

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208745Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208745

SUPPL #

HFD # 180

Trade Name Trulance

Generic Name plecanatide

Applicant Name Synergy Pharmaceuticals

Approval Date, If Known January 19, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)1

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!
!
! NO
! Explain:

Investigation #2

IND #

YES

!
!
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Maureen Dewey, M.P.H.
Title: Senior Regulatory Health Project Manager
Date: December 20, 2016

Name of Division Director signing form: Donna Griebel, M.D.
Title: Director, Division of Gastroenterology and Inborn Errors Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL

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

/s/

MAUREEN D DEWEY
01/19/2017

DONNA J GRIEBEL
01/19/2017

3. DEBARMENT CERTIFICATION

Synergy Pharmaceuticals Inc. 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 new drug application 208745 for plecanatide (SP-304).

Attached is the list of principal investigators associated with Phase 3 clinical studies SP304203-00, SP304203-01, and SP304203-03, respectively.



Evelyn Jaeger,
Vice President Regulatory Affairs &
Clinical Quality Assurance

26 Jan 2016

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208745 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: TRULANCE Established/Proper Name: plecanatide Dosage Form: 3 mg tablets		Applicant: Synergy Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Maureen Dewey		Division: DGIEP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>01/29/2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: IA
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	AP 01/19/2017
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (indicate date(s)) Review(s) (indicate date(s)) 	05/12/2016 9/8/2016; 5/11/2016
❖ Labeling reviews (indicate dates of reviews)	RPM: 11/22/16 DMEPA: 12/2/16; 1/18/2017 DMPP/PLT (DRISK): 9/19/16 OPDP/DDMAC: 9/21/16 COA: 12/5/16 CSS: <input checked="" type="checkbox"/> None Product Quality 1/5/17; 10/18/16 Other: <input type="checkbox"/> None DPMH (Maternal Health) 11/10/2016 Peds 10/20/2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	11/21/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>09/28/2016</u> If PeRC review not necessary, explain: _____ 	Minutes of PeRC 10/14/2016
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</p>	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) 	
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 8/5/2015
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 7/13/2013
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 6/29/2016
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 10/25/2016
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 1/19/2017
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 1/19/2017
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 1/12/2017
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None (14)
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	10/12/2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical review (10/12/2016), page 81, page 199
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input type="checkbox"/> None OBP 10/11/16 DPMH (Maternal Health) 11/10/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 11/10/2016
❖ OSI Clinical Inspection Review Summaries (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 11/21/16; 9/16/16; 8/31/16; 8/19/16; 8/16/16; 7/21/16; 7/11/16; 6/28/16; 6/10/16
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/2/16
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/6/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 10/14/16; 7/28/16
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 12/2/16
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/18/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 10/13/2016
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 7/28/2016 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/6/16; 1/12/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	10/3/2016
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable 11/22/16 Re-evaluation date: 12/5/2016 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/

MAUREEN D DEWEY
01/19/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: January 10, 2017; 4:00 PM – 5:00 PM
Application Number: NDA 208745
Product Name: Trulance (plecanatide) tablets
Indication: chronic idiopathic constipation
Applicant Name: Synergy Pharmaceuticals
Call Information: 1-855-828-1770
Subject: Label

FDA Participants:

Office of Drug Evaluation III

Julie Beitz, MD, Director

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D., Director

Laurie Muldowney, M.D., Medical Team Leader,

Lesley Hanes, M.D., Medical Officer

Joette Meyer, PharmD., Associate Director for Labeling

David Joseph, Ph.D., Pharmacology Team Leader

Yuk-Chow Ng, Ph.D., Nonclinical Reviewer

Maureen Dewey, M.P.H. Senior Regulatory Project Manager

Office of New Drugs Quality Assessment

Zhangfang Ge, Ph.D., CMC Team Leader

Office of Clinical Pharmacology (OCP)

Sue Chih Lee, Ph.D., Team Leader

Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics III

Yeh-Fong Chen, Ph.D., Statistical Team Leader

Division of Pediatric and Maternal Health Staff

Carolyn Yancy, M.D., Reviewer

Christos Mastroyannis, M.D., Reviewer

Tamara Johanson, M.D., Medical Team Leader

Office Biotechnology Products

Haoheng Yan, Ph.D., Reviewer

APPLICANT ATTENDEES

Synergy Pharmaceuticals, Inc.

Patrick Griffin, M.D., Chief Medical Officer

Evelyn Jaeger, Head, Quality Assurance and Regulatory Affairs

1.0 BACKGROUND:

NDA 208745 Trulance (plecanatide) was submitted on January 29, 2016 as a 505(b)(1) application. Plecanatide (SP-304) is a new molecular entity (NME) that is not approved or marketed in the United States. It is an immediate-release solid formulation tablet that is intended for chronic oral administration for the treatment of CIC in adults.

NDA 208745 has a standard review designation with a PDUFA goal date of January 27, 2017.

On January 9, 2017, the Agency provided the applicant with revisions to labeling (prescribing information and Medication Guide). The purpose of this telecon was to discuss the final labeling.

2.0 DISCUSSION:

FDA proposed on January 9, 2017:

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Plecanatide is structurally related to human uroguanylin and (b)(4), **and** functions as a guanylate cyclase-C (GC-C) agonist. Both plecanatide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, plecanatide has been shown to increase fluid secretion into the gastrointestinal (GI) tract, accelerate intestinal transit, and cause changes in stool consistency (b)(4)

In an animal model of visceral pain, plecanatide reduced abdominal muscle contractions, a measure of intestinal pain. The mechanism has not been studied.

Discussion:

During the teleconference the Sponsor and FDA agreed to the following revisions to Section 12.1 as seen in underlined font below:

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Plecanatide is structurally related to human uroguanylin, and similar to uroguanylin, plecanatide functions as a guanylate cyclase-C (GC-C) agonist. Both plecanatide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, plecanatide has been shown to increase fluid secretion into the gastrointestinal (GI) tract, accelerate intestinal transit, and cause changes in stool consistency.

In an animal model of visceral pain, plecanatide reduced abdominal muscle contractions, a measure of intestinal pain. The mechanism has not been studied.

SPECIAL POPULATIONS

8.2 Lactation

Risk Summary

There is no information regarding the presence of plecanatide in human milk, or its effects on milk production or the breastfed infant. No lactation studies in animals have been conducted. Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration [*see Clinical Pharmacology (12.3)*].

It is unknown whether the negligible systemic absorption of plecanatide by adults will result in a clinically relevant exposure to breastfed infants. Exposure to plecanatide in breastfed infants has the potential for deleterious local gastrointestinal adverse effects [*see Use in Specific Populations, (8.4)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRULANCE and any potential adverse effects on the breastfed infant from TRULANCE or from the underlying maternal condition.

Discussion:

FDA proposed the changes to 8.2 as noted in underlined font above; the sponsor verbally agreed.

3.0 ACTION ITEMS:

RPM will provide the clean versions of the discussed sections of the label to the sponsor via email. The Sponsor agreed to submit final labeling by Friday, January 13, 2017.

RPM and sponsor agreed to discuss administrative next steps informally over the phone.

The call concluded at 4:55 PM

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/s/

MAUREEN D DEWEY
01/11/2017

**PeRC Meeting Minutes
September 28, 2016**

PeRC Members Attending:

John Alexander (Acting PeRC Chairperson)

Meshaun Payne

Jacqueline Yancy

Donna Snyder

Hari Sachs

Wiley Chambers

Thomas Smith

Yeruk Mulugeta

Maura O'Leary

Rachel Witten

Gilbert Burkhart

Victor Baum

Adrienne Hornatko-Munoz

Dionna Green

George Greeley

Julia Pinto [REDACTED] NON-RESPONSIVE

Karen Davis Bruno

Raquel Tapia

Gerri Baer (Did not review [REDACTED] NON-RESPONSIVE [REDACTED] Plecanatide)

Agenda

9:00	NON-RESPONSIVE				
9:20	NON-RESPONSIVE				
9:30	NON-RESPONSIVE				
9:45	NON-RESPONSIVE				
10:00	NON-RESPONSIVE				
10:20	NDA 208745	Trulance (plecanatide) Partial Waiver/Deferral/Plan (with Agreed iPSP)	DGIEP	Maureen Dewey/James Carr	Treatment of Chronic Idiopathic Constipation in Adult Patients
10:30	NON-RESPONSIVE				
10:45	NON-RESPONSIVE				
11:00	NON-RESPONSIVE				
11:10	NON-RESPONSIVE				
11:25	NON-RESPONSIVE				

