1	1.4	1
	Gastrointestinal disorder				1	1.4	1		
	Gastrointestinal pain						1	1.4	1
	Total		14	20.0	21	14	20.0	19	2
Nervous system disorders	Headache	7	10.0	7	7	10.0	7	8	11.6
	Dizziness	2	2.9	2	1	1.4	1		
	Hyperaesthesia				1	1.4	1		
	Total	8	11.4	9	8	11.4	9	8	6
Investigations	C-reactive protein increased	2	2.9	2	2	2.9	2	1	1.4
	Blood creatine phosphokinase increased	1	1.4	1					
	Body temperature increased	1	1.4	1					
	Total	4	5.7	4	2	2.9	2	1	1.4
General disorders and administration site conditions	Fatigue	1	1.4	1	2	2.9	2	2	2.9
	Injection site erythema				1	1.4	1		
Total	1	1.4	1	3	4.3	3	2	2.9	
Infections and infestations	Nasopharyngitis				1	1.4	1	1	1.4
	Total				1	1.4	1	1	1.4
Vascular disorders	Hypotension	1	1.4	1	1	1.4	1	1	1.4
	Total	1	1.4	1	1	1.4	1	1	1.4
Renal and urinary disorders	Pollakiuria							2	2.9
	Total							2	2.9
Blood and lymphatic system disorders	Eosinophilia	1	1.4	1					
	Total	1	1.4	1					
Musculoskeletal and connective tissue disorders	Musculoskeletal pain							1	1.4
	Total							1	1.4
Reproductive system and breast disorders	Dysmenorrhoea							1	1.4
	Total							1	1.4
Total		21	30.0	37	26	37.1	35	12	17.4

MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in each treatment group, n = number of subjects with event, E = number of events.

Source: Table 14.3.1.2

Source: CSR, Table 12.2.1

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 7. C_{max} and AUC_{inf} values were 3.8- and 4.3-fold following administration of a single 20-mg s.c. dose of teduglutide compared with a dose of 5 mg teduglutide.

Table 7: Pharmacokinetic Parameters of Teduglutide Following Single Subcutaneous Dose of 5 or 20 mg

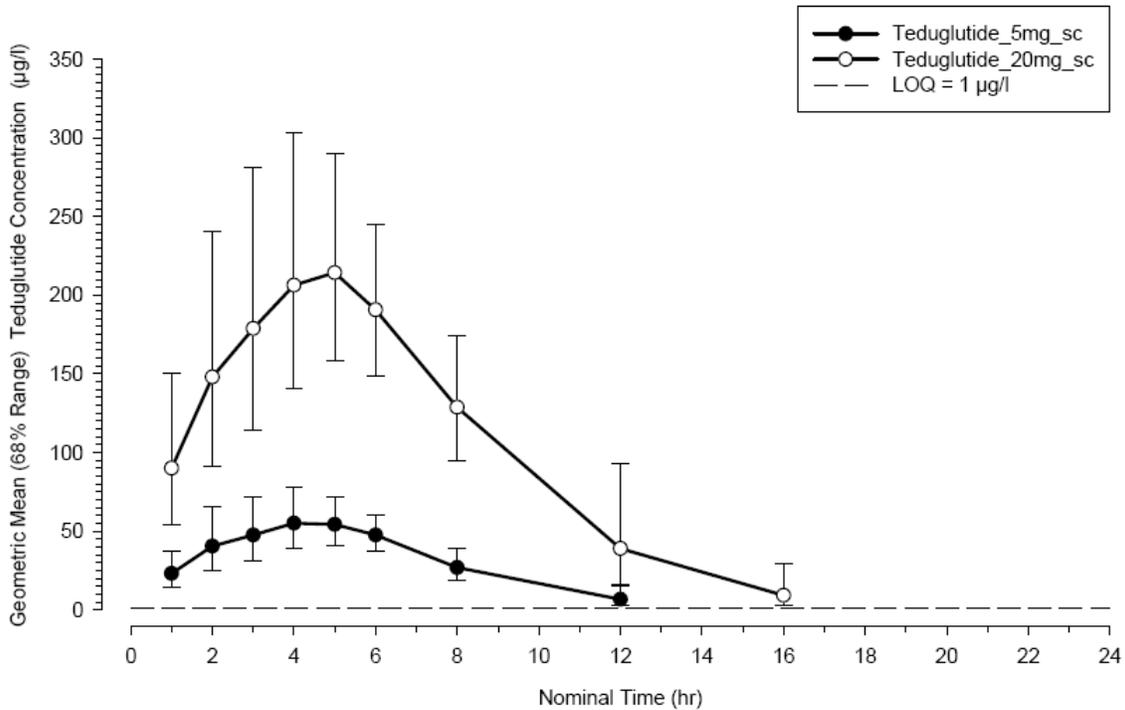
	AUC_{inf} ($\mu\text{g}\cdot\text{h/l}$)	C_{max} ($\mu\text{g/l}$)	AUC_t ($\mu\text{g}\cdot\text{h/l}$)	t_{max} (h)	t_{1/2} (h)
Treatment A (5 mg Teduglutide)					
N	67	70	70	70	67
Mean (SEM)	447.6 (11.01)	64.2 (2.80)	428 (11.0)	4.50 (0.12)	1.98 (0.10)
Median	448.4	61.0	432	4.16	1.81
Min/Max	268.2/742.1	30.3/189	261/738	2.07/8.07	0.92/4.85
Geom. Mean (68% range)	438.9 (359.6; 535.7)	60.8 (44.1; 84.0)	419 (339; 517)	-	1.86 (1.30; 2.65)
Treatment B (20 mg Teduglutide)					
N	70	70	70	70	70
Mean (SEM)	1913 (39.75)	242 (8.84)	1860 (41.8)	4.81 (0.14)	2.16 (0.12)
Median	1884	227	1820	5.07	1.87
Min/Max	1361/2844	114/398	1300/2810	2.08/8.20	1.11/5.60
Geom. Mean (68% range)	1885 (1589; 2237)	231 (170; 314)	1830 (1520; 2200)	-	1.99 (1.35; 2.93)

N= Number of observations; SEM: Standard Error of the Mean

Source: Clinical Trial Report, C09-001, Page 76

The mean teduglutide concentration-time profile is illustrated in Figure 1.

Figure 1: Mean Teduglutide concentration-time profiles for 5 mg s.c. and 20 mg s.c.



Source: Clinical Trial Report, C09-001, Page 75

4.2.8.4.2 Exposure-Response Analysis

Sponsor did not conduct exposure-response analysis due to the absence of QT prolongation of teduglutide in this TQT study.

Reviewer's Comments: Reviewer conducted an independent exposure-response analysis. A plot of $\Delta\Delta QTcF$ vs. teduglutide concentrations is presented in Figure 4. There is no evidence of QT prolongation with the increase of teduglutide concentration.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

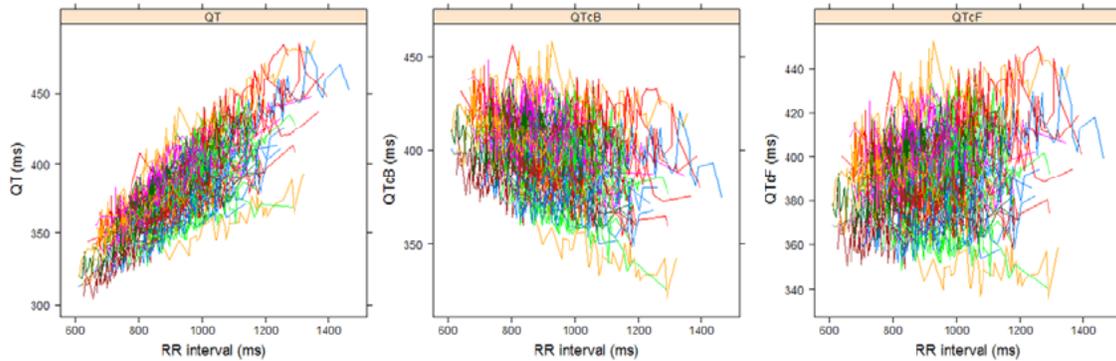
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8, it appears that QTcF is better than QTcB. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method			
	QTcB		QTcF	
	N	MSSS	N	MSSS
MOXIFLOXACIN	70	0.0073	70	0.0014
PLACEBO	69	0.0038	69	0.0014
TEDUGLUTIDE 20 mg	70	0.0044	70	0.0013
TEDUGLUTIDE 5 mg	70	0.0041	70	0.0015
All	72	0.0031	72	0.0010

The QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB) and Fridericia (QTcF).

Figure 2: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 9. The largest upper bounds of the 2-sided 90% CI for the mean differences between teduglutide 5 mg and placebo, and between teduglutide 20 mg and placebo are 3.0 ms and 5.2 ms, respectively.

