CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208232Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 108163

MEETING MINUTES

Camargo Pharmaceutical Services, LLC
Agent for Chiasma, Inc.
Attention: Ruth E. Stevens, Ph.D., MBA
Executive Vice President and Chief Scientific Officer
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Stevens:

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

We also refer to the meeting between representatives of your firm and the FDA on October 8, 2019. The purpose of the meeting was to discuss to discuss and obtain agreement on the planned content and presentation of the phase 3 clinical data to support an NDA resubmission.

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

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Tuesday, October 8, 2019; 1:00 – 2:00 pm
Meeting Location:	White Oak Campus; Building 22, Conference Room 1417
Application Number:	IND 108163
Product Name:	octreotide acetate capsules (Mycapssa)
Indication:	Treatment of acromegaly
Sponsor Name:	Chiasma, Inc.
Meeting Chair:	Lisa Yanoff, M.D.
Meeting Recorder:	Jennifer Johnson

FDA ATTENDEES

Office of Drug Evaluation II

Mary T. Thanh-Hai, M.D.	Acting Director

Division of Metabolism and Endocrinology Products

Lisa Yanoff, M.D.	Acting Director
Marina Zemskova, M.D.	Clinical Team Leader
Shannon Sullivan, M.D.	Clinical Team Leader
Geanina Roman-Popoveniuc, M.D.	Clinical Reviewer
Pam Lucarelli	Chief, Project Management Staff
Richard Whitehead, M.S.	Regulatory Project Manager
Jennifer Johnson	Regulatory Health Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology 2

Sury Sista, Ph.D.	Clinical Pharmacology Reviewer
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Team Leader

Office of Biostatistics, Division of Biometrics 2

Anna Ketterman, Ph.D.	Statistics Reviewer
Feng Li, Ph.D.	Acting Statistics Team Leader

Office of Scientific Investigations

Cynthia Kleppinger, M.D.	Medical Reviewer

SPONSOR ATTENDEES

Representing Chiasma, Inc.

Asi, Haviv, DMD	Vice President, Clinical Development
Shoshie Katz	Vice President, Regulatory Affairs and Quality Assurance

William H. Ludlam, M.D., Ph.D.	Senior Vice President, Clinical Development and Medical Affairs
Gary Patou, M.D.	Head, Clinical (b) (4)
Shlomo Melmed, M.D., MACP	Professor of Medicine, Executive Vice President and Dean, Cedars-Sinai Medical Center
(b) (4)	
Jill Sisco	President, Acromegaly Community
Ruth Stevens, Ph.D., MBA	Executive Vice President and Chief Scientific Officer, Camargo Pharmaceutical Services, LLC

1.0 BACKGROUND

The New Drug Application (NDA) 208232 for MYCAPSSA was submitted on June 12, 2015. FDA issued a Complete Response letter (CRL) dated April 15, 2016, in which the FDA determined that the NDA is not approvable in its present form. Following the CRL, a Type A meeting was requested and granted. An End of Review conference was held on June 8, 2016. A NDA amendment was submitted June 21, 2016, that included a proposal to address the FDA's concerns and the FDA minutes to the End of Review conference. The meeting minutes letter was issued on July 19, 2016.

Chiasma submitted an NDA amendment on August 12, 2016, which included a Type A meeting request and an amendment submitted September 23, 2016, which contained a revised meeting package, including a proposal for an additional phase 3 study. A Type C teleconference was held on October 31, 2016. The FDA provided preliminary meeting comments via email on October 30, 2016. Final written responses were issued in a letter dated January 6, 2017.

Chiasma submitted to the IND a Special Protocol Assessment (SPA) request on June 21, 2017, the confirmatory phase 3 study protocol OOC-ACM-303 to address the CRL. FDA issued a SPA Agreement Letter on August 4, 2017, a modified SPA agreement letter on May 11, 2018, and a SPA amendment notification was submitted to the IND on February 26, 2019.

FDA sent Preliminary Comments to Chiasma on October 4, 2019.

2.0 DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded), followed by meeting discussion (bolded/italicized).

Question 1:

The randomized, double-blind, placebo-controlled phase 3 Study OOC-ACM-303, in which patients were withdrawn from their injectable SRL therapy and randomized to MYCAPSSA or placebo, met its primary efficacy endpoint and all secondary hierarchical efficacy endpoints. The trial demonstrated a statistically significant and clinically meaningful response in patients with acromegaly treated with MYCAPSSA. All enrolled patients completed the trial and efficacy measures were available for all patients.

FDA stated in the CRL that Chiasma needed to satisfactorily resolve deficiency #2 before this NDA application can be approved. Specifically, that there needs to be data in the application that provide substantial evidence that MYCAPSSA is effective in patients with acromegaly because "At least some responders in your trial could have been responders simply on the basis that they did not have active disease at last assessment or because of the carryover effects of prior treatments on disease activity". Chiasma submits that the efficacy results in Study OOC-ACM-303, conducted under a SPA, provide the efficacy data that demonstrate MYCAPSSA is effective in patients with acromegaly.

Study OOC-ACM-303 provides information on the duration of the carry-over effect of long-acting SRL injections. Consistent with the published literature (Melmed S. and Klibanski A., submitted in NDA SN0026), the median time to loss of response in the placebo group of Study OOC-ACM-303 was 16 weeks, and the 75th percentile was 16.6 weeks. Therefore, Chiasma submits that efficacy results observed at 7 months in Study CH-ACM-01 were likely attributable to MYCAPSSA and were not confounded by carry-over effect of prior therapy.

In addition, the similar response rates observed in the primary efficacy endpoints, when worst observation carried forward (WOCF) imputation methodology was applied to both data sets for the purpose of comparing response rates in Study OOC-ACM-303 and Study CH-ACM-01, provide further confirmation that the treatment effect observed in Study CH-ACM-01 is due to MYCAPSSA. 58% of patients treated with MYCAPSSA met the primary efficacy endpoint in Study OOC-ACM-303 vs 53% in Study CH-ACM-01. In addition, 75% of patients treated with MYCAPSSA completed Study OOC-ACM-303 on study drug and did not require rescue medications, versus 66% on Study CH-ACM-01.

Please provide the FDA's view of the Study OOC-ACM-303 data and their ability to address CRL deficiency #2.

FDA Response to Question 1:
We agree that completed Study OOC-ACM-303 may address CRL deficiency #2. Whether the data are adequate for approval of your marketing application will be determined during review of the resubmission of your NDA.