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Trulance (plecanatide) Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Indication: Chronic Idiopathic Constipation
- This product triggers PREA as a new active ingredient, new indication, new dosage form, new dosing regimen, and new route of administration. The application has a PDUFA goal date of January 29, 2017.
- The division stated there were safety concerns (death in mice that correspond to patients 2 years of age) with this product; therefore, the division is requesting a partial waiver in patients from birth to less than 2 years of age.
- *PeRC Recommendations:*
 - The PeRC concurred with the plan for a partial waiver in patients 0 to less than 2 years of age because the product would be ineffective and/or unsafe and to a deferral in patients 2 to 17 years of age
 - The PeRC recommended that the division ask the sponsor to revise their studies to include patients from 6-12 years of age and 12-18 years of age in the same studies. Combining the age groups should allow earlier completion of trials in older children and earlier completion of the pediatric study plan, which currently extends to 2026. The PeRC recommended that the division ask the sponsor to try to make fewer studies that are doing the same thing (e.g., there are three separate dose-ranging trials and three separate confirmatory efficacy trials) and include all pediatric age groups 6 to less than 18 years of age and follow the step down approach when enrolling patients.
 - The PeRC also recommended the timeline for Study 3 could be moved up and this will eliminate the wait for data in the 12-18 year age group to start. Since Study 1 was ready to begin, the PeRC recommended allowing the study to proceed rather than delaying the study by trying to include other age groups. Study 2 and 4 could be combined into a single study that can be initiated at the time proposed for Study 2 and enroll the 6-12 year old age group later. Studies 5 and 6 would move up accordingly as well.

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/s/

MESHAUN L PAYNE
10/14/2016

Executive CAC**Date of Meeting:** July 26, 2016**Committee:** Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
David B. Joseph, PhD, DGIEP, Lead Pharmacologist
Yuk-Chow Ng, PhD, Presenting Reviewer**Author of Draft:** Yuk-Chow Ng, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA# 208,745**Drug Name:** Plecanatide (SP-304)**Sponsor:** Synergy Pharmaceutical Inc.**Background:**

Plecanatide is a 16-amino acid peptide that binds to guanylate cyclase-C and stimulates the production of cyclic guanosine 3',5'-monophosphate. Plecanatide is a gastrointestinal prokinetic drug that acts through stimulation of guanylate cyclase C in the intestinal mucosa, leading to increased secretion of intestinal fluid, and accelerated gastrointestinal transit. Plecanatide is under development for treatment of chronic idiopathic constipation.

Plecanatide was negative in the Ames assay, the *in vitro* L5178Y/TK+/- mouse lymphoma mutation assay, and the *in vivo* mouse bone marrow micronucleus assay.

As part of the nonclinical program, the Sponsor conducted a 2-year oral gavage carcinogenicity study in mice and a 2-year oral gavage carcinogenicity study in rats.

Mouse Carcinogenicity Study:

The Executive CAC recommendations (see meeting minutes dated 1/29/2013) for both male and female mice, were doses of 0, 10, 30, and 90 mg/kg/day by oral gavage. These doses were based on a sufficiently high multiple of local (intestinal) drug concentration relative to a pharmacologically active dose in a mouse model of DSS-induced colitis, as predicted by a mg/kg comparison of the high dose to the pharmacological dose in mice.

In the 104-week oral carcinogenicity study in CrI:[CD-1(ICR)BR] mice, males and females were administered 0 (vehicle), 10, 30, or 90 mg/kg/day plecanatide by oral gavage. The vehicle was water. Due to low survival in the control males and 10 mg/kg/day females, all surviving male and female animals were sacrificed beginning on week 98 (males) and 104 (females), respectively, based on the Executive CAC recommendations conveyed on November 18, 2014.

There were no significant neoplasms in the mouse study.

Rat Carcinogenicity Study:

The doses tested were in accordance with the Executive CAC recommendations (see meeting minutes dated 4/9/2013). For male rats, the Committee recommended doses of 0, 10, 30, and 100 mg/kg/day based on the large estimated rat to human multiple of local drug concentration in the intestinal tract, and the expectation that the local drug concentration in rats will achieve a maximum pharmacological effect. For female rats, the Committee recommended doses of 0, 10, 30, and 100 mg/kg/day based on reduced bodyweight gain in females at 300 mg/kg/day in the dose-ranging study.

In the 104-week oral carcinogenicity study in CD[CrI:CD(SD)] rats, males and females were administered 0 (vehicle), 10, 30, or 100 mg/kg/day plecanatide by oral gavage. The vehicle was water. The study was terminated on week 94 for males and females due to low survival in the control groups, in accordance with Executive CAC recommendations conveyed on 2/2/2015.

There were no significant neoplasms in the rat study.

Executive CAC Recommendations and Conclusions:

Mouse:

1. The Committee concluded that the study was adequate, noting prior Exec CAC review of the protocol.
2. The Committee concluded that there were no treatment-related neoplasms.

Rat:

1. The Committee concluded that the study was adequate, noting prior Exec CAC review of the protocol.
2. The Committee concluded that there were no treatment-related neoplasms.

Karen Davis Bruno, PhD
Chair, Executive CAC

cc:\n
/NDA 208,745/Division File, DGIEP
/David Joseph/Team leader, DGIEP
/Yuk-Chow Ng/Reviewer, DGIEP
/Maureen Dewey/PM, DGIEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
07/28/2016

KAREN L DAVIS BRUNO
07/28/2016



NDA208745

MID-CYCLE COMMUNICATION

Synergy Pharmaceuticals Inc.
Attention: Evelyn Jaeger
Head of Regulatory Operations
420 Lexington Avenue, Suite 2012
New York, NY 10170

Dear Ms. Jaeger

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for plecanatide.

We also refer to the teleconference between representatives of your firm and the FDA on July 14, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: July 14, 2016
Application Number: NDA 208745
Product Name: Trulance (plecanatide) tablets
Indication: chronic idiopathic constipation
Applicant Name: Synergy Pharmaceuticals

Meeting Chair: Joette Meyer
Meeting Recorder: Maureen Dewey

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, MD, Director

Division of Gastroenterology and Inborn Errors Products

Laurie Muldowney, M.D., Medical Team Leader,
Lesley Hanes, M.D., Medical Officer
Joette Meyer, PharmD., Associate Director for Labeling
David Joseph, Ph.D., Pharmacology Team Leader
Yuk-Chow Ng, Ph.D., Nonclinical Reviewer
Maureen Dewey, M.P.H. Senior Regulatory Project Manager

Office of New Drugs Quality Assessment

Zhangfang Ge, Ph.D., CMC Team Leader

Office of Clinical Pharmacology (OCP)

Sue Chih Lee, Ph.D., Team Leader
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics III

Yeh-Fong Chen, Ph.D., Statistical Team Leader
Scott Komo, Ph.D., Statistical Team Leader
Shalah Farr, Ph.D., Reviewer

Division of Pediatric and Maternal Health Staff

Carolyn Yancy, M.D., Reviewer
Christos Mastroyannis, M.D., Reviewer
Diane Snyder, M.D., Medical Team Leader
Denise Pica-Branco, Regulatory Project Manager

Office Biotechnology Products

Michele Dougherty, Ph.D., Team Lead
Joslyn Brunelle, Ph.D., Team Leader
Haoheng Yan, Ph.D., Reviewer

Clinical Outcomes Assessment Staff

Sarrit Kovacs, Ph.D., Reviewer

Office of Surveillance and Epidemiology

Jacqueline Sheppard, PharmD, Risk Management Analyst
Aleksander Winiarski, Project Manager

Eastern Research Group, Inc.

Pegghah Khorrami
Christopher Sese

APPLICANT ATTENDEES

Synergy Pharmaceuticals, Inc.

Patrick Griffin, M.D., Chief Medical Officer
Evelyn Jaeger, Head, Quality Assurance and Regulatory Affairs

(b)(4)

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

To date, no significant issues have been identified.

3.0 INFORMATION REQUESTS

Clinical:

1. The Dosage and Administration section of the Prescribing Information states that the recommended dosage of plecanatide is 3 mg (b)(4). No difference in efficacy was detected between the 3 and 6 mg dosage regimens in the clinical trials; however these trials were not adequately powered to detect a difference between these doses. While the safety appears similar with both dosage regimens, there does appear to be a slightly higher incidence of severe diarrhea and discontinuations due to diarrhea with the 6 mg dosage regimen. (b)(4)

Additional Discussion:

The sponsor does *not* plan to proceed with the 6 mg dosage regimen.