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Teduglutide 5 mg, Teduglutide 20 mg and Moxifloxacin 400 mg

	PLACEBO	MOXIFLOXACIN					TEDUGLUTIDE 20 mg				TEDUGLUTIDE 5 mg			
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF			Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj 90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	3.1	70	14.7	11.6	(9.8, 13.5)	(9.1, 14.1)	70	5.3	2.3	(0.4, 4.1)	70	3.6	0.5	(-1.3, 2.4)
2	2.4	70	15.8	13.4	(11.3, 15.4)	(10.6, 16.2)	70	2.1	-0.4	(-2.4, 1.7)	70	1.0	-1.4	(-3.4, 0.7)
3	0.8	70	14.1	13.3	(11.4, 15.3)	(10.6, 16.0)	70	0.8	0.1	(-1.9, 2.0)	70	-0.0	-0.8	(-2.8, 1.2)
4	-2.9	70	11.2	14.1	(12.1, 16.1)	(11.4, 16.9)	70	-1.9	1.0	(-1.0, 3.0)	70	-2.6	0.3	(-1.7, 2.3)
5	-4.3	70	9.0	13.3	(11.1, 15.5)	(10.3, 16.3)	70	-1.3	3.0	(0.8, 5.2)	70	-4.2	0.2	(-2.0, 2.4)
6	-3.1	70	10.4	13.5	(11.3, 15.7)	(10.5, 16.5)	70	-2.3	0.8	(-1.4, 3.0)	70	-2.7	0.3	(-1.9, 2.5)
8	-7.9	70	3.8	11.8	(9.6, 13.9)	(8.8, 14.7)	70	-8.1	-0.2	(-2.4, 2.0)	70	-9.0	-1.1	(-3.2, 1.1)
12	-1.7	69	8.3	9.9	(7.7, 12.1)	(6.9, 13.0)	70	-2.5	-0.9	(-3.1, 1.4)	70	-3.0	-1.3	(-3.5, 0.9)
16	3.5	69	13.8	10.3	(7.9, 12.7)	(7.0, 13.6)	69	4.5	0.9	(-1.5, 3.3)	70	4.0	0.4	(-2.0, 2.8)
24	-3.1	70	4.5	7.7	(5.8, 9.5)	(5.2, 10.2)	70	-1.4	1.7	(-0.1, 3.6)	70	-2.0	1.2	(-0.7, 3.0)

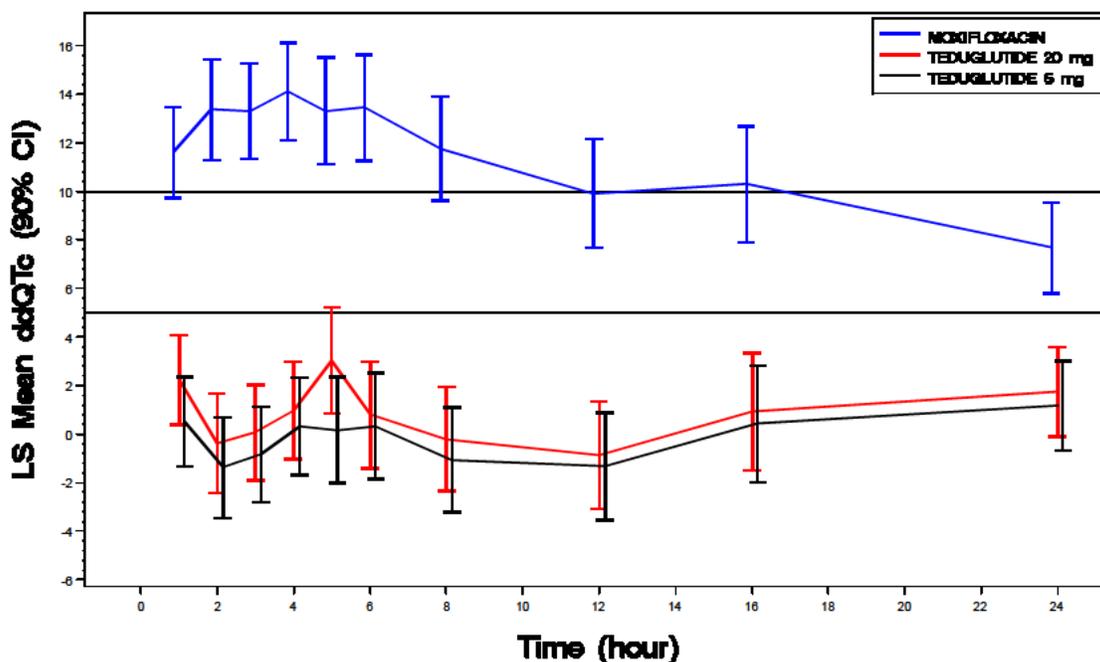
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 12.1 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 10.5 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

Figure 3 displays the time profile of $\Delta\Delta$ QTcF for teduglutide treatment groups and moxifloxacin 400 mg.

Figure 3: Mean and 90% CI Δ QTcF Time Course for Teduglutide (5 mg and 20 mg) and Moxifloxacin



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, and between 450 ms and 480 ms. No subject's QTcF is above 480 ms.

Table 10: Categorical Analysis for QTcF

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
MOXIFLOXACIN	70	69 (98.6%)	1 (1.4%)
PLACEBO	69	69 (100%)	0 (0.0%)
TEDUGLUTIDE 20 mg	70	70 (100%)	0 (0.0%)
TEDUGLUTIDE 5 mg	70	70 (100%)	0 (0.0%)

Table 11 lists the categorical analysis for Δ QTcF. No subject's change from baseline is above 60 ms.

Table 11: Categorical Analysis for Δ QTcF

Treatment Group	Total N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms
MOXIFLOXACIN	70	62 (88.6%)	8 (11.4%)
PLACEBO	69	69 (100%)	0 (0.0%)
TEDUGLUTIDE 20 mg	70	70 (100%)	0 (0.0%)
TEDUGLUTIDE 5 mg	70	70 (100%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between teduglutide 5 mg and placebo, between teduglutide 20 mg and placebo are 10.6 bpm and 11.2 bpm, respectively. No subject who experienced HR interval greater than 100 bpm was in teduglutide treatment groups.

Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR for Teduglutide 5 mg, Teduglutide 20 mg and Moxifloxacin 400 mg

Time (h)	PLACEBO	MOXIFLOXACIN				TEDUGLUTIDE 20 mg				TEDUGLUTIDE 5 mg			
	Δ HR	Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-2.0	70	1.1	3.1	(1.7, 4.5)	70	7.5	9.4	(8.1, 10.8)	70	7.3	9.3	(7.9, 10.6)
2	-0.0	70	0.9	0.9	(-0.6, 2.5)	70	8.4	8.4	(6.9, 10.0)	70	8.0	8.1	(6.5, 9.6)
3	7.0	70	5.6	-1.4	(-3.0, 0.3)	70	11.8	4.8	(3.2, 6.5)	70	10.7	3.8	(2.1, 5.5)
4	2.4	70	3.2	0.8	(-0.8, 2.5)	70	8.9	6.5	(4.9, 8.2)	70	8.3	5.9	(4.2, 7.5)
5	2.3	70	2.7	0.4	(-1.4, 2.2)	70	9.1	6.7	(4.9, 8.5)	70	8.1	5.7	(3.9, 7.5)
6	1.1	70	2.3	1.2	(-0.6, 3.0)	70	10.5	9.4	(7.6, 11.2)	70	9.2	8.0	(6.2, 9.8)
8	6.3	70	7.1	0.8	(-0.9, 2.6)	70	13.9	7.7	(5.9, 9.5)	70	12.9	6.7	(4.9, 8.5)
12	4.7	69	6.3	1.6	(-0.2, 3.4)	70	11.9	7.2	(5.4, 9.0)	70	10.3	5.6	(3.8, 7.4)
16	-0.7	69	0.9	1.6	(-0.2, 3.3)	69	5.9	6.5	(4.8, 8.3)	70	3.8	4.5	(2.8, 6.2)
24	3.7	70	5.0	1.3	(-0.4, 2.9)	70	6.4	2.7	(1.0, 4.3)	70	5.1	1.3	(-0.3, 3.0)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between teduglutide 5 mg and placebo, between teduglutide 20 mg and placebo are 0.9 ms 1.1 ms, respectively. Table 14 presents the categorical analysis of PR. Eleven subjects who experienced PR interval greater than 200 ms were in both teduglutide treatment groups.

Table 13: Analysis Results of Δ PR and $\Delta\Delta$ PR for Teduglutide 5 mg, Teduglutide 20 mg and Moxifloxacin 400 mg

Time (h)	PLACEBO	MOXIFLOXACIN				TEDUGLUTIDE 20 mg				TEDUGLUTIDE 5 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.4	70	-0.6	-0.2	(-2.1, 1.7)	70	-3.2	-2.9	(-4.7, -1.0)	70	-3.6	-3.2	(-5.1, -1.3)
2	-1.1	70	-2.0	-0.8	(-2.8, 1.1)	70	-4.4	-3.2	(-5.2, -1.3)	70	-3.9	-2.7	(-4.7, -0.8)
3	-1.7	70	-3.4	-1.6	(-3.5, 0.3)	70	-5.9	-4.2	(-6.1, -2.2)	70	-6.1	-4.4	(-6.3, -2.5)
4	-0.9	70	-3.4	-2.5	(-4.5, -0.5)	70	-6.2	-5.3	(-7.3, -3.3)	70	-5.8	-4.9	(-6.8, -2.9)
5	-2.6	70	-3.6	-1.0	(-3.0, 1.1)	70	-4.4	-1.8	(-3.9, 0.2)	70	-4.5	-1.9	(-4.0, 0.1)
6	-3.6	70	-3.6	-0.0	(-2.2, 2.2)	70	-3.5	0.1	(-2.0, 2.3)	70	-4.9	-1.2	(-3.4, 0.9)
8	-7.0	70	-7.4	-0.4	(-2.6, 1.8)	70	-8.2	-1.2	(-3.4, 1.0)	70	-8.3	-1.3	(-3.5, 0.9)
12	-3.6	69	-4.3	-0.7	(-3.2, 1.8)	70	-4.2	-0.6	(-3.1, 1.9)	70	-5.9	-2.4	(-4.9, 0.2)
16	1.0	69	0.9	-0.1	(-2.8, 2.6)	69	-0.6	-1.6	(-4.3, 1.1)	70	0.6	-0.4	(-3.0, 2.3)
24	-1.6	70	-2.3	-0.7	(-2.8, 1.4)	70	-3.5	-1.8	(-3.9, 0.3)	70	-3.4	-1.8	(-3.9, 0.3)

Table 14: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR \geq 200 ms
MOXIFLOXACIN	70	65 (92.9%)	5 (7.1%)
PLACEBO	69	64 (92.8%)	5 (7.2%)
TEDUGLUTIDE 20 mg	70	65 (92.9%)	5 (7.1%)
TEDUGLUTIDE 5 mg	70	64 (91.4%)	6 (8.6%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between teduglutide 5 mg and placebo, and between teduglutide 20 mg and placebo are 1.1 ms and 1.3 ms, respectively. Table 16 presents the categorical analysis of QRS. Four subjects who experienced QRS interval greater than 110 ms were in both teduglutide treatment groups.