Meeting Discussion: ***None; sponsor accepts FDA response.***

Question 2:

Chiasma believes the totality of clinical efficacy and safety data in Study OOC-ACM-303 and Study CH-ACM-01 and the safety data in the ongoing Study OOC-ACM-302 demonstrate a favorable risk-benefit of MYCAPSSA and provide a useful addition to the physician's armamentarium in the treatment of patients with acromegaly. MYCAPSSA demonstrated statistically significant and clinically meaningful efficacy in Study OOC-ACM-303. MYCAPSSA was safe and well tolerated, without injection site reactions. Patients not responding to MYCAPSSA can revert to their prior treatment without deterioration in long-term control of IGF-1. In Study OOC-ACM-303, among all patients not responding to oral therapy, in both MYCAPSSA and placebo arms, 91% returned to their baseline levels by 36 weeks when rescued with their prior SRL injections by 32 weeks (mean IGF-1 0.86 times upper limit of normal [ULN] at baseline, 0.87 times ULN at week 36).

a. Please provide the FDA's view of the ability of Studies CH-ACM-01 and OOC-ACM-303, taken together, to provide substantial evidence of efficacy of MYCAPSSA in the long-term maintenance treatment of acromegaly patients in whom prior treatment with injectable somatostatin analogs has been shown to be effective and tolerated.
b. Please provide the FDA's view of the ability of Studies CH-ACM-01 and OOC-ACM-303, taken together, to provide favorable risk-benefit of MYCAPSSA in the long-term maintenance treatment in acromegaly patients (b) (4)

(b) (4)

FDA Response to Question 2a:
As noted in our response to Question 1, we agree that Study OOC-ACM-303 was designed, conducted, and analyzed as agreed under Special Protocol Assessment and is adequate to address deficiency #2 in the CRL. Thus, the study is adequate to support resubmission of your NDA. While, as we have stated previously, we do not agree that the results from Study CH-ACM-01 provide substantial evidence of efficacy and safety of the drug in the intended population for reasons outlined in the CRL, we do not believe Study CH-ACM-01 is necessary to support resubmission.

Chiasma requests to clarify FDA response to question 2a (sent via email on October 7, 2019):

Safety Data for NDA Resubmission
Previously, at the FDA meeting (Reference ID: 425871) dated May 4, 2018, Chiasma received agreement that the presentation of safety (ISS) data in the NDA resubmission should include both OOC-ACM-303 and CH-ACM-01, presented separately, side by

side; and the core phase of each study should be presented separately from the extension phase of each study.

The safety data from 155 patients from CH-ACM-01(core) provides additional evidence of safety. Chiasma submits these data are important to include in the NDA resubmission because this trial represents 84 patient-years of MYCAPSSA exposure in acromegaly patients.

Efficacy Data for the NDA Resubmission
Previously, at the FDA meeting (Reference ID: 425871) dated May 4, 2018, Chiasma received agreement that the presentation of efficacy (ISE) data in the NDA resubmission should include both OOC-ACM-303 and CH-ACM-01, presented separately, side by side; and the core phase of each study should be presented separately from the extension phase of each study.

Additionally, Chiasma is providing new data in patients from CH-ACM-01. As discussed with FDA (Reference No: 3961161, page 21), to study the effect of MYCAPSSA withdrawal on IGF-1 control, Chiasma obtained new follow-up data on patients after stopping MYCAPSSA and before starting treatment with SRLs (see page 53 of the meeting package). Because most patients disease activity recurred (lost IGF-1 control) within 2 weeks of cessation of MYCAPSSA, Chiasma concludes that the response in CH-ACM-01 represents MYCAPSSA action.

Moreover, the CH-ACM-01 population is more representative of biochemical values observed in acromegaly patients maintained with SRLs in clinical practice.

Chiasma Request for Clarification
Chiasma seeks to understand why the preliminary comments for this meeting state that Study CH-ACM-01 is not necessary to support resubmission.

Meeting Discussion:
The meeting began with attendee introductions, followed by a 5-minute presentation by Jill Sisco, President of the Acromegaly Community. During her presentation, Jill Sisco stated that use of the oral formulation of octreotide for the treatment of acromegaly may improve both compliance and convenience and improve overall quality of life.

Following Jill Sisco's presentation, the sponsor asked for clarification why the study CH-ACM-01 is not necessary to support resubmission and why the study OOC-ACM-303 is adequate. FDA said the study CH-ACM-01 has already been reviewed and deficiencies outlined in the Complete Response Letter, and that its results don't support the target population indication for disease control, which is IGF-1 ≤ 1 X ULN, according to Endocrine Society Guidelines; an IGF-1 value < 1.3xULN used in Study CH-ACM-01 to define disease control does not indicate

biochemical control. However, FDA indicated that the data obtained from the study OOC-ACM-303 and from the study will be compared during the NDA review.

FDA asked for the clarification why the sponsor wants to include study CH-ACM-01 in NDA. The sponsor referred to the agreement made in the May 4, 2018, Type C written responses only letter; i.e., that ISS and ISE will include the results from both studies CH-ACM-01 and OOC-ACM-303. The sponsor asked whether this plan is still acceptable. FDA agreed that that the sponsor should include both studies in the NDA.

FDA stated that these two studies have enrolled different patient populations by the definition of the disease control (i.e., study CH-ACM-01 defined disease control at baseline and end of study if IGF-1 < 1.3XULN, and study OOC-ACM-303 used IGF-1 ≤ 1 X ULN). The sponsor disagreed and stated that the study populations of both studies are the same from a clinical perspective, as there is variability in assay results as well as fluctuation of IGF-1 assay in the same patient. Therefore, there is not much difference between 1.0 and 1.3xULN IGF-1 cut-off values and physicians need to look at the holistic symptoms in the patient. Multiple factors can affect IGF-1 levels over time, including BMI, caloric intake, nutrition, etc. The sponsor explained that they chose the cut-off of IGF-1 ≤1.0 in the design of study OOC-ACM-303 because it would be cleaner for proving that the drug works compared to placebo (i.e., defining maintenance of response in patients with IGF-1 levels above 1.0xULN); however, they believe that study CH-ACM-01 demonstrates a more real-world patient population. The sponsor believes that the patient baseline demographics in both studies are similar. FDA asked the sponsor to include justification in the NDA why do they believe that patient baseline demographics in both studies were similar.

The sponsor referred to prior discussions with FDA regarding confirmation of active disease in the CH-ACM-01 study population and noted that they have obtained new data on patients approximately two weeks after stopping Mycapssa in this study and before starting treatment with injectable SRLs which can support the efficacy of Mycapssa in study CH-ACM-01.