2. We are concerned about the data integrity from two specific clinical sites (below) as these sites have previous Agency enforcement action or warning letters. We recommend that patients who were enrolled in these study sites be removed from the primary efficacy analysis for study SP304203-03, as well as the safety analyses.

Resubmit the primary efficacy table for study SP304203-03 and the primary and secondary pooled safety tables and data analysis sets, excluding the following sites:

(b)(4)

Additional Discussion:

The sponsor agrees to remove the study sites from the primary efficacy and safety analyses and submit the revised tables by August 5, 2016. The sponsor requested clarification on which safety analyses should be resubmitted and FDA agreed to include this information as a post-meeting comment in the final meeting minutes.

Post-meeting Comment:

FDA specifically requests the following tables to be included in the formal submission. For each of these tables, please submit the following analyses separately:

(b)(4)

1. Patient Disposition in the Primary Pool (ITT-S population); refer to ISS Table 12
2. Demographic and other baseline characteristics of the Primary Pool (ITT-S population), refer to ISS Table 14
3. Adverse Events (Preferred Terms) Occurring in $\geq 0.5\%$ of Patients in the Primary Pool in Descending Order of Overall Frequency (ITT-S population), refer to ISS Table 21
4. Severe AEs by Organ Class and Preferred Term (ITT-S) Population, refer to ISS Table 26
5. Study-drug related AEs occurring in $\geq 0.5\%$ of patients in the Primary Pool, refer to ISS Table 24
6. AEs Leading to Discontinuation in the Primary Pool, refer to ISS Table 38
7. AEs reported in at least 1% of the combined 3mg or 6mg treatment group with incidence greater than placebo (b)(4)
8. Adverse Events (Preferred Terms) Occurring in $\geq 0.5\%$ of Patients in the Primary Pool by Time Period (ITT-S population), refer to ISS Table 29
9. Serious AEs (SAEs) by Organ Class and Preferred Term (ITT-S) Population, refer to ISS Table 31

3. We are considering revisions to your Pediatric Plan to be consistent with the partial waiver and deferrals for the other approved product in the same established pharmacologic class of guanylate cyclase-C (GC-C) agonists. Further information on the PREA PMRs will be forthcoming.

No additional discussion.

4. During our analysis of the safety data of the pooled phase 3 trials (SP304203-00 and -03), we found the following discrepancies between the reported adverse event discontinuation rates due to diarrhea and our analysis. Please clarify the discrepancy (see Table 1 below).

Table 1: Diarrhea Adverse Events Leading the Discontinuation in the Pooled Phase 3 Trials

	Plecanatide 3 mg once daily	Plecanatide 6 mg once daily	Placebo
Reported in PI	1.9%	1.8%	0.4%
FDA Reviewer's Analysis	2.4% (n=23)	2.7% (n=25)	0.5% (n=5)

(b)(4)

Additional Discussion:

The sponsor provided their rationale for calculation of diarrhea adverse events leading to discontinuation. FDA acknowledged the explanation and notified the sponsor that upon re-evaluation of the data, there is no discrepancy. No further discussion.

Maternal Health:

1. As required for other CG-C agonists, you will be asked to conduct as a PMR milk-only lactation trial in lactating women receiving plecanatide therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order to appropriately inform the lactation subsection of the PI.

The sponsor agreed to the requested PMR. A preliminary list of PMCs and PMRs will be communicated to the sponsor on September 23, 2016.

Clinical Outcomes Assessment:

For the following analyses, please remove the data from the two sites noted above.

1. Provide cumulative distribution function (CDF) plots using the PGA constipation severity item and PGA constipation change item to aid in determining clinically meaningful change from baseline in the following sign/symptom secondary endpoint scores:
 - CSBM stool frequency
 - SBM stool frequency
 - Stool consistency
 - Straining

Note: for the requested graphs below, specify the number of subjects included in each CDF curve in the graph legend, e.g. -1 point change (n=33).

2. Provide the following eight CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):
 - CDF plot of pooled treatment and placebo group data with PGA constipation severity baseline to Week 12 change score curves (i.e., -1 point change, -2 point change, -3 point change, -4 point change, no change, +1 point change) with sign/symptom change score on x-axis
3. Provide the following eight CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):
 - CDF plot of pooled treatment and placebo group data with PGA constipation severity baseline to overall average of 12 weeks change score curves (i.e., -1 point change, -2 point change, -3 point change, -4 point change, no change, +1 point change) with sign/symptom change score on x-axis
4. Provide the following eight of CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):
 - CDF plot of pooled treatment and placebo group data with PGA constipation change Week 12 curves (i.e., very much improved, much improved, minimally improved, no change, and minimally worse) with sign/symptom change score on x-axis
5. Provide the following eight CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):
 - Separate curves for the treatment versus placebo groups with sign/symptom change score on x-axis.
6. Provide the following Spearman correlations and scatterplots separately for each clinical trial:
 - Each of the four secondary endpoint change scores with the baseline to Week 12 PGA constipation severity change scores
 - Each of the four secondary endpoint change scores with the baseline to overall average of 12 weeks PGA constipation severity change scores
 - Each of the four secondary endpoint change scores with the Week 12 PGA constipation change scores

Additional Discussion:

The sponsor acknowledged the request and will submit the requested data by August 5, 2016.

Immunogenicity:

1. Provide a timeline for the submission of your partial re-validation report and revised test method document.

Additional Discussion:

The sponsor acknowledged the requests and will submit the partial re-validation report on August 2, 2016.

2. In addition, address all of the following items in the re-validation report:
 - i. In the recent response to the FDA on June 17, 2016, you briefly described the statistical plan you will use for justifying the fixed cut point approach in your ADA screening assay. You stated that “the mean, standard deviation and %RSD will be determined for each serum sample, and will be compared across plates, in order to support the fixed cut point approach.” In your re-validation report, provide detail statistical analysis for us to determine whether this approach can adequately justify using a fixed cut point. We recommend you refer to Figure 4 in the following publication as an example of what would represent an adequate statistical approach:

“Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. *J Pharm Biomed Anal.* 2008 Dec 15; 48(5):1267-81.”
 - ii. As per the FDA guidance “Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products”,¹ you should determine the sensitivity of the assay to have confidence when reporting immunogenicity rates. You did not report assay sensitivity in either of the submitted validation reports (TR15-0283 and TR16-0052). The assay limit of detection (LOQ) and limit of quantitation (LOD) were reported in the validation report TR15-0283; however, the LOQ and LOD were determined based on the finding that the assay meets acceptance criteria for precision and accuracy at a concentration of anti-plecanatide antibody of (b)(4). Your definition for LOQ and LOD is different from the definition of assay sensitivity for the anti-drug antibody (ADA) screening assay. As per the FDA guidance,¹ ADA assay sensitivity is defined as the lowest concentration at which the antibody preparation consistently produces either a positive result or readout equal to the cut point determined for that particular assay. Therefore, the LOQ and LOD you reported in the validation report do not represent assay sensitivity. In the re-validation report, define assay sensitivity using the aforementioned definition and the new cut point.

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm192750.pdf>

- iii. In the Document CTM-0144 Revision #001, Elisa Screening Assay for Anti-Plecanatide Antibodies Utilizing Delfia Detection for Client 0177, one of the system suitability criteria was defined as the signal from LQC (Low Quality Control at (b)(4) of Positive Control Antibody) (b)(4). The lower end of the criterion is significantly (b)(4) than the cut point of (b)(4) which indicates the concentration of LQC was inappropriate. To ensure that the sensitivity of the assay is consistent across assay runs, a low positive control (LQC) containing a concentration of ADA slightly above sensitivity of the assay should be used. In the re-validation report, select the concentration of LQC based on the re-evaluated assay sensitivity.
- iv. You stated in a recent response to FDA dated 5/27/2016, “assay intermediate precision was assessed by two analysts on a single day of testing. Given the subsequent observation of day-to-day variation [...] the validation did not adequately or appropriately capture potential assay variation.” As per the FDA guidance of Industry on assay development and validation:¹

“FDA recommends, at the minimum, that inter-assay precision be evaluated on at least 3 different days with two analysts each preparing a minimum of six otherwise independent preparations of the same sample using the same instrument platform and model. Intra-assay precision should be evaluated with a minimum of six independent preparations of the same sample per plate independently prepared by the same analyst...Samples should include negative controls and positive samples whose testing yields values in the low, medium, and high levels of the assay dynamic range. The sponsor should evaluate inter-instrument and inter-operator precision when relevant. Assays should have comparable precision between different operators under the same operating conditions.”