Table 15: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Teduglutide 5 mg, Teduglutide 20 mg and Moxifloxacin 400 mg

Time (h)	PLACEBO	MOXIFLOXACIN				TEDUGLUTIDE 20 mg				TEDUGLUTIDE 5 mg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.3	70	-0.1	0.1	(-0.2, 0.5)	70	0.1	0.3	(-0.0, 0.7)	70	0.0	0.3	(-0.1, 0.7)
2	-0.6	70	-0.4	0.2	(-0.2, 0.5)	70	-0.3	0.3	(-0.1, 0.7)	70	-0.4	0.2	(-0.2, 0.6)
3	1.3	70	0.8	-0.5	(-1.0, -0.0)	70	0.3	-0.9	(-1.4, -0.5)	70	0.4	-0.9	(-1.4, -0.4)
4	0.4	70	0.1	-0.3	(-0.8, 0.1)	70	0.3	-0.1	(-0.6, 0.3)	70	0.5	0.1	(-0.4, 0.5)
5	-0.1	70	-0.5	-0.4	(-0.9, 0.1)	70	0.4	0.5	(0.0, 1.0)	70	0.1	0.2	(-0.3, 0.7)
6	-0.3	70	-0.8	-0.5	(-1.0, -0.1)	70	0.5	0.8	(0.4, 1.3)	70	0.4	0.7	(0.3, 1.1)
8	-0.4	70	-1.0	-0.6	(-1.1, -0.1)	70	-0.5	-0.1	(-0.6, 0.4)	70	-0.3	0.1	(-0.4, 0.6)
12	0.8	69	0.3	-0.5	(-1.0, 0.0)	70	0.5	-0.2	(-0.7, 0.2)	70	0.3	-0.5	(-0.9, 0.0)
16	0.8	69	0.4	-0.3	(-0.8, 0.1)	69	1.1	0.3	(-0.1, 0.8)	70	0.7	-0.1	(-0.5, 0.4)
24	0.2	70	0.2	-0.0	(-0.4, 0.3)	70	0.1	-0.1	(-0.5, 0.2)	70	0.1	-0.2	(-0.5, 0.2)

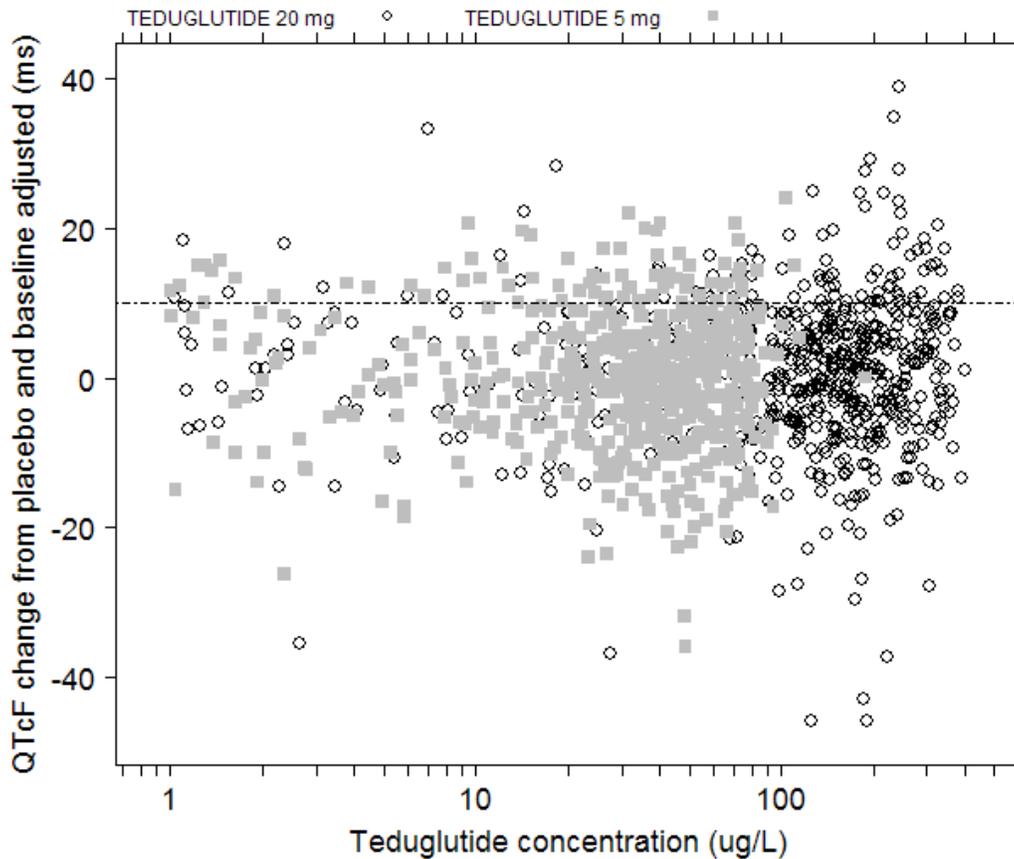
Table 16: Categorical Analysis for QRS

Treatment Group	Total N	QRS <110 ms	QRS \geq 110 ms
MOXIFLOXACIN	70	68 (97.1%)	2 (2.9%)
PLACEBO	69	67 (97.1%)	2 (2.9%)
TEDUGLUTIDE 20 mg	70	68 (97.1%)	2 (2.9%)
TEDUGLUTIDE 5 mg	70	68 (97.1%)	2 (2.9%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcF and teduglutide concentrations is visualized in Figure 4 with no evident exposure-response relationship.

Figure 4: $\Delta\Delta$ QTcF vs. Teduglutide Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 100% of the ECGs were annotated in the primary lead II, with 0% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Overall, six subjects had a PR > 200ms; four of them a PR >200ms was seen at baseline. No subject had a post-baseline increase $\geq 25\%$.

Two subjects had a QRS > 110 ms at baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

APPEARS THIS WAY ON
ORIGINAL

Highlights of Clinical Pharmacology		
Therapeutic dose	<p>Include maximum proposed clinical dosing regimen.</p> <p>0.05 mg/kg/day s.c. is the proposed clinical dose for subjects with SBS</p>	
Maximum tolerated dose	<p>Include if studied or NOAEL dose</p> <p>The highest dose tested in clinical trials was 80 mg/day for 8 days. It was well tolerated.</p>	
Principal adverse events	<p>Include most common adverse events; dose limiting adverse events</p> <p>Most common adverse events are Headache and Abdominal symptoms like pain and distention. None of the adverse events have been found to be dose limiting during the clinical trials program.</p>	
Maximum dose tested	Single Dose	<p>Specify dose</p> <p>20 mg</p>
	Multiple Dose	<p>Specify dosing interval and duration</p> <p>80 mg/day for 8 days</p>
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Cmax and AUC (geometric mean 68% range)</p> <p>For the 20 mg dose: in the QTc study Cmax: 231 (170; 314) AUC: 1885 (1589; 2237)</p>
	Multiple Dose	<p>Mean (SD)Cmax and AUC</p> <p>For the 80 mg/day dose on Day 1 Cmax: 562 (355.1) AUC: 5707 (972.2)</p>
Range of linear PK	<p>Specify dosing regimen</p> <p>Range of 10 to 80 mg/day for 8 days was tested and is linear.</p>	
Accumulation at steady state	<p>Mean (%CV); specify dosing regimen</p> <p>No accumulation was observed following once or twice daily sc injection (abdomen, thigh or arm) of 0.03 to 0.15 mg/kg for 21 days of dosing</p>	
Metabolites	<p>Include listing of all metabolites and activity</p> <p>No active metabolites of teduglutide have been identified</p>	
Absorption	Absolute/Relative Bioavailability	<p>Mean (%CV) 871 (14 [SD])%</p>
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent: 3 – 4 hours • Median (range) for metabolites

		No metabolites found
Distribution	Vd/F or Vd	Mean (%CV) 103 mL/kg
	% bound	Mean (%CV) no data available
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated <p>Teduglutide has an elimination half-life of approximately 2 hours. Following iv administration teduglutide plasma clearance was approximately 2 mL/min/kg, which is equivalent to GFR suggesting that teduglutide is mainly renally cleared.</p> <ul style="list-style-type: none"> • Other routes : <p>NA</p>
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent: Approximately 2 – 4 hours • Mean (%CV) for metabolites: NA
	CL/F or CL	Mean (%CV) 11.7 L/hr
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC In the current overall popPK analysis, age did not have a significant effect on the pharmacokinetics of teduglutide, therefore subjects aged 65 and older are not expected to have different teduglutide exposure from subjects less than 65 years of age because of age alone.
	Sex	Specify mean changes in C _{max} and AUC In the current overall PopPK analysis, overall, body weight and sex on CL/F and body weight on V _c /F were identified as the most significant covariates describing the variability of teduglutide. The inclusion of body weight on V _c /F decreased its between-subject variability (BSV) from 59% to 39%, whereas body weight and sex on CL/F only decreased BSV from 32% to 28%.
	Race	Specify mean changes in C _{max} and AUC In the current overall PopPK analysis, no significant differences were observed due to race.