FDA asked if the sponsor expects to include the data from CH-ACM-01 study in the (b) (4) ***or just as supportive data for the NDA. FDA indicated that if the sponsor plans to use data from the study CH-ACM-01 for*** (b) (4) (b) (4) (b) (4) (b) (4) ***The sponsor summarized slide 5 (safety information) and slide 6 (summary of study OOC-ACM-303).***

FDA asked when the sponsor plans to complete the open-label extension study, and the sponsor said that the study would continue up through the PDFUA action time. FDA said that they prefer to see all completed study results at the time of submission. The sponsor referred to the agreed-upon cut-off for the open-label extension study data discussed during the May 2018 Type C meeting (written responses letter dated May 4, 2018); additional extension study data will be submitted in the 120-day safety update. FDA said that they would abide by previous agreements.

FDA noted that maintenance of response was about 68-80% for the long-acting (Sandostatin LAR) product and about 50% for Mycapssa. The sponsor said that the long-acting product's maintenance of response rate was similar to Mycapssa. As per the Sandostatin LAR label, the maintenance of response rate was 42% in two combined trials and 57% in the third trial. FDA also noted that although 90% of patients completing the OOC-ACM-303 study went on to enroll in the extension phase, these patients were pre-selected based on tolerability and/or efficacy of the drug.

FDA asked the sponsor to include in NDA a sub-group analysis per dose level of prior SRL injection prior to treatment. The sponsor indicated that an analysis using the stratification for low-dose versus high dose had been done, and that results demonstrated that there was no difference in response between the sub-groups. The sponsor also agreed to include other sub-group analyses (i.e., gender, age, region) in the submission.

The sponsor asked if FDA has any specific issues with respect to risk-benefit assessment; FDA told the sponsor that all data need to be reviewed before raising any issues and understanding which subgroup(s) of patients will benefit from the drug.

The sponsor was asked to clarify the discordance between the primary endpoint and the second secondary endpoint in study OOC-ACM-303 as stated in the briefing package. The sponsor referred to the slide 2 of their slide presentation that included the results for primary and secondary endpoints from Study OOC-ACM-303 on slide 2. They reiterated that all patients completed the study, and that all endpoints were derived and analyzed per the SPA-approved protocol and statistical analysis plan (SAP). The primary endpoint defines a patient as a non-responder when the average of the 34 and 36-week IGF-1 assessment is above 1.0xULN. The response rates were 58.2% in Mycapssa group and 19.4% in placebo group. The second secondary endpoint was defined as having 2 consecutive IGF-1 values above 1.0xULN after being treated for at least 2 weeks with 4 capsules per day (from week 36 as estimated by the Kaplan-Meier approach as shown on slide 3). FDA asked to include the clarification regarding the different response definitions in NDA submission.

The sponsor was asked to clarify the results of the analysis of the secondary endpoint, median time to loss of response. FDA stated that "failure" is not clearly defined, and that they want to avoid ambiguities. The sponsor referred FDA to the Kaplan-Meier curve on slide 3,and reiterated that the time to loss of response was defined in the SAP, and that the median time to loss of response had not been reached for the Mycapssa arm since less than 50% of patients lost response. FDA said that they wanted to see the mean time to loss of response, not whether they met the primary endpoint, and that the SAP defined only time to loss of response, not median loss of response. FDA would like to know when patients dropped out and thought that the mean would be helpful. The sponsor referred to the Kaplan-Meier curve and said that it showed not all lost response. In their view, the mean is a biased estimand and proposed to submit both analyses. FDA agreed with the proposed plan. FDA also asked the sponsor to provide information regarding patients not losing response (i.e., they should be given a time based on the duration of time they were in the study) and the sponsor agreed.

FDA asked to clarify why 5 patients in the placebo group who maintained their biochemical response at end of the treatment continued treatment with Mycapssa in the open-label phase. The sponsor reiterated that these patients required further treatment due to persistence of patients showed loss of biochemical control during the study due to IGF-1 fluctuation but were responders by the primary endpoint measurement at the end of the study. The other 2 out of 5 patients were symptomatic during the study and continued into the open-label study extension. Dr. Melmed noted that patients may experience symptoms in the presence of biochemical control of IGF-1. FDA requested that the sponsor submit case narratives in the NDA for these 5 placebo patients.

At the end of the meeting, the sponsor indicated that they plan to resubmit the NDA in early December 2019. The sponsor asked if they may ask for a mid-cycle review teleconference with the Division. FDA said that current guidelines do not require this meeting. FDA will request for additional clarification and information early in the review cycle when necessary.

FDA Response to Question 2b:

Please refer to the response to question 2a above. Please note that while your data are acceptable to support resubmission, a benefit risk assessment can be made only after review of your resubmission.

Chiasma requests to clarify FDA response to question 2b (sent via email on October 7, 2019):

We appreciate the feedback that OOC-ACM-303 can address CRL deficiency #2 and that the study is adequate to support resubmission of the NDA. Therefore, based upon

your preliminary comments we conclude that FDA determined the NDA resubmission is ready.

Given the favorable safety profile as well as the robust results of OOC-ACM-303, a SPA approved protocol, we seek clarification at the meeting to understand what issues FDA will be focusing on for the overall benefit to risk assessment.

We respectfully seek your clarification of any unresolved concerns that Chiasma should be addressing in the NDA resubmission.

***Meeting Discussion:* See meeting discussion section following question 2a.**

Question 3:
Chiasma remains blinded to the individual patient treatment assignment during the randomized, controlled treatment (RCT) for Study OOC-ACM-302, which is ongoing. BIMO datasets will not be provided in the NDA resubmission.

Does the FDA agree with this plan?

FDA Response to Question 3:
Yes, that is acceptable. However, we request that you include in your NDA narratives for all deaths, serious adverse events, and adverse events leading to discontinuation from ongoing study OOC-ACM-302. We acknowledge that this is an ongoing, blinded trial, but safety data from this trial should be submitted with the NDA for review. Unblinding of the trial for purposes of presenting the safety should not occur, and data should be presented by treatment arm without identification of the treatment (e.g., treatment A, treatment B, treatment C). We may discuss unblinding of the trial if a significant safety concern is identified.