In the re-validation report, revise the concentration for LQC and re-assess the inter-assay and intra-assay precision.

- v. One of the fundamental parameters for ADA assay validation is assay robustness. As per the FDA guidance¹, robustness is an indication of the assay’s reliability during normal usage and is assessed by the capacity of the assay to remain unaffected by small but deliberate variations in method and instrument performance that would be expected under relevant, real-life circumstances in routine laboratory practice. You did not include an assessment of assay robustness in either of the assay validation reports (TR15-0283 and TR16-0052). In the re-validation report, include an assessment of robustness.

Additional Discussion:

The sponsor acknowledged the requests and will submit the re-validation report on August 2, 2016.

Clinical Pharmacology/Biopharmaceutics:

We acknowledge the receipt of your submission dated June 8, 2016, containing a protocol for alternative dosing procedures and an analytical results report. At this time, we cannot commit to reviewing this information during this NDA review cycle.

Additional Discussion:

The sponsor acknowledged that the alternate dosing protocol and analytical results were not submitted at the time of the original NDA. The sponsor inquired whether FDA could provide a timeframe for reviewing the alternate dosing data if it was not reviewed during this cycle. FDA reminded the sponsor that these comments are preliminary and the review of this submission is still ongoing. These comments are subject to change as the reviews are finalized.

Nonclinical:

In the 2-year mouse carcinogenicity study (#12-2324), the presentation of the statistical analysis of tumor incidences as divided into multiple tables (pages 3414-3467) is unclear. Provide a tabular presentation of this data using the same tabular format as shown in the 104-week rat carcinogenicity study (#1896-011, pages 781-815), by July 22, 2016.

Additional Discussion:

The sponsor will submit the requested data by July 22, 2016.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology do not believe a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. Our final determination on the need for a REMS will be made once the review of your application is complete.

5.0 ADVISORY COMMITTEE MEETING

At this time there are no plans for an AC Meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting is scheduled for October 25, 2016, 3:00 PM – 4:00 PM.

In addition, please note the following projected milestone dates:

Labeling, PMR/PMC to Applicant:	September 23, 2016
Pediatric Review Committee:	September 28, 2016

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/s/

MAUREEN D DEWEY
07/20/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 074883
NDA 208745

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Synergy Pharmaceuticals Inc.
420 Lexington Avenue, Suite 2012
New York, NY 10170

ATTENTION: Evelyn Jaeger
Vice President Regulatory Affairs & Clinical Quality Assurance

Dear Ms. Jaeger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and to your New Drug Application (NDA) dated and received on January 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plecanatide Tablets, 3 mg (b)(4)

We also refer to:

- Your correspondence to your IND, dated and received November 18, 2015, requesting review of your proposed proprietary name, Trulance.
- Your correspondence to your NDA, dated and received February 23, 2016, requesting review of your proposed proprietary name, Trulance.

We have completed our review of the proposed proprietary name, Trulance and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5295. For any other information regarding this application, contact James Carr, Regulatory Project Manager in the Office of New Drugs, at 240-402-6624.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
05/12/2016



IND 74883

MEETING MINUTES

Synergy Pharmaceuticals Inc.
Attention: Evelyn Jaeger
Head of Regulatory Operations
420 Lexington Ave., Suite 2012
New York, NY 10170

Dear Ms. Jaeger

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for plecanatide.

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2015. The purpose of the meeting was to discuss the plecanatide nonclinical, clinical, and chemistry, manufacturing, and controls (CMC) programs to support the submission of a New Drug Application (NDA) for the treatment of chronic idiopathic constipation (CIC) in adults.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

LCDR James Carr, MPAS, PA-C
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 5, 2015, 3:00PM-4:00PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: 74883
Product Name: Plecanatide
Indication: CIC
Sponsor/Applicant Name: Synergy Pharmaceuticals, Inc

Meeting Chair: Laurie Muldowney
Meeting Recorder: James Carr

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products
Laurie Muldowney, M.D., Medical Team Leader, Division of Gastroenterology and Inborn Errors Products
Preeti Venkataraman, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products
Danuta Gromek-Woods, Ph.D., CMC Team Leader, Office of New Drug Products
David Joseph, Ph.D., Pharmacology Team Leader, Division of Gastroenterology and Inborn Errors Products
Yuk-Chow Ng, Ph.D., Nonclinical Reviewer, Division of Gastroenterology and Inborn Errors Products
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III
Min Min, Ph.D., Statistical Reviewer, Division of Biometrics III
Susan Kirshner, Ph.D., Susan Kirshner, Ph.D., Team Lead, Office Biotechnology Products
Kevin Bugin, M.B.A., Chief Project Management Staff, Division of Gastroenterology and Inborn Errors Products
James B. Carr, MPAS, PA-C, Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products

SPONSOR ATTENDEES

Patrick Griffin, M.D., Chief Medical Officer, Synergy Pharmaceuticals Inc.
Laura Barrow, Pharm.D, Senior Vice President, Clinical Operations, Synergy Pharmaceuticals Inc.
Paul Eng, Ph.D., Senior Vice President, Drug Development, Synergy Pharmaceuticals Inc.
John Foss, Ph.D., Senior Director, Product Development, Synergy Pharmaceuticals Inc.
Evelyn Jaeger, Head, Quality Assurance and Regulatory Affairs, Synergy Pharmaceuticals Inc.

1.0 BACKGROUND

Plecanatide (SP-304) is a guanylate cyclase-C (GC-C) agonist that is structurally related to the endogenous guanylin peptide family. Plecanatide is being developed by Synergy Pharmaceuticals Inc. (Synergy) for the treatment of CIC and Irritable Bowel Syndrome with Constipation (IBS-C). The drug substance, plecanatide, is a 16 amino acid synthetic peptide with two disulfide bridges that is manufactured for clinical use by (b)(4)

The End-of-Phase 2 meeting was held July 31, 2013, and the Pre-NDA meeting request was received June 3, 2015.

2. DISCUSSION

2.1. Nonclinical

Question 1: Does the Agency agree that the nonclinical studies conducted are sufficient to support marketing authorization for the CIC indication?

FDA Response to Question 1:

Your nonclinical program appears to be sufficient to support an NDA submission for the CIC indication.

Discussion 1: No further discussion.

Question 2: Does the Agency agree that the in vitro and in situ experiments completed are sufficient to characterize plecanatide metabolism and metabolites in the gastrointestinal tract?

FDA Response to Question 2:

With regards to metabolism and metabolites, you have stated in your meeting package that a series of in vitro studies were performed to examine the potential metabolism of plecanatide by CYP450 enzymes that may be present in the GI tract (page 34). In that regard, please clarify if you have evaluated whether plecanatide is a substrate for these CYP450 enzymes that may be present in the GI tract. It is also not clear in the meeting package whether you have evaluated the active metabolite SP-338 in the CYP inhibition/induction studies and transporters substrate/inhibition studies as you have proposed in previous meeting package (IND 74883, serial number 82, 27 June, 2013). Our previous comment in the EOP2 meeting minutes on July 31 regarding these in vitro studies were made with the understanding that you would evaluate both plecanatide and its major active metabolite SP-338 in these CYP and transporters studies. If you have done so, then we agree that the in-vitro and in-situ experiments

completed are sufficient to characterize plecanatide metabolism and metabolites in the gastrointestinal tract.

Discussion 2:

FDA agrees that Sponsor does not need to evaluate whether plecanatide is a substrate for CYP enzymes that are present in the GI tract.

2.2. Clinical



Discussion 3: *No further discussion.*

Question 4: Does the Agency agree that the planned clinical development program for plecanatide is comprehensive and that the planned exposure and long-term safety data are adequate, such that no further safety or efficacy studies are needed to permit filing and review of the NDA for the proposed indication?

FDA Response to Question 4:

We agree that no further efficacy studies are needed for filing; however, it appears that the number of patients exposed to plecanatide for greater than 12 months at the time of filing will not be adequate. Please see response to Question 5a.

Discussion 4: *Please see discussion following response to Question 5.*

Question 5(a): Does the Agency agree with Synergy's plans regarding the timing for achieving the exposure numbers as outlined in Table 13 for the 3 mg and 6 mg dosages?

FDA Response to Question 5(a):

No, we do not agree.

(b) (4)

(b) (4)

(b) (4)

We

remind you that per the ICH E1 guidance, at least 100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety database. We refer you to the ICH E1 Guidance for further details:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf.