	Hepatic & Renal Impairment	<p>Specify mean changes in Cmax and AUC</p> <p style="text-align: center;">Hepatic Impairment</p> <table border="0" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th style="text-align: center;">Hepatic Impaired</th> <th style="text-align: center;">Normals</th> </tr> </thead> <tbody> <tr> <td>AUC_(0-inf) (ng·hr/mL)</td> <td style="text-align: center;">1948.9</td> <td style="text-align: center;">2177.0</td> </tr> <tr> <td>Cmax (ng/mL)</td> <td style="text-align: center;">215</td> <td style="text-align: center;">244</td> </tr> </tbody> </table> <p>Hepatic study with single dose of 20 mg</p> <p style="text-align: center;">Renal Impairment</p> <p>Geometric mean PK data from a renal insufficiency pk study in subjects with moderate to severe renal impairment treated with a 10 mg sc dose:</p> <table border="0" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th colspan="6" style="text-align: center;">Group</th> </tr> <tr> <th></th> <th style="text-align: center;">1</th> <th style="text-align: center;">2</th> <th style="text-align: center;">3</th> <th style="text-align: center;">4</th> <th style="text-align: center;">5</th> <th style="text-align: center;">6</th> </tr> </thead> <tbody> <tr> <td>AUC_{inf} (µg·h/L)</td> <td style="text-align: center;">1333</td> <td style="text-align: center;">875.5</td> <td style="text-align: center;">1610</td> <td style="text-align: center;">934.1</td> <td style="text-align: center;">2073</td> <td style="text-align: center;">800.4</td> </tr> <tr> <td>Cmax (µg/L)</td> <td style="text-align: center;">160</td> <td style="text-align: center;">101</td> <td style="text-align: center;">192</td> <td style="text-align: center;">136</td> <td style="text-align: center;">213</td> <td style="text-align: center;">102</td> </tr> </tbody> </table> <p>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)</p>		Hepatic Impaired	Normals	AUC _(0-inf) (ng·hr/mL)	1948.9	2177.0	Cmax (ng/mL)	215	244		Group							1	2	3	4	5	6	AUC _{inf} (µg·h/L)	1333	875.5	1610	934.1	2073	800.4	Cmax (µg/L)	160	101	192	136	213	102
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AUC _{inf} (µg·h/L)	1333	875.5	1610	934.1	2073	800.4																																	
Cmax (µg/L)	160	101	192	136	213	102																																	
Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in Cmax and AUC</p> <p>In a definitive study, teduglutide at concentrations up to 2000 ng/mL (40-fold the peak concentration achieved in humans at a dose of 0.05 mg/kg/day) did not result in direct or time-dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 metabolism in human liver microsomes in vitro. Additionally when incubated with human hepatocytes, teduglutide at concentrations up to 2000 ng/mL did not induce CYP1A2, CYP2B6 or CYP3A4. These results suggest that teduglutide would not be expected to be involved in any clinically relevant drug-drug</p>																																					

		<p>interactions related to CYP activity.</p> <p>It is expected that WARNING labeling will inform prescribers regarding the pharmacodynamic effects of teduglutide and the potential impact of increased absorption resulting from teduglutide treatment. Prescribers will be cautioned that patients receiving concomitant drugs requiring titration or with a narrow therapeutic index should be monitored closely for possible dose adjustment of those therapies, and that due to increased fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to hypervolemia, especially during initiating therapy.</p>
	Food Effects	<p>Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)</p> <p>Effects of meal types on pk were not studied. Teduglutide is administered subcutaneously.</p>
Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p> <p>In a study with single doses given for eight days, doses of 80 mg had about a 5.6 times increase in Cmax and about a 6.6 times increase in AUC compared to a dose of 10 mg. The dose of 10mg is about 0.14 mg/kg assuming a 70 kg subject.</p>	

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

/s/

MOH JEE NG
04/27/2012

JOANNE ZHANG
04/27/2012

JINGYU YU
04/27/2012

NITIN MEHROTRA
04/27/2012

MONICA L FISZMAN
04/27/2012

NORMAN L STOCKBRIDGE
04/27/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 203441

Name of Drug: GATTEX (teduglutide [rDNA origin]) powder for subcutaneous injection

Applicant: NPS Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: 11-30-2011

Receipt Date: 11-30-2011

Background and Summary Description

GATTEX (teduglutide [rDNA origin]) powder for subcutaneous injection is a glucagon-like peptide-2 (GLP-2) analog developed under IND 058213 to treat short bowel syndrome.

GATTEX was granted orphan designation for this indication on June 29, 2000. The drug is a 33-amino acid peptide new molecular entity (Type 1).

The NDA submission is in eCTD format and will be an ODE level sign-off.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. The word “WARNING” appears immediately above the header “1 INDICATIONS AND USAGE” in both the FULL PRESCRIBING INFORMATION: CONTENTS and the FULL PRESCRIBING INFORMATION sections. This appears to be a typographical error.
2. In the FULL PRESCRIBING INFORMATION, the sponsor should ensure that all identifying numbers are presented in bold print and precede the heading or subheading by at least two square em’s (i.e., two squares of the size of the letter “m” in 8 point type).
3. In the FULL PRESCRIBING INFORMATION: CLINICAL STUDIES, and throughout the label as appropriate, remove references to study phase (e.g., Phase 3) and avoid using internal company study titles (e.g., STEPS Protocol CL0600-020 should be renamed Study 1).

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies within 2 weeks of the date of the letter. The resubmitted labeling will be used for further labeling discussions.

Matthew Scherer	4-2--12
<hr/>	
Regulatory Project Manager	Date
Wes Ishihara	4-2-12
<hr/>	
Chief, Project Management Staff	Date

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.

The information presented in Highlights Warnings and Precautions and Drug Interactions regarding increased absorption of concomitant drugs is redundant.

- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading - if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
[http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.h
tm.](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm)

No pharmacologic class is provided. Gattex is a glucagon-like peptide 2 (GLP-2) agonist, however, this is not yet recognized as a pharmacologic class.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

This applies to both the Highlights and FPI.

- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.”

The proposed PCI Statement does not reference the Medication Guide.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Proposed statement should include IFUs in addition to the Medication Guide.

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

/s/

MATTHEW C SCHERER
04/02/2012

RICHARD W ISHIHARA
04/02/2012

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 23, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

Director, Investigations Branch
Kansas District Office
11630 West 80th Street
Lenexa, KS 66214-3383

Director, Investigations Branch
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215

Director, Investigations Branch
New Jersey District Office
Waterview Corp Center
10 Waterview Blvd., 3rd floor
Parsippany, NJ 07054

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA for Pre-Approval
Data Validation Inspection**, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 203-441

DRUG: Gattex® (Teduglutide [rDNA origin] powder for
subcutaneous injection)

SPONSOR: NPS Pharmaceuticals
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921

CONTACT: Sandra C. Cottrell
Vice President, Regulatory Affairs & Drug Safety
Tel: 908-450-5525
Fax: 908-450-5351
scottrell@npsp.com

This memo requests that you arrange for inspection of the clinical and analytical portions of the following clinical study. Note that the clinical inspection is covered separately by a GCP inspection assignment. [Dr. Khairy Malek; file PDUFA 1701] The ORA investigator assigned to the GCP inspection should confirm dosing and blood sampling/shipping records in support of the pharmacokinetic interpretations. A DBGK scientist with specialized knowledge may participate in the inspection of the analytical sites to provide scientific and technical expertise. Please contact OSI upon receipt of this assignment to arrange scheduling of the inspection. Due to the PDUFA review due date, this inspection should be completed by July 31, 2012.

Study # 1: CL0600-004
Study Title: A Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome [A 24-week double-blind, randomized, parallel group study comparing two doses of teduglutide (0.05 mg/kg/day and 0.10 mg/kg/day) and placebo]

Clinical Site 1: Oddzial Kliniczny Żywienia i Chirurgii
SPSK im. Prof. Witolda Orłowskiego CMKP
ul. Czerniakowska 231
00-416 Warszawa POLAND

Clinical Investigator: Marek Pertkiewicz, M.D.