***Meeting Discussion:* None; sponsor accepts FDA response.**

Question 4:
Chiasma has explored two different dose titration regimens during the clinical development program of MYCAPSSA in acromegaly: a starting dose of 40 mg, titrating to 60 mg and 80 mg, if required (assessed in the core studies CH-ACM-01, OOC-ACM-303, and OOC-ACM-302), and a second titration regimen of a 60-mg starting dose, titrating up or down as required to 40 mg or 80 mg (assessed in the open-label extension [OLE] of OOC-ACM-303). The latter regimen requires only one titration step and is consistent with the SRL titration regimens of injectable SRLs, octreotide LAR and lanreotide. Based on the safety data collected in Study CH-ACM-01, Study OOC-ACM-303, and the OLE of Study OOC-ACM-303, Chiasma proposes the following:

The starting dose of MYCAPSSA will be (b) (4)
(b) (4)

(b) (4) (b) (4) based on IGF-1 levels and/or clinical signs/symptoms.

Does FDA agree with this dose titration regimen, with a starting dose of (b) (4) mg?

FDA Response to Question 4:
It is premature to discuss (b) (4) information without having reviewed the data. (b) (4)

Please note that in general, FDA considers data derived from well-controlled study(s) to provide substantial evidence of the effectiveness of the product in the proposed doses in the intended population (e.g., core study OOC-ACM-303). Uncontrolled extension trial(s) provide data on long-term safety and durability of the effect of the drug but has limited information on efficacy and safety of the starting dose and titration regimen.

***Meeting Discussion:* None; sponsor accepts FDA response.**

Question 5:
Will this NDA resubmission require the FDA to seek the opinion of the FDA Advisory Committee before deciding on the approvability of the application?

FDA Response to Question 5:
At this time, we do not expect that this NDA resubmission requires the FDA to seek the opinion of the FDA Advisory Committee.

***Meeting Discussion:* None; sponsor accepts FDA response.**

Additional Comments:

Note: See meeting discussion section following Question 2a for discussion regarding Additional Comments 1, 6 and 9. No discussion took place for Additional Comments 2, 3, 4, 5, 7 and 8.

1. **In the text of your briefing package you are stating the following (page 14): "58% of the patients on MYCAPSSA maintained their IGF-1 response compared to 19% of the patients on placebo;" i.e., 12 subjects (42%) on Mycapssa and 23 (81%) subjects on placebo lost the response.**

   At the same time, on page 30, you are writing:
   "Twenty-six (26) of 28 patients treated with placebo (93%) lost response anytime throughout the study vs 46% on MYCAPSSA (13 of 28 patients).

Based on these data only 7% of placebo patients maintained their response throughout the DPC period vs 54% on MYCAPSSA."

We were not able to find congruency in your statements. Please clarify your statements.

Chiasma Clarification (sent via email on October 7, 2019):
Both analyses were prespecified in both the protocol and statistical analysis plan under the Special Protocol Assessment (SPA) and address different aspects of the efficacy effect.

The primary endpoint measures the proportion of patients responding at the end of DPC trial based upon the average of week 34 and week 36.

The secondary endpoint informs on the durability of MYCAPSSA and placebo responses throughout the 9-month study using a Kaplan-Meier analysis. Patients are considered non-responders if they had lost response at anytime during the study instead of just at the end of the study (primary endpoint).

The primary and secondary endpoints (42% versus 46% MYCAPSSA non-responders, respectively) are measuring different aspects of efficacy and are not expected to yield identical results. The secondary endpoint is a more stringent endpoint than the primary endpoint. MYCAPSSA non-responder rates are similar (42% versus 46%) demonstrating the robustness of the MYCAPSSA treatment effect. The placebo non-responder rates are higher by this more stringent secondary endpoint (81% versus 93%) due to loss of control of these untreated patients.

In summary, Chiasma concludes the results with these two endpoints are complementary and consistent and both demonstrate the treatment effect of MYCAPSSA.

2. **For us to be able to reproduce your results, please provide clear and well commented analysis programs that you utilized to produce all your major results (primary and secondary endpoints). Also, to improve clarity of your analyses, we recommend that you include a program flow, i.e., a detailed description of your program, in each of your codes. Please include detailed flow charts in the analysis data reviewers guide (ADRG).**

3. **Please provide the names of the datasets and programs that were utilized to produce all major tables and results. Incorporate this information in the footnote of each table.**

4. **At the time of submission, include graphical visualization of relationship between adverse events and treatment duration. Suggestions and ideas for graphs of adverse events are provided on CTSPEDIA website https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome.**

5. **For clarity, in all your time-to-event plots, please include the number of subjects at risk on the bottom of your graphs.**

6. **Clarify the results of the analysis of the secondary endpoint, median time to loss of response. You stated that median time to loss of response was not reached (> 36 weeks) for patients treated with Mycapssa; however, 42 % of the patients on Mycapssa lost biochemical response at the end of DCP period, and 46% of the patients on Mycapssa lost control anytime throughout the DCP study period. In our opinion, these results are discordant.**

   You define median time to loss of response as "*the earliest time when the IGF-1 of 2 consecutive visits was > 1 times ULN after the patient was treated for at least 2 weeks with four capsules per day* " (page 30). However, not all patients were on 4 capsules a day in the fixed dose period (beyond week 24). Clarify whether these patients were included in the median time to loss of response analysis. If so, what definition did you apply to this patient cohort?

   Chiasma Clarification (sent via email on October 7, 2019):
   Chiasma requests clarification of the FDA's response since the median time to loss of response is the time by which 50% of patients have lost response, 46% of patients have lost response on MYCAPSSA, and the median time to loss of response on MYCAPSSA has not been reached.

   FDA questions the definition of median time to loss of response. Yes, it is correct that the prespecified analysis (in the protocol and SAP) included the earliest time when the IGF-1 of 2 consecutive visits was > 1 times ULN after the patient was treated for at least 2 weeks with four capsules per day" (page 30).

   However, only one patient was not treated with 4 capsules a day by week 24, was not rescued, and had two consecutive IGF-1 values above 1 before the end of the study. This patient was censored for this secondary endpoint per the SAP. For the primary endpoint this patient was a non-responder.

   Per this definition, patients that had not been treated with the highest dose for at least 2 weeks could not be regarded as patients who have lost their response, unless they have discontinued study drug treatment for any reason.

7. **Please provide information on how many patients entering the fixed dose period maintained their response.**

8. **Please analyze the responders by the previous SRLs dosing regimen required for the disease control during the screening period (e.g., Sandostatin LAR > 120 mg/month or Somatuline Depot > 30 mg/month, Sandostatin LAR 90 mg/month or Somatuline Depot 20 mg/month, Sandostatin LAR < 60 mg/month or Somatuline depot < 10 mg/month).**

9. **We note that 5 patients in the placebo group who maintained their biochemical response at end of the treatment period were transitioned to Mycapssa in the OLE phase due to active acromegaly symptoms. Please clarify why these patients required treatment with active drug if their disease was biochemically controlled. The scientific society guidelines (AACE, 2004, Endocrine Society, 2014) recommend using normalized serum IGF-1 values as a therapeutic goal, as this correlates with control of acromegaly. Additionally, all currently marketed SRLs were approved for the treatment of acromegaly based on their effect to achieve IGF-1 within normal limits.**

   Chiasma Clarification (sent via email on October 7, 2019):
   Three of the 5 placebo treated patients exhibited loss of biochemical control anytime during the course of the trial but not at the end of the trial, the primary efficacy endpoint, due to IGF-1 fluctuation (same 3 placebo patients described in the answer to FDA additional comment 1 above) and so had recent biochemical evidence of active disease in the absence of treatment.