In addition, FDA's Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291158.pdf>) states that "For chronically used treatments indicated for chronic diseases, it is often important to know the time course of events and whether the event rate or risk changes over the duration of exposure. Usually, it is important to have a sufficient denominator of patients followed long enough to observe and estimate the time-dependent risk (e.g., every three or six months of continued exposure). In such cases, it is important to fully collect important serious event data as exposure progresses."

Please adjust your timeline such that an adequate number of exposures will be achieved for a chronically used treatment indicated for a chronic disease.

Question 5(b): Does the Agency agree with Synergy's plans regarding the content and format of data to include in the 120-day safety update report?

FDA Response to Question 5(b):

Please see our response to 5(a) regarding the content of data to be included in the 120-day safety update report. The proposed format of data appears acceptable.

Discussion 5:

FDA cannot agree at this time that the amended proposal with updated numbers will be adequate. The product is intended for use in a chronic condition in which there are approved therapies and the drug is a relatively new class. The major concern is immunogenicity. The FDA recommended that the sponsor submit their updated proposal with justification based on exposure limited to the gut and justification for combining the two dose levels. FDA will meet internally to review the proposal and will respond in the final meeting minutes. Sponsor will include a rationale as to why a uroganylin analog might not be immunogenic in the gut.

Post-meeting comment: Sponsor submitted additional information including numbers of patients who had 12 months of consecutive exposure to plecanatide at each the 3mg and 6mg doses (i.e., excluding those patients who completed phase 2 clinical studies and had a break in therapy before the long term safety study that resulted in <6 months of exposure at any time). The exposure numbers of patients were reported to be 159 at the 3 mg dose and 325 at the 6 mg dose. These numbers appear to be acceptable to the Division.

Question 6: Does the Agency agree that this information provides sufficient evidence to state that plecanatide can be taken with or without food in the Pharmacokinetics and Dosage and Administration sections of the Label?

FDA Response to Question 6:

Based on the information provided, including that patients took the proposed formulation in Phase 3 trials without regard to food and assuming the Phase 3 formulation will be the same as the to-be-marketed formulation, we agree that there may be sufficient evidence to state in the label that plecanatide can be taken with or without food.

Discussion 6: No further discussion.

Question 7: Does the Agency agree with Synergy's approach to evaluate the immunogenicity potential of plecanatide in human plasma obtained in clinical studies?

FDA Response to Question 7:

Tables 22, 23, and 24 indicate that you will have immunogenicity data from two controlled safety and efficacy studies, SP304203-00 and -03 and one controlled long term safety study SP302303-01. For studies SP304203-00 and -03, samples were obtained at baseline, week 4 and week 14. Study SP304203-01 is ongoing with sampling time points at baseline, and weeks 4, 12, 28, 52, and 72. FDA acknowledges your note that not all patients in study SP304203-01 will have a 12 week time point. The proposed collection times are adequate for submission of an NDA. However, you state that for the 6 mg dose 52 week time point, data from only 38 people will be provided in the NDA submission. Please see FDA's response to comment 5(a) regarding the safety data requirement.

You provided an SOP and validation protocol for an assay to screen for anti-plecanatide antibodies. FDA's guidances on anti-drug antibody (ADA) assessment and method development describe a tiered approach to evaluation of ADA that includes screening, confirmatory, and neutralizing assays. You did not provide your plans for the confirmatory and neutralizing assays so we cannot comment on those.

Your assay validation protocol for the screening assay did not describe how you intend to validate the assay cut point. The assay cut point is critical to ensuring assay suitability. For more information on setting the assay cut point, assay validation, and immunogenicity risk assessments see:

- **CDER. Draft Guidance for industry on assay development for immunogenicity testing of therapeutic proteins. Docket No. FDA-2009-D-0539.**
- **CDER. Draft Guidance for Industry: Immunogenicity assessment for therapeutic protein products. 2013. Docket No. FDA-2013-0092.**

In your briefing package you state “Synergy has included plans to evaluate the immunogenicity potential of plecanatide using human plasma from clinical studies and the associated timelines for submission of this information in this Briefing Package.” FDA is unclear what you mean by “the associated timelines for this information” and therefore, cannot comment on submission timelines at this time.

Discussion 7:

FDA recommended that the sponsor submit the screening assay validation information when it becomes available in approximately 2 weeks. FDA expressed concerns that there is no confirmatory assay to eliminate false positive samples from the screening assay, which may confound the ability to establish relationships between ADA and safety and efficacy.

Question 8: Does the Agency agree with the proposed pooling strategies, selection of clinical data to be included in the ISS and ISE, and the need for no additional integrated analyses to support the NDA?

FDA Response to Question 8:

Yes, we agree with the proposed pooling strategy for the ISS, as well as including Study SP304-20212 in the ISS to support the pooled analyses in CIC patients. The proposed pooling strategies for the ISE appear appropriate, however, the presentation in your tables should also include the results of the individual studies juxtaposed to the combined analyses. Keep in mind that the pooled efficacy analyses will not be considered for labeling if these were not prespecified and agreed upon analyses.

Discussion 8: No further discussion.

Question 9: Does the Agency have any comments regarding the proposed programming code submission strategy for the phase 2 and 3 studies and the ISS and ISE?

FDA Response to Question 9:

Your proposed approach appears acceptable. In addition to the programs for the primary and key secondary efficacy endpoints analyses, please make sure to submit your programs for producing the derived variables from the raw data sets with clear explanation. Please also include all FDA communications including all protocols, SAP and amendments, as well as any meeting minutes/written responses, in your NDA submission.

Discussion 9:

FDA reiterated their initial responses.

Question 10: Does the Agency agree with the data submission plan/format for the individual clinical studies and ISS and ISE databases to be included in the NDA?

FDA Response to Question 10:

Your proposed approach appears acceptable. However, we would like to remind you that all raw datasets from Phase 2 and 3 studies from which the analysis datasets are derived should be submitted, even those not in SDTM format. In addition, please include the define files associated with all analysis datasets.

Discussion 10: *No further discussion.*

Question 11: *Does the Agency agree that demonstrating similar safety and efficacy for the 3 mg and 6 mg dose strengths in both two adequate and well controlled clinical trials and integrated safety and effectiveness analyses supports this marketing approval strategy?*

FDA Response to Question 11:

If similar safety and efficacy is demonstrated for both the 3mg and 6mg dose strengths in your phase 3 trials, typically the lower dose would be recommended for marketing. If you intend to propose both doses, you will need to justify why both doses should be marketed. The doses that are ultimately reported in the label will be determined upon review of the application.

Discussion 11: *No further discussion.*

Question 12: Does the Agency agree, if the individual study results and integrated analysis of safety do not reveal a serious risk associated with the use of plecanatide, that no risk evaluation and mitigation strategy (REMS) or any other REMS elements (e.g., medication guide, patient package insert, communication plan, elements to assure safe use, implementation plan) are required for the plecanatide NDA for CIC?

FDA Response to Question 12:

Whether or not individual study results and integrated safety analysis reveal a serious risk associated with the use of plecanatide will be a review issue. Therefore, we cannot agree that no REMS or REMS elements will be required.

Discussion 12:

Sponsor clarified their question regarding whether REMS or REMS elements will be required with submission of the NDA. FDA stated there is no requirement to include REMS or REMS elements in the submission.

Question 13: Does the Agency agree that the plecanatide NDA can be submitted electronically in CTD format in accordance with applicable FDA and ICH Guidance documents and FDA submission requirements?

FDA Response to Question 13:

ESUB: Our standard is eCTD (i.e. with xml backbone) and we have no published guidance for sending in other electronic formats at this point. However, FDA will not reject the submission if sponsor uses the eCTD folder structure (i.e. m1-m5), without the XML backbone, as described in the eCTD guidance:-

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf>.

Please also refer to the eCTD website for eCTD Specifications and Guidance:-

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

Also, please note that by May 5, 2017, all NDAs will be required to submit in eCTD format Please refer to Page 4 of the eCTD Guidance (which outlines the timetable) located at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf>

Discussion 13: *No further discussion.*

Additional Question 14: Synergy would like to discuss the extent of exposure calculation for patients that entered the open-label long-term safety study several months following completion of phase 2 clinical studies. Given that the interval between completion of the lead-in study and the start of the long-term safety study was often on the order of several months, can the individual exposure time be summated as a single time period?

Discussion additional question 14:

Sponsor's approach to presenting the cumulative exposure data for patients who had a break in treatment is acceptable for the primary safety analysis. They will provide sensitivity analyses looking at these two patient groups separately.