Analytical Site 1: [REDACTED] (b) (4)

Analytical Investigator: [REDACTED] (b) (4)
Bioanalysis Principal Investigator

Analytical Method: LC/MS/MS for the measurement of teduglutide (ALX-0600) concentrations in human plasma

Analytical Site 2: [REDACTED] (b) (4)

Analytical Investigator: [REDACTED] (b) (4)
Project Director, [REDACTED] (b) (4)

Analytical Method: Electrochemiluminescent immunoassays for measurement of antibodies to teduglutide in human plasma, and immunogenicity measurement for (b) (4) specific impurities (b) (4)

Analytical Site 3: (b) (4)

Analytical Investigator: (b) (4)
Laboratory Director

Analytical Methods: Electrochemiluminescent immunoassays for measurement of antibodies to teduglutide in human plasma and immunogenicity measurement for (b) (4); (b) (4) method to detect anti-teduglutide antibodies and immunogenicity measurement for (b) (4); and In vitro cell based bioassay with a Luminescence detection platform for detection of neutralizing activities to teduglutide in human plasma

All pertinent items related to the analytical methods used for the measurement of teduglutide (ALX-0600) concentrations in human plasma (Site #1) and the measurement of antibody of teduglutide (ALX-0600) as well as anti-(b) (4) in human plasma (Site#2 and #3), and the measurement of neutralizing antibodies for teduglutide (Site #3) should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submissions should be compared with the original documents at the site. **The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical sites and the sponsor should be examined for their content.

Page 4 - BIMO Assignment, NDA 203-441 Gattex® (Teduglutide [rDNA origin] powder for subcutaneous injection)

Following identification of the investigators background material will be forwarded directly.

Headquarters' Contact Person: Young Moon Choi, Ph.D. for domestic inspection
(301)796-1516

Arindam Dasgupta, Ph.D. for foreign inspection
(301)796-3326

cc:

CDER OSI PM TRACK

OSI/Moreno/Taylor/Haidar/Skelly/YMC/Dasgupta/Patel/Dejernet/CF

HFC-130/ORA HQ DFFI IOB BIMO

OSI/Malek

HFR-SW350/Bromley/Stevens

HFR-CE250/Smith/Harris

HFR-CE350/Rolli/Harlan

OCP/DCP-3/Bashaw/Fang

DGIEP/Scherer

Draft: YMC 2/23/2012

Edit: MFS 2/23/12

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FACTS: (b) (4)

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/s/

YOUNG M CHOI
02/24/2012

MICHAEL F SKELLY
02/24/2012
Dr. Haidar added to signature block.

SAM H HAIDAR
02/24/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: February 16, 2012

Reviewer(s): Manizheh Siahpoushan, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s): Gattex (Teduglutide [rDNA origin]) for Injection
5 mg per vial

Application Type/Number: NDA 203441

Applicant/sponsor: NPS Pharmaceuticals

OSE RCM #: 2011-4410

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed packaging configuration, container labels, carton labeling, Prescribing Information, Medication Guide, and Instructions for Use for Gattex (Teduglutide [rDNA origin]) Injection for areas of vulnerability that could lead to medication errors. Additionally, The Applicant is proposing to have a Risk Evaluation and Mitigation Strategy (REMS) associated with Gattex upon approval of the product. The proposed goals of the REMS are:

- To support informed decisions between patients and their healthcare providers who are considering treatment with Gattex by educating them on the appropriate use and the risks of Gattex.
- To mitigate the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, cholecystitis, cholangitis, cholelithiasis, and pancreatitis through ongoing collection and monitoring of safety data.
- To educate prescribers and patients on the potential risks of increased absorption of concomitant oral medications with narrow therapeutic index or requiring titration associated with Gattex therapy.
- To establish the long-term safety of Gattex during and after therapy by periodic monitoring of patients for malignancies (except basal cell carcinoma).

The REMS will include Gattex Medication Guide and Instructions for Use, Dear Health Care Provider Letter, List of classes of oral medications with narrow therapeutic index or requiring titration, prescriber overview, prescriber enrollment form, patient enrollment form, and data collection forms for safety monitoring. DMEPA will evaluate the Medication Guide and Instructions for Use components of REMS in this review.

1.1 REGULATORY HISTORY

This product received orphan drug designation for the Short Bowel Syndrome (SBS) indication, on June 29, 2000.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 30, 2011 submission:

- Active Ingredient: Teduglutide [rDNA origin]
- Indication of Use: A novel recombinant analog of the naturally occurring human glucagon-like peptide-2 (GLP-2) indicated for treatment of adult patients with Short Bowel Syndrome (SBS) to improve intestinal absorption of fluid and nutrients.
- Route of administration: Subcutaneous
- Dosage form: Powder for Injection
- Strength: 5 mg per vial

- Dose and Frequency of Administration: 0.05 mg/kg administered once daily, subcutaneously to alternating sites between one of the four quadrants of the abdomen, or into alternating thighs or alternating arms.
- How Supplied: Supplied in a sterile, single-use, 3 mL vial containing 5 mg of Gattex as a white lyophilized powder to be reconstituted with 0.5 mL Sterile Water for Injection supplied in disposable pre-filled syringes. Available in a 30-vial kit and a one-vial kit.

30-vial Kit:

- *Thirty single-use vials of drug
- *Thirty disposable prefilled syringes containing Sterile Water for Injection USP for reconstitution with 30 separate needles to attach to the syringes.
- *Thirty sterile disposable 1 mL syringes with needle for dosing
- *Sixty-eight alcohol swabs

One-vial Kit:

- *One single-use vial of drug
- *One disposable prefilled syringe containing Sterile Water for Injection USP for reconstitution with a separate needle to attach to the syringes.
- *One sterile disposable 1 mL syringe with needle for dosing
- *One alcohol swab

- Storage: Prior to dispensing: The vials containing the drug product will be stored at 2°C to 8°C (36°F to 46°F), Do not freeze. The product has to be dispensed with a (b) (4) “use by” dating and specify “Store at room temperature up to 25°C (77°F). Do not freeze. The contents of the 30-vial kit (i.e. prefilled syringes containing sterile Water for Injection, needles, dosing syringes with needles, and alcohol swabs) will be stored at room temperature.
- Container and Closure systems: The container closure system for teduglutide for injection is comprised of 3-mL, Type I glass tubing vials (b) (4)

(b) (4) The Sterile Water for Injection is supplied in prefilled, single-use, (b) (4) glass syringes (b) (4)

Additionally, The Applicant intends to have a Risk Evaluation and Mitigation Strategy (REMS) associated with Gattex because Gattex has been associated with the risks of enhancement of colon polyp growth, cholecystitis, cholangitis, cholelithiasis, pancreatitis, and the potential of increased absorption of concomitant oral medications with a narrow therapeutic index or requiring titration. Because of these risks, Gattex will be available only through a restricted distribution program. Under the Gattex program, only enrolled prescribers, network specialty pharmacies, and patients can prescribe, dispense, and receive Gattex, respectively.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container labels and carton labeling submitted on 8/16/00
- Prescribing Information submitted on 11/30/11
- Medication Guide submitted on 11/30/11
- Instructions for Use submitted on 11/30/11
- An assembled 30-count patient kit containing 30 empty drug product vials, 30 (b) (4) prefilled syringes with Sterile Water for Injection (sWFI), 30 sterile disposable needles, 30 disposable 1 mL dosing syringes with needle, and 68 alcohol swabs, submitted on December 22, 2011.
- An assembled 30-count kit with non-product spacer (no drug product) submitted on December 22, 2011.
- An assembled 1-count patient kit submitted on December 22, 2011.
- A 30-count (cold ship) carton of drug vials containing 30 empty drug product vials submitted on December 22, 2011.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following sections describe our risk assessment of the Gattex product design as well as the associated label and labeling.

3.1 ALL LABELING

- The dosage form statement that describes the active ingredient is not a recognized dosage form in USP. The statement ‘(b) (4)’ should be revised to read: ‘for injection’.

3.2 PRESCRIBING INFORMATION

- The use of the (b) (4) ((b) (4)) under the Dosage Forms and Strengths Sections of the Highlights and the Full Prescribing Information, as well as the How Supplied/Storage and handling Section can lead to confusion and potential for errors.
- It is unclear what the word (b) (4) means in the final concentration statement (i.e. (b) (4) 10 mg/mL) obtained after reconstitution with 0.5 mL sterile Water for Injection, in *Dosage Forms and Strengths* Sections of the Highlights and the Full Prescribing Information, as well as *Description* Section of the Full Prescribing Information.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- The statement [REDACTED] (b) (4) in *Dosage and Administration* Section of the Highlights of the Prescribing Information contains negative language (i.e. what not to do) and may have the opposite of the intended consequence.
- The statement ‘Discard unused portion.’ does not appear after the statement ‘Single-use product.’ in *Dosage and Administration* Section of the Highlights of the Prescribing Information.
- It is unclear if the proposed 5 mg per vial strength statement is the deliverable quantity of Gattex. The Applicant needs to clarify if the total vial content is 5 mg or more, as well as the extractable amount of the product (i.e. the statement ‘A maximum of 0.38 mL of reconstituted solution can then be withdrawn from the vial.’ should state specifically the amount of the product in ‘mg’ that is delivered in 0.38 mL).
- The abbreviations sWFI and SC appear throughout the Prescribing Information.
- *How Supplied/Storage and Handling* Section does not indicate the type and size of the plastic dosing syringe with needles (i.e. 1 mL, 26G 5/8 in) or the needles provided to be attached to the glass pre-filled syringes containing sterile Water for Injection (i.e. 22G, 1½ in).