   Patients may experience symptoms in the presence of biochemical control of IGF-1. 86% of the patients randomized at entry (on their prior SRL injections) had at least one active acromegaly symptom despite having normalized IGF-1 levels, and 43% had at least 3 active symptoms. The other two of the five placebo-treated patients were symptomatic during the study, deemed to require treatment by their physicians, and preferred to continue receiving MYCAPSSA.

   This is consistent with the endocrinology treatment guidelines (Katznelson 2014) which state "Because of the variable nature of the disorder, an individualized treatment strategy is necessary. Goals of treatment are biochemical normalization, reduction of mortality risk, attenuation of symptoms, control of tumor mass, and maintenance of pituitary function.

   FDA Response (sent via email on October 8, 2019):
   We note that 5 patients in the placebo group who maintained their biochemical response at end of the treatment period were transitioned to Mycapssa in the OLE phase due to active acromegaly symptoms. Please clarify why these patients required treatment with active drug if their disease was biochemically

controlled. The scientific society guidelines (AACE, 2004, Endocrine Society, 2014) recommend using normalized serum IGF-1 values as a therapeutic goal, as this correlates with control of acromegaly. Additionally, currently marketed SRLs were approved for treatment of acromegaly based on their effect to achieve IGF-1 within normal limits, and your product is expected to meet this requirement.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[3] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[4]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.regulations.gov

identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated

Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications.[5]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items that were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor slide presentation.

[5] https://www.fda.gov/media/85061/download

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARINA ZEMSKOVA
11/08/2019 10:33:42 AM
signing for Lisa Yanoff, M.D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108163

MEETING MINUTES

Genentech, Inc.
Attention: Sabina Zimmerman, Ph.D.
Associate Regulatory Program Director
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Zimmerman:

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

We also refer to the meeting between representatives of your firm and the FDA on May 21, 2014. The purpose of the meeting was to discuss and obtain agreement on the proposed content and format for your New Drug Application (NDA) submission via the 505(b)(2) regulatory pathway for the treatment of acromegaly.

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 Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Pre-NDA Meeting Minutes for oral octreotide acetate

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Wednesday, May 21, 2014; 12:00-1:30 pm
Meeting Location: CDER, White Oak Campus

Application Number: IND 108163
Product Name: Oral octreotide acetate
Indication: Treatment of acromegaly
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Jennifer Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director
Dragos Roman, M.D.	Clinical Team Leader
Marina Zemskova, M.D.	Clinical Reviewer
Jessica Hawes, Ph.D.	Nonclinical Reviewer
Ronald Wange, Ph.D.	Supervisor, Pharmacology/Toxicology
Pamela Lucarelli	Chief, Project Management Staff
Jennifer Johnson	Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics II

Cynthia Liu, Ph.D.	Biometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Immo Zadezensky, Ph.D.	Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology
Division of Medication Error Prevention and Analysis

Mishale Mistry, Pharm.D., MPH	Reviewer

Division of Risk Management

Cynthia LaCivita, Pharm.D.	Team Leader

Office of Scientific Investigations, Division of Good Clinical Practice Assessment Branch
Cynthia Kleppinger, M.D. Medical Officer

Office of Orphan Drug Products
John Milto, Pharm.D. Regulatory Review Officer

SPONSOR ATTENDEES
Representing Genentech, Inc.

Anthony Calandra, Ph.D.	Global Regulatory Leader, Regulatory Affairs
Manfred Doerner, Ph.D.	Technical Development Leader
Elena Fisheleva, M.D.	Global Development Team Leader, Clinical Science
Susanne Fors, M.Sc.	Senior Director, Regulatory Affairs
Alison Greene, MPH	Principal Scientist, Patient Reported Outcomes
Tianhua Hu, Ph.D.	Biometrics Submission Team Leader
Angelika Jahreis, M.D., Ph.D.	Associate Group Medical Director, Clinical Science
Lutz Mueller, Ph.D.	Nonclinical Toxicology
Jeffrey Siegel, M.D.	Senior Group Medical Director, Clinical Science
Natasha Singh, Pharm.D., R.Ph.	Principal Safety Scientist, Drug Safety
Richard Steinbach, R.Ph.	Technical Regulatory
Dietrich Tuerck, Ph.D.	Nonclinical DMPK
Jianmei Wang, Ph.D.	Senior Statistical Scientist, Biostatistics
Erica Winter, Pharm.D.	Principal Scientist, Clinical Pharmacology
Sabina Zimmerman, Ph.D.	Associate Program Director, Regulatory Affairs

Representing Chiasma, Inc.
Asi Haviv, M.D. VP Clinical Development

1.0 BACKGROUND

Chiasma, Inc. (the original sponsor of this application until it was transferred to Genentech on March 11, 2014) has been developing an oral formulation of octreotide acetate, a somatostatin analog, and plans to submit a New Drug Application (NDA) via the 505(b)(2) regulatory pathway for the treatment of patients with acromegaly. This product is being provided as single-strength oral capsules containing 20 mg of octreotide (a free peptide). Currently approved therapies for acromegalic patients include Sandostatin Injection (subcutaneous/intravenous route), which is administered daily, and Sandostatin LAR Depot Injection (intramuscular route) and Somatuline Depot Injection (intragluteal route), which are administered monthly. The sponsor plans to rely upon the reference product Sandostatin (octreotide acetate) Injection (approved under NDA 019667), as well as literature, to support its planned 505(b)(2) NDA application. Citing the need for a more convenient formulation for acromegalic patients, the sponsor is utilizing Transient Permeability Enhancer (TPE) in its oral formulation (an enteric-coated capsule designed to pass through the stomach intact and disintegrate when it reaches the higher pH of the small intestine where oral octreotide acetate is released into the lumen).