2.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our DATE communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete

application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission. In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

5.0 ISSUES REQUIRING FURTHER DISCUSSION

6.0 ACTION ITEMS

7.0 ATTACHMENTS AND HANDOUTS

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/s/

JAMES B CARR
09/21/2015



IND 074883

MEETING PRELIMINARY COMMENTS

Synergy Pharmaceuticals, Inc.
Attention: Gary Jacobs, PhD
President and CEO
420 Lexington Ave., Suite 2012
New York, NY 10170

Dear Dr. Jacobs:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SP-304 (plecanatide) Tablets.

We also refer to your May 7, 2013, correspondence requesting a meeting to discuss the phase 3 development of plecanatide for chronic idiopathic constipation.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type V
Meeting Category: End of Phase 2

Meeting Date and Time: July 31, 2013, 10:00 to 11:00 a.m.
Meeting Location: White Oak Building 22, Room 1309

Application Number: IN D074883
Product Name: SP-304 (plecanatide)
Indication: Treatment of chronic idiopathic constipation
Sponsor/Applicant Name: Synergy Pharmaceuticals, Inc.

FDA ATTENDEES (tentative)

Donna Griebel, MD, Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, MD, FAAP, CPI, Deputy Director, DGIEP
Rob Fiorentino, MD, Medical Team Leader, DGIEP
Sue-Chih Lee, PhD, Team Leader, Division of Clinical Pharmacology III
Dilara Jappara, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology III
Zana Marks, MD, Medical Officer, DGIEP
Stephen Wilson, PhD, Director, Division of Biometrics III
Behrang Vali, Statistical Reviewer, Division of Biometrics III
Angelica Dorantes, Biopharmaceutics Team Leader, Office of New Drug Quality Assessment (ONDQA)
Eddie Ng, PhD, Pharmacologist, DGIEP
Matthew Scherer, MBA, Senior Regulatory Project Manager, DGIEP

Introduction

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 31, 2013, 10:00 to 11:00 a.m., White Oak Building 22, Room 1309, between Synergy Pharmaceuticals (Synergy) and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting

communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1. BACKGROUND

Synergy is developing plecanatide for the treatment of chronic idiopathic constipation (CIC) and IBS-C. Plecanatide is a hexadecapeptide guanylate cyclase C agonist that mimics uroguanylin. This is an end of phase 2 meeting to discuss the continuing development of plecanatide for the CIC indication.

2. DISCUSSION

Question 1. Does the Agency agree with this plan for evaluating the metabolism of plecanatide and the potential for drug-drug interaction via intestinal transporters and cytochrome P450 enzymes?

FDA Response:

Your proposal appears to be reasonable.

Question 2. Assuming consistent results are obtained between the completed study (SP304202-10; capsules) and the planned study (SP304203-00; tablets) does the Agency agree that these two studies can be used to establish the effectiveness of and support the safety of plecanatide?

FDA Response:

We cannot agree that these two studies will be sufficient. If the results from SP304203-00 are marginal or lack robustness for the 6mg cohort, you would risk not having sufficient evidence from this single study to support its approval.

In addition, since bioequivalence cannot be established based on PK between the tablet and capsule, you will need to provide adequate justification that the clinical data from the phase 2b study with the capsule can still provide supportive evidence for the results of the single phase 3 trial with the tablet.

With regards to safety, because plecanatide is anticipated to be taken chronically (or indefinitely) these two studies alone will not provide sufficient long term safety data for plecanatide. We recommend that your long-term safety trial evaluates a sufficient number of patients who receive the proposed dose(s), for at least one year, as well as incorporate an appropriate comparator arm to allow interpretability of the safety profile and adverse events. Please refer to ICHE1A Guidance for Industry: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-

Threatening Conditions,
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129517.pdf>

Question 3A. Does the FDA concur that the following Study [SP304202-10](#) design elements, instruments, methods and analyses meet the criteria for an adequate and well-controlled trial for the purpose of registration of plecanatide in the indication treatment of chronic idiopathic constipation?

FDA Response:

Study SP304202-10 could serve as an adequate and well-controlled trial for CIC; however, whether or not the interpretability of the data and validity of the study results support the proposed claim will be a review issue.

Question 3B. Does the FDA concur that the CSBM Overall Responder rate observed in Study [SP304202-10](#) (CSR Section 11.4.1.1.1 CSBM Responder Rates) represents a clinically meaningful effect on CSBM frequency?

FDA Response:

The clinical meaningfulness of the study results will be a review issue because it depends on the interpretability of the data and validity of the study results. That being said, in general, the reported treatment difference for the 3mg dose appears to be similar to other drugs approved for CIC.

Question 3C. Does the FDA concur that Study [SP304202-10](#) meets the necessary criteria for an adequate and well-controlled study and can therefore qualify as one of two pivotal registration trials in support of the registration of plecanatide 3.0 mg in the indication treatment of chronic idiopathic constipation?

FDA Response:

See our response to Question 3A.

Question 3D. Does the FDA agree that the data from Study [SP304202-10](#) suggests that in addition to testing 3.0 mg QD plecanatide, a higher dose of plecanatide may be included for the phase 3 program ([Section 10.3.3.1](#))?

FDA Response:

We agree there do not appear to be safety issues that would preclude studying 6.0 mg in phase 3.

Question 4A. Does the Agency agree with the proposed primary efficacy endpoint?

FDA Response:

The proposed primary endpoint could support an indication for CIC.

Question 4B. Does the Agency agree with the proposed secondary efficacy endpoints?

FDA Response:

With the exception of stool consistency based on the BSFS, we consider the proposed secondary endpoints to be exploratory in nature and unlikely to support label claims. In addition, the Daily Symptom Diary does not appear to be a validated instrument for purposes of supporting symptomatic claims.

Question 4C. Does the Agency agree with the changes to this proposed study relative to the inclusion/exclusion criteria, sample size, and design of Study [SP304202-10](#)?

FDA Response:

The study appears to capture a suitable patient population for evaluating CIC. The sample size appears appropriate. See previous comments regarding general design issues.

Question 5A. Does the Agency agree with the approach to ECG monitoring in the proposed studies?

FDA Response:

Your approach to ECG monitoring appears reasonable; however, it is not clear if there was a specific concern that you intend to address by the proposed ECG monitoring plan.

Question 5B. Does the Agency have any comments on the other important components of the proposed studies, [SP304203-00](#) and [SP304203-01](#), such as whether the frequency of safety and laboratory assessments is acceptable?

FDA Response:

No additional comments.

Question 5C. Does the Agency agree that a thorough QTc (TQT) study is not needed for the NDA assuming limited systemic exposure?

FDA Response:

Please submit your rationale for not conducting a TQT study to evaluate the effects of your product on QT prolongation. This should be submitted as a separate document to the IND. The QT Interdisciplinary Review Team (QT-IRT) will review it and make the final decision regarding the need for TQT study.

Question 6. Assuming that Synergy treats at least 100 CIC patients 65 years and older with the highest plecanatide dose intended for clinical use and that efficacy and safety data are available for analysis of this subpopulation, does the Agency agree that Synergy will be able to include labeling claims for this special population?

FDA Response:

You will need to clarify what labeling claims you seek to include for patients >65. Requirements for labeling for patients > 65 are described in 21 CFR 201.80; whether sufficient number of patients >65 have been adequately evaluated will be determined during the review.

Question 7. Does the FDA agree that the number of planned patients to be included in the safety database is adequate to support submission of the marketing application for CIC ([Section 10.3.4](#))?

FDA Response:

We agree, however a sufficient number of subjects within the safety database should be followed on treatment for at least one year. Also, see our response to Question 2.

Question 8. Does the Agency agree that Synergy may submit a Pediatric Study Plan within 60 days after the date of the end-of-Phase 2 meeting?

FDA Response:

Your PSP should include planned neonatal/juvenile animal studies to support initiating dosing in pediatrics. These studies will need to be completed and reviewed prior to initiating pediatric studies.

Please see comments below in the section titled, PREA REQUIREMENTS.

Question 9. Assuming agreement is reached on the PRO instrument with SEALD, does the Division concur that “treatment of chronic idiopathic constipation [REDACTED] (b)(4) [REDACTED] is an approvable indication?”

FDA Response:

It is premature to comment on the labeling claims to be supported by your proposed PRO instrument.