3.3 MEDICATION GUIDE

- We note that the Applicant uses simplified wording [REDACTED] (b) (4) throughout the Medication Guide, such as [REDACTED] (b) (4). Words such as [REDACTED] (b) (4) might be confusing.
- For clarity and brevity, improvements can be made to the presentation of information under ‘What is Gattex?’, ‘How should I use Gattex?’, and ‘How should I store Gattex?’. See Section 4 *Conclusions and Recommendations*.

3.4 INSTRUCTIONS FOR USE

- Improvements to the format of the Instructions for Use are needed (i.e. lack of space between words in various instances).
- The use of the word [REDACTED] (b) (4) can be confusing.
- The clarity of instructions under ‘From your Gattex patient kit’, # 1, can be improved by addition of a statement.

[REDACTED] (b) (4)

3.5 PACKAGING CONFIGURATION

The proposed 30-count patient kit and 1-count patient kit packaging configuration is consistent with the Applicant’s proposed once daily dosing of Gattex and all the supplies

required for patients to administer each daily dose of Gattex. For the 30-count kit, the Applicant proposes that the 30 vials of drug are (b) (4)

However, the Applicant does not indicate if they will provide the (b) (4) 'use by' dating (i.e. in the form of stickers) to the specialty pharmacy, or if the pharmacy is expected to create their own method to provide this information on patient kits. (b) (4)

Additionally, the Applicant does not indicate in the labeling of this product if a patient may need more than one 30-count patient kit to be mailed to them. It is not clear from the Prescribing Information if there is a maximum daily dose requirement for this product (i.e. maximum daily dose of Gattex is 0.38 mL). Therefore, we predict that a patient who weighs 110 kg would need more than one vial per day, and more than one kit for a one month supply of this product.

The Applicant is proposing two types of pre-filled syringes to be available for distribution (b) (4)

(b) (4) We recommend that the Applicant provide only one type of the pre-filled syringe for patients in both the 1-count and the 30-count patient kits to ensure safety.

3.6 ALL CONTAINER LABELS AND CARTON LABELING

- The established name and the dosage form lack prominence.
- Information regarding the amount of the product delivered in the maximum extractable volume of 0.38 mL after reconstitution, is not provided on the container labels and carton labeling of Gattex (i.e. 'After reconstitution with 0.5 mL sterile Water for Injection, each 0.38 mL contains x mg of Gattex.').

- The storage information for patients, ‘Store at room temperature up to 25°C (77°F) which appears in the Prescribing Information, Medication Guide, carton labeling, and the pre-filled syringe label, is too general and is not in accordance with the USP definition of controlled room temperature (i.e. 20°C to 25°C (68°F to 77°F) per USP 10.30.60 *Controlled Room Temperature*). Additionally, the storage information is not included on the Gattex container labels.

3.7 CONTAINER LABELS

Pre-filled Syringe Labels

- The container labels for the pre-filled syringes containing the sterile Water for Injection intended for reconstitution of Gattex, do not display the word ‘Diluent’ in a prominent manner.

Gattex Vial Label

- The (b) (4) color used to present the proprietary name, the established name, and the dosage form lacks prominence due to lack of contrast with the white background.
- The route of administration statement ‘For subcutaneous use only.’ does not appear on the principal display panel of the Gattex container label.
- The strength statement ‘(b) (4)’ is redundant and should be revised to ‘5 mg per vial’.
- The statement ‘For single use- Discard the unused portion.’ does not appear on the principal display panel of the container label.
- The manufacturer information is too prominent and occupies the entire side panel of the Gattex container label. Making this information less prominent by using a smaller font would provide space for other important information such as the extractable concentration and storage information.
- The container label does not state how long the product is good for, once it is reconstituted.

3.8 CARTON LABELING

- The product strength statement does not appear following the established name and the dosage form where they appear on the carton labeling of Gattex.
- The proprietary name, the established name, and the dosage form statements that appear on the right hand side of the principal display panel of all carton labeling, below the multi-color graphic, is repetitive.
- The multi-color graphic across the principal display panel of all carton labeling, as well as above the proprietary name, Gattex is too prominent and can distract from the proprietary name and other important information such as the route of administration.

- The route of administration statement, ‘For subcutaneous use only.’ appears in all capital letters and lacks prominence.
- A warning statement to alert the pharmacists to replace the place holder with the trays of vials containing Gattex in the 30-count patient kit, does not appear on the carton labeling.
- The company logo, ‘nps’ is too prominent and can distract from the proprietary name, the established name, dosage form, strength, and route of administration statements.
- A warning statement such as ‘Place vials in the 30-count patient kit.’ does not currently appear on the carton labeling of the 30-count (cold ship) drug vials to prevent errors that may result in the specialty pharmacy while preparing the 30-count patient kit (i.e. the vials may not be taken out of the 30-count (cold ship) box of the drug vials to replace the place holder in the 30-count patient kit).
- The empty place holder box in the 30-count patient kit may be misinterpreted as a box containing vials with the active drug.
- There is no diagram to help explain to patients and healthcare providers where each component of the kit is located.
- There is no place to record a dispense date and expiration date on the kit.
- The instructions to remind the pharmacists to dispense the active drug vials with the 30-count patient kit appear on the back panel of the carton labeling and may be overlooked.
- The statement (b) (4) which appears (b) (4) on the back panel of all carton labeling (as well as the inside panel of the 30-count patient kit lid label) should be revised to ‘Gattex (teduglutide [rDNA origin]) for injection’ to be consistent with the other presentations in all labeling.
- Under ‘Each Kit Contains:’, the type and size of the plastic dosing syringes (i.e. 1 mL, 26G 5/8 in) as well as the needles to be attached to the glass pre-filled syringes containing sterile Water for Injection (i.e. 22G, 1½ in) is not indicated.
- Under ‘Each Kit Contains:’, the statement (b) (4) can be simplified by revising the statement to ‘One Diluent syringe (0.5 mL)’.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling are unacceptable because they may introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented prior to approval of the supplement:

A. Prescribing Information

1. We recommend deleting (b) (4), (b) (4), where it appears in *Dosage Forms and Strengths* of the Highlights and the Full

Prescribing Information, as well as *How Supplied/Storage and Handling* Section in the Full Prescribing Information. The (b) (4) statement used to define (b) (4) of Gattex, may lead to confusion and errors when determining the required dose for the patients.

2. The word (b) (4), used to define the final concentration after reconstitution with 0.5 mL sterile Water for Injection ‘i.e. (b) (4) 10 mg/mL’, in *Dosage Forms and Strengths* Sections of the Highlights and the Full Prescribing Information, as well as *Description* and *How Supplied/Storage and Handling* Sections of the Full Prescribing Information, is ambiguous and does not help clarify what the concentration is after reconstitution. The Applicant needs to define the word (b) (4), and indicate if the use of this terminology is necessary. We defer to the Division to determine if the use of the word (b) (4) to define the final concentration of the product after reconstitution, is appropriate.
3. We recommend revising the third bullet point (b) (4), in *Dosage and Administration* Section of the Highlights of the Prescribing Information, to use a positive statement such as ‘Gattex should be administered by subcutaneous injection only.’ Additionally, we recommend appending the statement ‘Discard unused portion.’ to ‘Single-use product’ statement. Thus, the third bullet point should read as follows: ‘For subcutaneous injection only. Single use product. Use within 3 hours after reconstitution. Discard any unused portion.’
4. It is not clear if the proposed 5 mg per vial strength of Gattex is the deliverable quantity of Gattex. The Applicant needs to clarify if the total vial content is 5 mg or more, as well as the extractable amount of the product in ‘mg’ (i.e. the statement ‘A maximum of 0.38 mL of reconstituted solution can then be withdrawn from the vial.’ should specify the amount of the product in ‘mg’ that is delivered in 0.38 mL). As currently presented, it is unclear if a patient would receive 5 mg Gattex or less, in the proposed maximum extractable volume of Gattex (i.e. 0.38 mL).
5. We recommend including the type and size of the plastic dosing syringe with needles (i.e. 1 mL, 26G 5/8 in) as well as the needles to be attached to the glass pre-filled syringes containing the Diluent (i.e. 22G, 1½ in) in *How Supplied/Storage and Handling* Section.
6. Revise the Prescribing Information to remove the abbreviations ‘sWFI’ and ‘SC’. The abbreviation ‘SC’ is on the ISMP ‘List of Error-Prone Abbreviations, Symbols, and Dose Designations’¹ because it has been mistaken as ‘SL’ or sublingual. As part of a national campaign to reduce medication errors related to error prone medical abbreviations, the FDA agreed not to approve labels and labeling that include the use of error-prone

¹ Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

abbreviations. Therefore replace ‘sWFI’ with ‘sterile Water for Injection’ and ‘SC’ with ‘subcutaneous’.

B. Medication Guide

1. We recommend replacing the word (b) (4) with ‘injection’ or ‘dose’. The use of the word (b) (4) may be confusing. Additionally, words such as ‘injection’ or ‘dose’ have been used in other approved Medication Guides and are recognized by patients.
2. To improve clarity, we recommend revising the first seven bullet points under ‘How should I use Gattex?’ to appear as follows (please note the replacement of the word (b) (4) with dose):

‘For detailed instructions, see the Instructions for Use at the end of this Medication Guide.’