The sponsor submitted a Pre-IND meeting request on March 2, 2010, which was denied and written responses were issued on August 30, 2010. (Note: orphan drug designation was granted for this product for the treatment of acromegaly by the Office of Orphan Products Development on June 17, 2010). The sponsor opened its IND 108163 with an original submission on November 9, 2010. The IND was placed on partial clinical hold on December 9, 2010, due to inadequate nonclinical data to support multiple-dose studies. The sponsor submitted a complete response to clinical hold on March 4, 2011, and the hold was removed on March 30, 2011.

An End-of-Phase 2 meeting was held on August 9, 2011, and minutes issued on September 8, 2011. On September 15, 2011, the sponsor submitted an amendment which contained toxicology information from a 3-month oral capsule dose toxicology study in cynomolgus monkeys, an excipient assessment report evaluating the excipients sodium caprylate and glyceryl tricaprylate, and responses to nonclinical comments from the EOP2 meeting minutes. On November 3, 2011, a response advice letter issued. On December 31, 2012, the sponsor submitted a request for proprietary name review of its proposed trade name Octreolin but then submitted a withdrawal request on March 25, 2013.

On March 28, 2013, the sponsor submitted an amendment containing a toxicity report for Study 1300-009 entitled "Octreolin: A 9-Month Oral Capsule Dose Toxicity Study in Cynomolgus Monkeys", as well as a request for a waiver of carcinogenicity studies. On May 30, 2013, a letter of agreement with this waiver request issued. An amendment was submitted on April 26, 2013, which contained a new protocol for Study CHI-007, entitled, "A Phase I, Open-label Study to Evaluate the Safety and Pharmacokinetics of 40 mg Oral Octreotide Acetate in Subjects with End-stage Renal Disease (ESRD) and Subjects with Severe Renal Impairment, Compared to Matched Normal Health Subjects". On June 28, 2013, a response advice letter issued.

On September 20, 2013, the sponsor submitted a guidance meeting request to discuss product development issues with Agency CMC personnel. A Written Responses-Only (WRO) meeting granted letter issued on October 7, 2013, and the WRO letter issued on November 22, 2013. (The sponsor submitted a follow-up amendment on January 31, 2014, seeking feedback regarding alcohol-induced dose dumping, and a response letter issued on March 10, 2014.)

The sponsor submitted an amendment on October 18, 2013, which contained a statistical analysis plan, a PK/PD analysis plan and an updated Phase 3 protocol for Study CH-ACM-01 entitled, "Phase 3 Efficacy and Safety of Oral Octreotide Acetate in Patients with Acromegaly Who Are Currently Receiving Parental Somatostatin Analogs". On February 20, 2014, a response advice letter issued.

The new sponsor (Genentech) requested a Pre-NDA meeting on March 12, 2014, and a meeting granted letter issued on April 3, 2014. Background materials were submitted by the sponsor on April 11, 2014. Preliminary comments were sent to the sponsor by electronic mail on May 19, 2014, and the sponsor sent clarification responses to relevant FDA requests included in the preliminary comments on May 20, 2014.

2.0 DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded), followed by the sponsor's clarification response where applicable (italicized), followed by the meeting discussion (bolded/italicized).

Clinical

1. Does the Agency agree that the PK studies described herein and the clinical efficacy and safety data from the Phase III study have established an adequate "bridge" between OOA and the Sandostatin IR that will enable an OOA NDA submission using the 505(b)(2) regulatory pathway?

   FDA Response: We do not agree. Whether the PK studies and the Phase III study constitute an adequate bridge between OOA and Sandostatin will require full review of the data in the NDA submission. Please see responses to Question 2 asking for additional clarifications.

   Sponsor Clarification Response via email on May 20, 2014:
   We intend to rely on Sandostatin IR as the Listed Drug.

   We have established a PK bridge to Sandostatin IR to support the 505(b)(2) application, as acknowledged by the Agency at the End of Phase II meeting with FDA. The relative bioavailability studies CHI-001 and CHI-002 demonstrated that a single 20 mg dose of Oral Octreotide results in a systemic exposure which is comparable to a 0.1 mg dose of immediate release octreotide in Healthy Volunteers. Can the Agency please clarify if there are any concerns with this PK bridge?

   The Phase 3 study was not designed to establish a bridge to Sandostatin IR. It was designed to demonstrate the safety and efficacy of the oral formulation of octreotide in patients responding to injectable SSAs following a switch to oral octreotide. Can the Agency clarify if they agree with the Sponsor's approach to using the Phase 3 study to demonstrate safety and efficacy of the oral formulation of octreotide and not as part of the bridge to Sandostatin IR?

   Discussion during FDA meeting: See meeting discussion section following Clinical Question 2.

2. Genentech intends to submit a 505(b)(2) application for OOA based upon the efficacy and safety profile of the drug demonstrated in the Phase III study CH-ACM-01, the clinical pharmacology studies described herein, the existing information in the public domain for Sandostatin IR, and the Agency's previous findings of efficacy and safety for Sandostatin. Does the Agency agree that these data are sufficient to support the application?

   FDA Response: Your plan appears reasonable. However, reliance on the findings of efficacy and safety of immediate-release Sandostatin will depend on whether you have succeeded in establishing a bridge between OOA and immediate-release

Sandostatin. See our response to Question 1. Whether the results of clinical studies will support the proposed indication for oral octreotide acetate will be a review issue.

Please note that if you plan to rely also on the Agency's previous findings of efficacy and safety for Sandostatin LAR, you will have to establish a "bridge' between your product and Sandostatin LAR.

Clarify which Sandostatin product you intend to rely upon.

As Phase III study CH-ACM-01 is a single arm trial and interpretability of efficacy and safety data from such a trial will be challenging, please address the following at the meeting and in detail in any future NDA submission:

a. Clarify how the diagnosis of acromegaly was established and how it relates to current diagnostic standards.
b. Clarify why patients controlled on long-acting SSA were selected for the trial when, according to the briefing package, you intend to bridge this drug to a short acting SSA.
c. Clarify the reason why after a one month drug washout period, 88% of individuals were still "responders" on the baseline assessment.
d. Clarify whether past radiation (TBI or cyberknife) therapy was an exclusion criteria for this trial.
e. Clarify how potential confounders (i.e., latent effect of pre-trial medications or other treatment modalities for acromegaly) susceptible to affecting efficacy result interpretation were handled.
f. Clarify whether you believe the observed responder rate (~50-60% response) at endpoint is consistent with what you would have predicted based on the population selected (i.e., 100% responders at screening), the timing of the assessment for the primary endpoint and the PK and PD comparisons between OOA and subcutaneous immediate release octreotide.
g. Comment on the durability of the response.
h. Provide your scientific arguments as to why you believe the response observed in the trial is due to your product and not to other factors such as lack of disease progression or spontaneous improvement, and provide any evidence that you have to support your argument.