3. ADDITIONAL MEETING COMMENTS

FDA ADDITIONAL COMMENTS

- **We recommend that you collect intensive PK samples in a subset of patients in your proposed phase 3 study (SP304203-00) with the tablet formulation.**
- **For the SP304203-00 study, usage of the proposed mITT analysis set/population as the primary analysis set/population for all efficacy analyses is not acceptable. An all-randomized set of patients (i.e., all patients who were randomized into the study) should be utilized as the primary analysis set/population for all efficacy analyses. It is acceptable to utilize the currently proposed mITT analysis set/population for sensitivity analysis purposes.**

DATA STANDARDS

Please provide the following for all adequate and well-controlled clinical studies (per 21 CFR 314.126) that you plan to include in your eventual NDA submission:

1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.
2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>). We recommend that the data definition file comply with the latest CDISC/Define.XML standard.
3. A well commented and organized software program written for each analysis dataset and efficacy table created.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP). The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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/s/

MATTHEW C SCHERER
07/30/2013



IND 74883

MEETING MINUTES

Synergy Pharmaceuticals, Inc.
Attention: Gary S. Jacob, Ph.D.
Chief Executive Officer
420 Lexington Avenue, Suite 1609
New York, NY 10170

Dear Dr. Jacob:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Plecanatide (SP-304).

We also refer to the meeting between representatives of your firm and the FDA on June 5, 2013. The purpose of the meeting was to discuss the CMC development plans to support the plecanatide phase 3 program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Cathy Tran-Zwanetz
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: End of Phase 2- CMC

Meeting Date and Time: June 5, 2013 from 2:00 PM- 3:00 PM
Meeting Location: FDA White Oak, Building 22, room 1315

Application Number: IND 74883
Product Name: Plecanatide (SP-304)
Indication: Chronic Constipation
Sponsor Name: Synergy Pharmaceuticals, Inc.

Meeting Chair: Marie Kowblansky, Ph.D.
Meeting Recorder: Cathy Tran-Zwanetz

FDA ATTENDEES

Marie Kowblansky, Ph.D., CMC Lead
Zhengfang Ge, Ph.D., ONDQA Reviewer
Tapash Ghosh, Ph.D., ONDQA Reviewer- Biopharmacology
Catherine Tran-Zwanetz, Regulatory Project Manager

SPONSOR ATTENDEES

Alan Joslyn, Ph.D., Member Synergy Board of Directors
Kunwar Shailubhai, Ph.D., Chief Scientific Officer
Steve Comiskey, Ph.D., Vice President Product Development
Patrick Griffin, M.D., Chief Medical Officer
David Lin, Ph.D., M.B.A., Regulatory Affairs, Consultant
David Kashiwase, B.S., M.B.A., Regulatory Affairs, Consultant

1.0 BACKGROUND

The purpose of this CMC EOP2 meeting is to obtain agreement from the Agency on key aspects of the proposed CMC development program that will support the phase 3 clinical program and NDA of plecanatide at the intended therapeutic dose of 3.0 mg QD in patients with CIC. Preliminary meeting comments were sent to the sponsor on June 4, 2013. The sponsor sent an email response to the comments on June 4, 2013.

2. DISCUSSION

Question 1:

Does the Agency agree that these studies adequately characterize plecanatide (Section 10.1.3.1)?

FDA Response

Your proposed approach to structure elucidation is reasonable, but we suggest that you also include C-13 NMR as part of your structure elucidation package.

Synergy Preliminary Response

Synergy Pharmaceuticals understands the FDA Responses provided. No further discussion is necessary.

DISCUSSION:

No discussion needed.

Question 2:

Does the Agency agree that the drug substance specifications are adequate to support both the phase 3 clinical program and the NDA (Section 10.1.4.1)?

FDA Response

FDA Response: Your proposed drug substance specification is reasonable, but we recommend that you also include testing for: pH, chirality, particle size distribution, and quantitative determination of all possible impurities [REDACTED] (b)(4) [REDACTED]. If you can provide appropriate justification, it may be acceptable to exclude these tests from the specification. Also, please see additional comments regarding impurities under question 3.

Elemental impurities testing will need to be conducted for the individual metals listed in USP <232>. Since USP has deferred implementation of this chapter to allow time for alignment with ongoing ICH negotiations in this area, we recommend that elemental impurity limits be defined based on ICH recommendations, which are currently in DRAFT form. You should also be aware that your proposed specification will be further evaluated in the context of your full NDA submission.

Synergy Preliminary Response

Synergy agrees with the additional tests proposed by FDA. These tests will be conducted retrospectively on drug substance batches previously produced and in parallel with phase 3. These data will be included in the NDA to support the proposed specifications. Synergy proposes to conduct optical rotation to address the Agency's request to include chirality testing. Does the FDA agree with this proposal?

DISCUSSION:

The FDA agrees that this proposal is sufficient. The tests listed above are required for the NDA submission. All these tests will not be available prior to the phase 3 trials, however they will be done retrospectively on clinical batches and will be included in commercial batches.

Question 3:

Does the Agency agree with the approach for establishing the drug substance peptide impurity thresholds (Section 10.1.3.2 and Section 10.1.4.1)?

FDA Response

The reporting, identification, and qualification impurity thresholds, (b) (4) (b) (4) as proposed in Table 11 of your briefing package, are acceptable. However, your proposed limit of (b) (4) in the drug substance specification for unspecified impurities is not in agreement with the above proposal. According to your proposed thresholds, all impurities present at levels above (b) (4) need to be identified, and thereby specified. It will not be necessary to complete your identification studies prior to initiating phase 3 studies; these studies will need to be completed prior to NDA submission. Also, based on your proposed qualification threshold, you will need to qualify the (b) (4) impurity for which you have set a limit of (b) (4).

Synergy Preliminary Response

Synergy believes that (b) (4) has been qualified to a limit of (b) (4). The qualification data will be discussed with the Pharmacology reviewer at a future date.

DISCUSSION

Both parties agreed and no further discussion was needed.

Question 4:

Does the Agency agree that the proposed stability protocol and proposed data package from each site are adequate to support both the phase 3 clinical program and the NDA (Section 10.1.5)?

FDA Response

As presented in the briefing package, your proposed stability program is reasonable to support the phase 3 clinical program and the NDA.

Synergy Preliminary Response

Synergy Pharmaceuticals understands the FDA Responses provided. No further discussion is necessary.

DISCUSSION:

No discussion needed.

Question 5:

Does the Agency agree with the proposed comparability protocol to support inclusion of alternative drug substance manufacturers (Section 10.3.1.1)?

FDA Response

The information you plan to submit is insufficient. In addition to the above information and the comparability protocol in section 10.3.1.1 you will need to provide at least three months of long term and accelerated stability data (at least three time points) for at least one batch of drug product manufactured with drug substance from the new site.

Synergy Preliminary Response

Synergy Pharmaceuticals understands the FDA Responses provided. No further discussion is necessary.

DISCUSSION:

No discussion needed.

Question 6:

Does the Agency agree with the proposed comparability protocol (b) (4)
(b) (4) ?

FDA Response

Your proposed comparability protocol is acceptable.

Synergy Preliminary Response

Synergy Pharmaceuticals understands the FDA Responses provided. No further discussion is necessary.

DISCUSSION:

No discussion needed.

Question 7:

Does the Agency agree that the proposed dissolution method is acceptable for release and stability testing of the drug product (Section 10.2.2.2 and Table 24)?

FDA Response

The proposed method seems appropriate. However, before we can provide our final response regarding its acceptability, we need to review the complete information/data supporting the proposed dissolution method. Please submit the final dissolution method development report with the following information:

- Solubility data for the drug substance as a function of pH range;
- Detailed description of the dissolution method being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least ^{(b)(4)} % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;
- Provide data supporting the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, ratio of amorphous/crystalline content, tablet hardness, water content, etc.); and
- Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

Synergy Preliminary Response

As requested by FDA, Synergy is preparing a dissolution development report and proposes to submit this report for FDA review in about 60 days. Does the FDA agree with this proposal?

DISCUSSION

The FDA will review the submission and provide follow up. Because this is a topically-acting drug without significant systemic exposure, when developing your dissolution method please be mindful of the discriminatory ability of the method and the clinical relevance of the specification. Please include the solubility of the drug substance a ^{(b)(4)}

Question 8:

Does the Agency agree that the drug product specifications are adequate to support both the phase 3 clinical program and the NDA (Section 10.2.5.1)?

FDA Response

The testing that you propose for the drug product specification is reasonable, but the acceptability of the proposed acceptance criteria will be determined at the time of NDA

review. Based on your proposed impurity thresholds, you will need to conduct qualification studies for some of the impurities (eg., (b)(4)).