- Use Gattex exactly as your healthcare provider tells you to.
 - Gattex will be mailed to you by a specialty pharmacy. Your healthcare provider will give you details when you enroll.
 - Gattex is injected under the skin (subcutaneous injection) 1 time each day at the same time.
 - Gattex has to be mixed with the Diluent provided in the pre-filled syringe, prior to injection.
 - Your healthcare provider will tell you how much Gattex to use.
 - Gattex must be injected within 3 hours after you mix it with the Diluent.
 - Inject your dose of Gattex under the skin (subcutaneous injection), as you are told by your healthcare provider. Do not inject Gattex into a vein or muscle.
 - If you miss a dose, take it as soon as you remember that day. Take your next dose the next day at the same time you take it every day. Do not take 2 doses at the same time.
 - If you use more than 1 dose, call your healthcare provider right away.’
3. Under ‘How should I store Gattex?’, we recommend replacing the statement (b) (4) in the third bullet point by ‘to take a dose’ or ‘to give an injection’, and replacing the statement (b) (4) to ‘you have mixed for a dose’ or ‘you have mixed for an injection’.

C. Instructions For Use

1. Revise the general format to include spaces between words where appropriate. As currently presented, there are various spacing errors throughout the Instructions for Use. For example the words ‘1 type’ or ‘your workspace’ are presented as one word with no space.
2. We recommend replacing the word (b) (4) with ‘injection’ or ‘dose’ throughout the Instructions for Use to remain consistent with the Medication Guide (after revised).
3. We recommend providing a statement such as ‘your healthcare provider will tell you how many vials of Gattex you will need for your injection’ under #1 *From your Gattex patient kit*. This statement will clarify the instructions for the patient, if the patient will need more than the maximum extractable volume of 0.38 mL per vial, for each injection.
4. We recommend replacing ‘prefilled glass syringe containing sterile Water for Injection’ (or different variations of this statement) with the name, ‘Diluent’ (after revising the prefilled syringe labels). Using the name, ‘Diluent’ (when the syringe label is revised to be called ‘Diluent’) can further simplify the instructions to follow by patients.
5. *How Do I Prepare a Dose of Gattex*- sections A. 5a and A. 5b, which explain how to open the two different types of the pre-filled syringes. The Applicant has not provided detailed instructions on what part of the syringe and the cap the patient should hold and which way the cap should be bent (i.e. bend the cap sideways until the cap comes off). We recommend revising A.5a. and A.5b. under *How Do I Prepare a Dose of Gattex?* to provide more clarity regarding the instructions for use for the two different types of the Diluent syringes. The revised format of section A under *How Do I Prepare a Dose of Gattex*’ should appear as follows, however the Applicant needs to provide specific details, especially to the section 5a:
‘A. Attach the Needle to the Diluent glass syringe
 5. Put the prefilled glass syringe and 22G 1 1/2in needle in front of you on your workspace.
 - Hold the prefilled glass syringe by the barrel.
 - a. If you have the Diluent syringe with the white snap-off cap: Snap or twist off the white cap. Only the top portion of the white cap should be snapped off. The lower portion of the white cap will remain in place (Figure 2a). Throw the cap away.
 - b. If you have the Diluent syringe with the gray screw top: Unscrew the top counter clockwise (to the left) (Figure 2b). Throw the top away.
6. Replace the abbreviation ‘IV’ with ‘intreavenous’ in Section E. The use of abbreviations is error prone and can lead to confusion. Patients may misinterpret the intended meaning for something else.

D. All Container Labels and Carton Labeling

1. Revise the established name and the dosage form to have a prominence commensurate with the prominence of the proprietary name, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2). Additionally, the established name and the dosage form should be revised as follows: ‘(Teduglutide [rDNA origin]) for Injection’
2. Provide information regarding the amount of the product delivered in the maximum extractable volume of 0.38 mL per vial, after reconstitution. The statement may appear as follows: ‘After reconstitution with 0.5 mL sterile Water for Injection, each 0.38 mL contains x mg of Gattex.’
3. Revise the storage information statement ‘Store at room temperature up to 25°C (77°F) which appears in the Prescribing Information, Medication Guide, carton labeling, and the pre-filled syringe label, to be in accordance with the USP definition of controlled room temperature (i.e. 20°C to 25°C (68°F to 77°F) per USP 10.30.60 *Controlled Room Temperature*). As currently presented, the storage statement is too general.

E. Container Labels

Pre-filled syringe labels

1. Revise the pre-filled syringe labels to include the word ‘Diluent’ as the prominent identifier for the pre-filled syringe containing sterile Water for Injection. As currently presented, the syringe label does not provide this, which may make it difficult for patients to identify what the pre-filled syringe contains. Additionally, include the statement ‘for Gattex’ in a less prominent presentation immediately under the name, ‘Diluent’, followed by the quantity, ‘0.5 mL’. The revised presentation should appear as follows (note the prominence of the name, Diluent as compared to the proprietary name, Gattex, and that of Gattex compared to ‘Sterile Water for Injection, 0.5 mL):

“Diluent

for Gattex

Sterile Water for Injection, 0.5 mL”

2. Include the ‘Rx only’ statement on the pre-filled syringe label if space permits, as Sterile Water for Injection is considered a prescription product. Additionally, ensure the ‘Rx only’ statement is not printed in bold letters and does not have greater prominence than the other information on the syringe label. If space permits, we recommend placing the ‘Rx only’ statement on the right or left hand side of the bottom portion of the syringe label.
3. Reduce the prominence of the NDC number by unbolding it. As currently presented, the NDC number appears more prominent than the other information on the label.

Gattex Vial Label

1. Increase the contrast of the proprietary name, the established name, and the dosage form by using a darker color font. As currently presented, the (b) (4) color does not provide sufficient contrast with the white background and is difficult to see.
2. Revise the strength statement (b) (4) to appear as '5 mg per vial'. As currently presented, the statement (b) (4) is redundant.
3. Include the route of administration statement 'For subcutaneous use only' immediately below the product strength statement after revision (i.e. 5 mg per vial) and ensure the statement is prominent. Additionally, present this information in title case lettering (i.e. For subcutaneous use only). The use of all capital letters (i.e. FOR SUBCUTANEOUS USE ONLY) decreases readability due to the rectangular shape that is formed by words set in all capital letters.
4. Include the 'Single-use vial- Discard unused portion' immediately below the route of administration statement, if space allows. Alternatively, this statement may appear on the side panel where the manufacturer information appears. The presentation of the proprietary name, the established name, dosage form, strength, and route of administration may appear as follows:

“Gattex

(Teduglutide [rDNA origin]) for injection

5 mg per vial

For subcutaneous use only

Single use vial- Discard unused portion.”

5. Decrease the prominence of the manufacturer information that appears on the side panel of the vial label. Reducing the prominence of this information can provide space for other information such as 'For single use. Discard unused portion.' (If space does not allow for this information to appear on the principal display panel), as well as the storage information.
6. Provide the storage information on the side panel of the vial label. This information may appear as follows:
“Store at room temperature, 20°C to 25°C (68°F to 77°F). Do not freeze.”
7. If space permits, include information regarding the stability of Gattex once reconstituted, on the side panel. The statement should appear as follows:
'Use within 3 hours of reconstitution.'

F. Carton Labeling

1. Increase the contrast of the established name and the dosage form by using a darker font color. As currently presented, the (b) (4) color does not provide enough contrast with the white background, is difficult to see.

2. Include the strength statement '5 mg per vial' in the line immediately below the established name where it appears on the carton labeling. As currently presented, the carton labeling does not include the strength statement.
3. Delete or reduce the prominence of the multi-color graphic that appears across the principal display panel of the carton labeling and extending to the side panels, as well as the multi-color graphic that appears above the proprietary name. The presentation of the graphic is too prominent and can distract from the proprietary name, product strength, and route of administration statements.
4. Increase the prominence of the route of administration statement by increasing the font size. Additionally, we note that this statement is presented in all capital letters (i.e. FOR SUBCUTANEOUS USE ONLY) which decreases readability. Revise the statement to appear in title case (i.e. For subcutaneous use only). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.
5. Reduce the prominence of the company logo 'nps' that appears on the carton labeling. As currently presented, 'nps' competes in prominence with the proprietary name, the established name, and the route of administration statement.
6. Delete the proprietary name, the established name, and the dosage form statement that appears on the right hand side of the principal display panel of all carton labeling, below the multi-color graphic. This information is repetitive.
7. Include a warning statement under 'Attention Pharmacist:' to replace the placeholder inside the 30-count patient kit with the trays of vials containing Gattex before shipment to the patient and repeat the entire 'Attention Pharmacist:' statement on the principal display panel and the top panel of the carton labeling. The Applicant needs to ensure that the 30-count patient kit will not be shipped to the patient without placement of the Gattex vials in the patient kit.
8. 30-count patient kit, under Attention Pharmacist: Delete the statement 'Prior to Dispensing: Store at 2°C to 8°C (36°F to 46°F). Do not freeze.' Since the Applicant will be providing the specialty pharmacy a separate shipment of the Gattex vials (cold ship), and the 30-count patient kit will be shipped to the specialty pharmacy with a placeholder for the Gattex vials and not the actual Gattex vials, presenting the storage information before dispensing on the 30-count patient kit may be confusing for the patients because patients will be instructed to store the kit including the Gattex vials at room temperature and use by the (b) (4) 'use by' dating.
9. 30-count patient kit: Include a placeholder on the principal display panel and the top panel of the carton labeling to alert the specialty pharmacy staff to fill in the (b) (4) expiration date prior to shipment to the patient. The place holder

may appear as follows:

<p>Dispensed on: ----- (date)</p> <p>Expires on: ----- (^(b)₍₄₎ days after dispensing)</p>

10. Include the type and size of the plastic dosing syringes (i.e. 1 mL, 26G 5/8") as well as the needles to be attached to the glass pre-filled syringes containing the Sterile Water for Injection (i.e. 22G, 1½"), under 'Each Kit Contains:' on both the 1- and 30-count patient kits.
11. Revise the heading 'Gattex (teduglutide [rDAN origin]) powder for subcutaneous injection' that appears in ^(b)₍₄₎ font to read 'Gattex (teduglutide [rDAN origin]) for injection' to be consistent with the revised format throughout the label and labeling. Additionally, revise the third bullet point in this section (i.e. ^(b)₍₄₎) to read: 'Reconstitute each vial with the enclosed prefilled syringe containing 0.5 mL Sterile Water for Injection, USP.'
12. Include the contents of the Diluent (pre-filled syringes containing sterile Water for Injection) on the carton labeling of the 1- and 30-count patient kits. We note that you list the active and inactive ingredients of the Gattex vial, however the active and inactive ingredients of the Diluent do not appear on the carton labeling and this information may be needed by the patient or the healthcare provider.
13. Revise the statement ^(b)₍₄₎ to read 'Thirty Diluent prefilled syringes for reconstitution.'
14. We are concerned that pharmacist and pharmacy technicians may misinterpret the place holder carton in the 30-count patient kit as a carton containing the active drug and may forget to replace this carton with the active drug vials. Thus, we recommend that you consider revising the design of the place holder carton such that it automatically comes out of the carton when the top panel is opened (i.e. the place holder carton is attached to the inside of the top panel). Alternatively, remove the place holder carton completely and have an empty well. In the bottom of the well, a printed message may appear, to instruct pharmacists to place the active drug vials from the refrigerator in this well.
15. Consider adding a diagram of the contents and where they are located on the inside of the top panel so that patients and healthcare providers can easily locate all the components contained in the kit.

If you have further questions or need clarifications, please contact Nitin Patel, project manager, at 301-796-5412.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MANIZHEH SIAHPOUSHAN
02/16/2012

ZACHARY A OLESZCZUK
02/16/2012

CAROL A HOLQUIST
02/17/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 203441 BLA#	NDA Supplement #:S- BLA STN #
Efficacy Supplement Type SE-	
Proprietary Name: GATTEX Established/Proper Name: teduglutide [rDNA origin] Dosage Form: powder for subcutaneous injection Strengths: 5 mg	
Applicant: NPS Pharmaceuticals Agent for Applicant (if applicable):	
Date of Application: 11-30-11 Date of Receipt: 11-30-11 Date clock started after UN:	
PDUFA Goal Date: 9-30-12 (Sunday)	Action Goal Date (if different): 9-28-12
Filing Date: 1-29-12	Date of Filing Meeting: 1-4-12
Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 1	
Proposed indication(s)/Proposed change(s): <ul style="list-style-type: none"> • treatment of adult patients with Short Bowel Syndrome (SBS) • GATTEX is used to improve intestinal absorption of fluid and nutrients. 	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> The drug product includes a single-use 3 mL glass vial containing 5 mg of teduglutide as a lyophilized powder for reconstitution with 0.5 mL sterile water for injection (sWFI) that will be copackaged in a single-use prefilled syringe. An additional disposable syringe (1 mL) for administration of the reconstituted solution will also be copackaged with the product.	<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation (orphan designation granted 6-29-2000) <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 058213				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		x		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>x</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>x</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>x</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>x</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>	<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>															
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>			<p>x</p>																	

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			x	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	x			5-year Waxman-Hatch; 7-year orphan exclusivity requested
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>			x	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			x	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	x			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	x			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	x			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			x	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	x			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	x			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			x	Electronic submission. DO notified by sponsor.

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			x	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		x		Orphan designation.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			x	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			x	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			x	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		x		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	x			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>	x			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	x			
Is the PI submitted in PLR format? ⁴	x			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)		x		Patient Labeling Team to be consulted
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	x			- QT consult sent - OBP consulted for immunogenicity assay - DDOP/DBOP consult TBD - CDRH consult TBD
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s):		x		

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 9, 2010 and April 25, 2011	x			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		x		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1-4-12

BLA/NDA/Supp #: 203441

PROPRIETARY NAME: GATTEX

ESTABLISHED/PROPER NAME: teduglutide

DOSAGE FORM/STRENGTH: powder for subcutaneous injection/5 mg

APPLICANT: NPS Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- treatment of adult patients with Short Bowel Syndrome (SBS)
- GATTEX is used to improve intestinal absorption of fluid and nutrients.

BACKGROUND:

GATTEX (teduglutide [rDNA origin]) powder for subcutaneous injection is a glucagon-like peptide-2 (GLP-2) analog developed under IND 058213 to treat short bowel syndrome. GATTEX was granted orphan designation for this indication on June 29, 2000. The drug is a 33-amino acid peptide new molecular entity (Type 1).

The NDA submission is in eCTD format and will be an ODE level sign-off.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew Scherer	y
	CPMS/TL:	Wes Ishihara	n
Cross-Discipline Team Leader (CDTL)	Ruyi He		y
Clinical	Reviewer:	John Troiani	y
	TL:	Ruyi He	y
Clinical Pharmacology	Reviewer:	Lucy Fang	y
	TL:	Yow-Ming Wang	y
Clinical Pharmacology – Division of	Reviewer:	Anshu Marathe	y

Pharmacometrics	TL:	Christine Garnett	n
	Reviewer:	Lisa Kammerman (has since be reassigned to Behrang Vali who was not present)	y
Biostatistics	TL:	Mike Welch	y
	Reviewer:	Tamal Chakraborti	y
Nonclinical (Pharmacology/Toxicology)	TL:	Sushanta Chakder	n
	Reviewer:	TBD	n
Statistics (carcinogenicity)	TL:	TBD	n
	Reviewer:	Joao Pedras-Vasconcelos	n
Immunogenicity (assay/assay validation) <i>(for BLAs/BLA efficacy supplements)</i>	TL:	Susan Kirshner	n
	Reviewer:	Yichun Sun	y
Product Quality (CMC)	TL:	Marie Kowblansky	y
	Reviewer:	Bryan Riley	y
Quality Microbiology <i>(for sterile products)</i>	TL:	Bryan Riley	y
	Reviewer:	Zhong Li	y
Facility Review/Inspection	TL:	David Doleski	n
	Reviewer:	Manizheh Siahpoushan	n
OSE/DMEPA (proprietary name)	TL:	Zachary Oleszczuk	n
	Reviewer:	Reema Jain	n
OSE/DRISK (REMS)	TL:	Kendra Worthy	n
	Reviewer:	TBD	n
OC/OSI/DSC/PMSB (REMS)	TL:	TBD	n
	Reviewer:	TBD	n
Bioresearch Monitoring (DSI)	TL:	TBD	n
	Reviewer:	TBD	n

Other reviewers	TBD	n
Other attendees	Julie Beitz, Victoria Kusiak, Giuseppe Randazzo, Donna Griebel, Andrew Mulberg, Joyce Korvick, Chantal Phillips	

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: no issues discussed</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: Need for an AC is to be determined. The drug is first in class, however, there is another approved drug for this indication (Zorbtiv) that has a related mechanism of action. Gattex is an NME and there are potential safety concerns (e.g., benign neoplasia) as listed in the Warnings and Precautions section of the proposed package insert. A meeting to make a final decision on the need for an AC meeting will be held early in the review cycle (mid to late February).</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:

<p><i>or efficacy issues</i></p> <ul style="list-style-type: none"> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Initially, Biostatistics recommended a refuse to file because the NDA lacked analysis datasets and appropriate subgroup analyses. The sponsor has since submitted these items.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments: OBP was consulted to examine the immunogenicity assay protocol and results; it did not make a filing recommendation.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Initial recommendation was refuse to file because of an inadequate environmental assessment. NPS has since submitted a revised and sufficient EA.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Quality Microbiology was not present, but did complete a filing review and noted that the NDA should be filed from a Clinical Microbiology standpoint.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Facility/Microbiology Review (BLAs only)		<input checked="" type="checkbox"/> Not Applicable
Comments:		<input type="checkbox"/> FILE
		<input type="checkbox"/> REFUSE TO FILE
		<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT		
Signatory Authority: Victoria Kusiak, Deputy Director, ODE III		
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):		
Comments: None		
REGULATORY CONCLUSIONS/DEFICIENCIES		
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:	
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.	
	<u>Review Issues:</u>	
	<input type="checkbox"/> No review issues have been identified for the 74-day letter.	
	<input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.	
	<u>Review Classification:</u>	
	<input checked="" type="checkbox"/> Standard Review (confirmed at planning meeting 1-12-2012)	
	<input type="checkbox"/> Priority Review	
ACTIONS ITEMS		
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).	
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).	
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.	
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter	
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) 	

	<ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input checked="" type="checkbox"/>	Other: request additional consults as needed

Matthew Scherer	1-24-2012
Regulatory Project Manager	Date
Wes Ishihara	1-26-2012
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MATTHEW C SCHERER
01/26/2012

RICHARD W ISHIHARA
01/27/2012

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