Sponsor Clarification Response via email on May 20, 2014:

a. Sponsor Clarification:

- *Current diagnostic standards for acromegaly are based on AACE acromegaly guidelines 2011[i], as follows:*
  - *clinical symptoms of acromegaly and associated comorbidities*
  - *elevated serum IGF-1 levels*
  - *failure to suppress GH below 1µg/L during an oral glucose tolerance test (OGTT)*

Reference ID: 4656466

- *Patients enrolled in this study had all been previously diagnosed with acromegaly. Enrollment criteria in Study CH-ACM-01, outlined below, are in alignment with the current diagnostic standards:*
  - *All patients enrolled into this trial had documented evidence of GH-secreting pituitary tumor that is abnormally responsive to glucose*
  - *Diagnosis was confirmed by either OGTT and/or elevated IGF-1 levels above upper limit of normal [132 patients based on OGTT (85%), 128 based on IGF-1 (83%)]*
  - *All patients received long acting SSAs on screening.*

b. Sponsor Clarification:
We have established a PK bridge to Sandostatin IR to support the 505(b)(2) application. The Phase 3 study was not designed to establish the bridge to Sandostatin IR. It was designed to demonstrate the safety and efficacy of the oral formulation of octreotide in patients responding to injectable SSAs following a switch to oral octreotide. The study protocol hence allowed inclusion of patients receiving both immediate release and long acting formulations of octreotide. The fact that there were no patients on Sandostatin IR in the study reflects the current standard of care.

c. Sponsor Clarification:
We would like to clarify that there was no washout period in this study. The baseline visit occurred in most patients within approximately 2 weeks following their last injection of extended release SSA. At this time, it is expected that most or all patients would be responders, consistent with the observed response rate (88%).

d. Sponsor Clarification:
The study protocol excluded all patients who received pituitary radiotherapy (both conventional and stereotactic) within 10 years prior to screening. This is important because the benefits of radiotherapy on GH hypersecretion may be delayed, up to several years (AACE acromegaly guidelines 2011).

e. Sponsor Clarification:
The study was designed to minimize the effect of any potential confounders on the outcome, as outlined below:

- *<u>Previous SSAs treatment</u>: The duration of residual IGF-1 suppression after withdrawal of long acting SSAs is not known, but complete washout is expected to occur within 8-12 weeks from withdrawal, in a patient with active disease. During the approximately 8 month study, it is unlikely that residual effects of SSAs would have been observed. The lack of latent effects of previously received injectable SSAs was corroborated by data collected on the 90 patients who had elevated IGF-1 levels and thus required an increase in the dose of oral octreotide to achieve biochemical control of acromegaly.*
- *<u>Medical treatment other than SSAs</u> : the protocol required at least 3 months wash out from pegvisomant prior to screening and at least 2 months of washout from dopamine agonists prior to screening.*

- *<u>Radiotherapy:</u> Since the benefits of radiotherapy on GH hypersecretion may be delayed, up to several years (AACE acromegaly guidelines 2011), patients who had received these treatments within 10 years were excluded from the Phase 3 study.*
- *<u>Surgery</u>: After surgery of a pituitary adenoma, serum IGF-1 levels may take months to decline into the normal range. Because of this, the Phase 3 study excluded patients who underwent pituitary surgery within 6 months prior to screening. Based on the current standard of care, patients should only receive treatment with somatostatin analogs if they had had an inadequate response to surgery.*

f. Sponsor Clarification:
The comparable PK between oral octreotide and Sandostatin IR would predict that most patients controlled on an effective dose of injectable octreotide would also be controlled on oral octreotide.

A number of factors help explain why the observed response rate in our phase 3 study is not 100%.

- *variability in absorption of OOA*
- *food effect*
- *early dropout due to GI adverse events*
- *observed biochemical fluctuation over time as observed for patients on stable injectable long acting SSAs (100% response rate at screening vs. 88% response rate at baseline)*

During the study, between 53-65% of patients achieved response on oral octreotide, relative to the observed 88% -100% background response rate on injectable SSAs. We believe that the timing of the primary endpoint at 7 months reflects chronic use of OOA. This is corroborated by the fact that 90% of patients who achieved control of IGF-1 during the dose titration phase and continued in the study maintained control at the end of the fixed dose phase.

g. Sponsor Clarification:
In the study, 90% of patients who achieved control of IGF-1 during the dose titration phase and continued in the study maintained control at the end of the fixed dose phase. The NDA submission will also include long term data from the extension portion of the study in which patients received OOA for an additional 6 months.

h. Sponsor Clarification:
We believe that the response observed in the trial is due to treatment with OOA and not due to spontaneous improvement.

The inclusion and exclusion criteria were designed to include only patients who were not expected to have spontaneous improvement and who required chronic therapy with SSAs to control their acromegaly. The study excluded newly diagnosed patients, patients who could be controlled with SSAs administered less frequently that every 4 weeks, and patients who received radiotherapy within 10 years, or surgery within 6 months (see also the Sponsor clarification to FDA's response to Question 2e).

The following factors highlight disease activity in patients enrolled in the trial:

- *Of the patients treated in our study, 90 patients required a stepwise increase in the dose of oral octreotide during the dose escalation period of the study. These patients all had elevated IGF-1 levels, demonstrating that they still had active acromegaly.*
- *Despite being biochemically controlled on standard of care, 81% of subjects still exhibited persistent acromegaly symptoms at baseline.*

Discussion during FDA meeting: ***During the discussion, Genentech reiterated their position 1) that they have established a PK bridge to Sandostatin immediate-release injection by showing similar exposure between the 20 mg oral dose of oral octreotide acetate and the 0.1 mg dose of immediate- release Sandostatin injection based on PK data; 2) that the proposed Phase 3 single-arm clinical trial is not intended to build a clinical bridge with Sandostatin immediate-release, hence no side-by-side comparison of the two drug products was planned in Phase 3; and 3) that the intention of the clinical program was to develop oral octreotide acetate as an oral alternative to injectable Sandostatin for those patients who respond to oral octreotide.***

FDA asked for clarification as to why there was a drop in the number of responders between screening (100% "responders") and baseline when 12% of patients no longer met the responder definition. Genentech indicated that this happened due to natural fluctuations in the levels of GH and IGF-1, and that these fluctuations were relatively close to the GH and IGF-1 thresholds used for the definition of responder.

FDA asked why the sponsor selected patients who were controlled on the long-acting Sandostatin formulation if they're bridging to the short-acting formulation; the sponsor said that they allowed both Sandostatin formulations in the inclusion criteria but that patients are treated mostly with the long-acting Sandostatin.