Synergy Preliminary Response – June 4, 2013

Synergy believes that (b)(4) has been qualified to a limit of (b)(4). The qualification data will be discussed with the Pharmacology reviewer at a future date.

DISCUSSION

Both parties agree to the proposal.

Question 9:

Does the Agency agree that the proposed stability protocol and proposed data package from each site are adequate to support both the phase 3 clinical program and the NDA (Section 10.2.6)?

FDA Response

If the proposed stability protocol for the drug product is as described in Table 34 (not Table 17, as indicated on page 59 of the briefing package), it is considered acceptable.

Synergy Preliminary Response – June 4, 2013

Synergy Pharmaceuticals understands with FDA Responses provided. The Synergy acknowledges the table number correction noted by FDA. No further discussion is necessary.

DISCUSSION:

No discussion needed.

Question 10:

Does the Agency agree with the proposed comparability protocol to support inclusion of alternative drug product tablet manufacturers (Section 10.3.2.1)?

FDA Response

To support the approval of an alternate manufacturing site for the drug product, you would need to provide dissolution profile comparison (i.e., 10, 15, 20, 30, 45, and 60 minutes) and f2 data for the drug product (all strengths) manufactured at the approved manufacturing facility vs. the drug product (all strengths) manufactured at the newly proposed alternate facility.

Synergy Preliminary Response – June 4, 2013

Synergy Pharmaceuticals understands the FDA Responses provided. No further discussion is necessary.

DISCUSSION:

No discussion needed.

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/s/

MARIE KOWBLANSKY
06/18/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208745

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Synergy Pharmaceuticals Inc.
Attention: Evelyn Jaeger
Head of Regulatory Operations
420 Lexington Avenue, Suite 2012
New York, NY 10170

Dear Ms. Jaeger

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for plecanatide.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 25, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Tuesday, October 25, 2016 3:00 PM – 4:00 PM
Meeting Location: Building 22, Conference Room 1311
Application Number: NDA 208745
Product Name: plecanatide tablets
Indication: chronic idiopathic constipation
Applicant Name: Synergy Pharmaceuticals
Meeting Chair: Joette Meyer
Meeting Recorder: Maureen Dewey

FDA ATTENDEES (tentative)

Office of Drug Evaluation III

Julie Beitz, MD, Director

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D., Director

Laurie Muldowney, M.D., Medical Team Leader

Lesley Hanes, M.D., Medical Officer

Joette Meyer, PharmD., Associate Director for Labeling

David Joseph, Ph.D., Pharmacology Team Leader

Yuk-Chow Ng, Ph.D., Nonclinical Reviewer

Maureen Dewey, M.P.H. Senior Regulatory Project Manager

Office of New Drugs Quality Assessment (OPQ)

Hitesh Shroff, Ph.D., ADL

Zhangfang Ge, Ph.D., CMC Team Leader

Office of Clinical Pharmacology (OCP)

Sue Chih Lee, Ph.D., Team Leader

Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics III

Yeh-Fong Chen, Ph.D., Statistical Team Leader

Scott Komo, Ph.D., Statistical Team Leader

Shalah Farr, Ph.D., Reviewer

Division of Pediatric and Maternal Health Staff

Mona Khurana, M.D., Acting, Pediatric Medical Team Leader

Carolyn Yancey, M.D., Reviewer

Tamara Johnson, M.D., Maternal Health Medical Team Leader

Christos Mastroyannis, M.D., Reviewer
Denise Pica-Branco, Regulatory Project Manager

Office Biotechnology Products

Michele Dougherty, Ph.D., Team Lead
Joslyn Brunelle, Ph.D., Team Leader
Fred Mills, Ph.D., Team Leader
Haoheng Yan, Ph.D., Reviewer

Clinical Outcome Assessments (COA) Staff

Sarrit Kovacs, Ph.D., Reviewer

Office of Surveillance and Epidemiology

Jacqueline Sheppard, PharmD, Risk Management Analyst
Aleksander Winiarski, Project Manager

Eastern Research Group, Inc.

Pegghah Khorrami
Christopher Sese

APPLICANT ATTENDEES

Synergy Pharmaceuticals, Inc.

Patrick Griffin, M.D., Chief Medical Officer
Evelyn Jaeger, Head, Quality Assurance and Regulatory Affairs



INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

None.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

Late Cycle Meeting AGENDA

- 1. Introductory Comments** – 2 minutes (Maureen Dewey)
- 2. Information Requests** – 10 minutes

Immunogenicity:

- Clarify which part of the Technical Report: CAPA-16-0003 contains the validation on assay robustness.

Clinical Pharmacology:

- In the proposed label, you stated that subjects who received either a low-fat, low calorie (LF-LC) meal or a high fat, high calorie (HF-HC) meal reported looser stools than fasted subjects up to 24 hours after dosing. Conduct a statistical analysis for BSFS score to demonstrate that the difference in BSFS score under fed and fasted conditions were statistically significant to support your proposed label.

3. Postmarketing Requirements (PMR)/Postmarketing Commitments – 15 minutes

Lactation study:

Perform a milk-only lactation trial in lactating women receiving plecanatide therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Lactation subsection of the labeling. Because the juvenile animal toxicity study demonstrated increased sensitivity to plecanatide in the youngest mice, it is important to determine how much drug is present in human milk and whether it accumulates in human milk and could potentially impact a breastfed infant.

PREA PMRs:

PeRC meeting recommendations (held September 29th, 2016) included the following changes to the agreed upon initial pediatric study plan (iPSP):

- Change the Waiver for the study of pediatric patients to <2 years of age (b) (4). This change is recommended since the product would be unsafe in patients <2 years of age secondary to the risk of dehydration and dehydration-related death as seen in juvenile mice (1 to 2 week-old) in non-clinical studies.
- Change the Partial Deferral of studies for patients to 2 to <18 years of age.
- Start the phase 2 dose-ranging studies in the older cohort (study #1) and then 6 to <12 years of age (study #3).
- Combine the confirmatory studies of the 6 to <12 years of age and 12 to <18 year of age groups (Studies 2 and 4) for a shortened study timeline.
- Move up the timeline for the 2 to <6 years of age dose-ranging and confirmatory studies (studies #5 and #6), based on the earlier completion of studies in patients 6 to < 12 years of age. Deferral of this age group is also based on review of data from a FDAAA PMR guanylate cyclase-C (GC-C) receptor biopsy study in pediatric patients and resolution of the related safety concerns.

FDAAA PMR:

a. Immunogenicity Assay Validation - Additional Comments

Your anti-plecanatide antibody screening (ADA) assay, at current status, is not suitable for clinical use. You should optimize the assay and submit a complete ADA assay validation report. The complete validation report should include, at the minimum, the following parameters: (1) cut point, (2) sensitivity, (3) specificity and selectivity, (4) precision, (5) reproducibility when relevant, and (6) robustness. See the FDA draft guidanceⁱ for detailed advice on each parameter.

In addition to the immunogenicity comments you received during the mid-cycle communication (7/20/2016), the FDA has the following comments on the documents received after the mid-cycle, including the partial validation report TR16-0210, testing method CTM-0144-Rev002 and technical report CAPA-16-0003(submitted on 8/2/2016):



The FDA strongly recommends you conduct investigation on the source of the difference seen in the mean and variance. For example, if these differences were primarily due to analysts and/or reagent preparations, you should consider implementing additional analyst training and quality control procedures. Testing methods should be finalized before entering the assay validation phase.



¹ Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products, Guidance for industry DRAFT GUIDANCE April 2016

(b) (4)



b. Biopsy of Pediatric GC-C Receptor Study

- Characterize guanylate cyclase-C (GC-C) mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients undergoing diagnostic GI endoscopies as part of their routine medical care. Biopsy samples should be obtained from children having upper or lower GI tract endoscopies or colonoscopies; stratified equally by age group (birth to <24 months, \geq 24 months to < 6 years, 6 years to < 12 years, 12 years to <18 years).

4. Major labeling issues – 15 minutes

We have preliminary comments on the version of the Prescribing Information that was submitted October 7, 2016.

Section 6 ADVERSE REACTIONS

(b)(4)



5. Review Plans – 1 minute (Maureen Dewey)

- Labeling/PMR remaining

6. Wrap-up and Action Items – 2 minutes (Maureen Dewey)

ⁱ Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products, Guidance for industry DRAFT GUIDANCE April 2016

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/s/

JOYCE A KORVICK
10/13/2016
signing for Dr. Donna Griebel