FDA expressed concern that there was a reduction of almost 50% in the number of responders when patients were switched from Sandostatin to oral octreotide. Given that Genentech has selected the oral octreotide starting dose as a dose that had been shown to provide similar drug exposure as a therapeutic Sandostatin dose, such a loss of efficacy was odd. Genentech responded that there were multiple explanations for this observation, including high variability in drug absorption, a possible food effect, adverse events resulting in discontinuations (primarily gastrointestinal adverse events, 34% of patients dropping out mostly at the beginning of the trial), and fluctuations in IGF-1 serum levels. Even under these conditions, patients who reached biochemical control on oral octreotide maintained such control. In addition, some of the patients who were not responders with respect to the protocol definition for IGF-1 control (two consecutive IGF-1 values above the predefined threshold of 1.3 SDS) later actually experienced reductions in their IGF-1 levels, and all patients were "responders" with respect to GH reduction. Some patients had lower absorption of oral octreotide than previously anticipated, and such patients may benefit from higher oral octreotide doses.

FDA commented that a single-arm study is not as informative as a controlled study such as an active control trial using a non-inferiority design. There is always a concern in interpreting data from a single-arm trial wherein some patients may improve spontaneously. Genentech indicated that patients were selected based on criteria that would only allow patients with active pituitary tumors to be enrolled and that spontaneous resolution of such tumors is expected to be a very rare, reportable event. FDA stated that the Division is moving away from single-arm studies because they limit the ability to interpret accurately efficacy and safety results.

FDA questioned how much one can understand about the drug if exposure does not predict response, particularly in the face of an uncontrolled clinical trial with limited efficacy, and questioned if the PK data were sufficiently characterized. Genentech responded that the PK-PD relationship is not well known for octreotide, in general, and, therefore, such exposure-response predictions cannot be accurately made. FDA asked if the sponsor demonstrated bioequivalence; the sponsor replied that they did not conduct a formal bioequivalence study, and that it was their understanding that a strict bioequivalence study was not required and that a relative bioequivalence study was sufficient. FDA also indicated that in absence of demonstration of bioequivalence through a bridging PK study, the sponsor will have to demonstrate that differences in exposure do not affect safety and/or efficacy, and therefore additional data may be required. In the end, FDA indicated that the adequacy of an oral octreotide-Sandostatin immediate-release bridge is a review issue.

The sponsor reiterated that the trial was not done for bridging purposes and that it demonstrated adequate long-term control of GH and IGF-1 levels. FDA asked if the sponsor compared the PK characteristics of responders versus non-responders; the sponsor stated that no PK data was collected in non-responders during the maintenance phase or at the end of the trial. FDA noted that poor absorption may cause loss of response in those patients, and asked the sponsor if they checked for exposure levels; the sponsor replied that additional response was achieved in all titration steps.

FDA asked about the PD effect of the drug, and at a given dose, how soon was a decrease in GH and IGF-1 levels seen. The sponsor responded that GH levels decreased after 2 hours, and clarified that full PK characteristics were assessed during the fixed dose phase, hence the reason they don't have PK data in the non-responders (maintenance phase). FDA asked if the sponsor targeted the therapeutic level of the drug, and the sponsor stated that this wasn't the aim of the trial since every patient is assumed to have a different therapeutic level.

FDA reminded the sponsor that Sandostatin LAR is not that much different than Sandostatin immediate-release with respect to GH and IGF-1 control, and asked if the sponsor expected adequate GH control with their drug based on the information they had before the trial. The sponsor replied that they did not have that information beforehand. FDA reminded the sponsor that bioequivalence was not demonstrated in a

single-dose PK study. FDA asked what would be the maintenance dose, and the sponsor replied that individual dose titration to the desired clinical effect is the goal, given that there is no well-established exposure-response relationship for octreotide. The sponsor noted that they are conducting a small study examining possible factors influencing variability of response among patients.

Genentech clarified that they will use the 505(b)(2) approach primarily for the pharmacology and safety sections of the NDA.

3. Does the Agency agree that the results from the Phase III study CH-ACM-01 are clinically meaningful, demonstrate efficacy, and would support the following indication statement:

   Oral octreotide acetate is indicated for long-term maintenance therapy in acromegaly patients (b) (4) (b) (4)

FDA Response: **Acceptance of the efficacy data generated in the Phase III study CH-ACM-01 as being adequate for approval will require a full review of the NDA. Refer also to the comments and requests made in the response to the previous Question 2.**

We note that maintenance of GH/IGF-1 suppression was observed only in slightly more than half of the patients enrolled. We also note that several malignancies not mechanistically related to the underlying disease occurred in the trial, an unusual occurrence for such a small dataset of 151 patients. Your NDA submission needs to address these issues in detail including issues such as biological plausibility and previous literature experience.

Sponsor Clarification Response via email on May 20, 2014:
Please see above the Sponsor's clarification to Question 2f about the response rate seen in the Phase 3 study. For those patients who respond to oral octreotide, an oral alternative provides a viable and meaningful treatment option, alleviating the treatment burden associated with chronic injections. In addition, in clinical practice, patients will be monitored for biochemical control and can be switched back to long acting SSAs if they do not respond to oral octreotide. Does the Agency have any additional comments about the observed response rate?

We acknowledge the agency's concerns regarding malignancies observed in the Phase 3 study. We began investigating these cases as soon as we became aware of them:

- *The 4 malignancy cases reported during the course of the study were medically reviewed and assessed as unrelated to study treatment. Three of the four malignant neoplasms were reported within the first 3-4 months of treatment and two out of the four patients had background medical histories, suggesting that these may have been pre-existing.*
- *Overall, these cases are largely consistent with the known disease burden and the increased propensity of malignancy in acromegaly.*

- *Information regarding the individual cases along with additional details, biologic plausibility and published literature, will be included in the submission.*

Does this address the agency's concern?

Discussion during FDA meeting: ***See meeting discussion following Clinical Question 2.***

4. OOA was granted orphan designation in June 2010 based on the potential for the drug to make a significant contribution to patient care. Does the Agency agree that data from the Phase III study CH-ACM-01 with OOA in acromegaly patients supports orphan exclusivity for OOA?

FDA Response: FDA does not award, comment on, or grant exclusivity prior to approval of a drug product; therefore, concurrence at this time would be premature. Upon approval of NDA, and upon confirmation that the approved indication is equivalent to the orphan designation indication, 7 years of exclusivity would be granted, assuming that no other oral octreotide acetate product is approved for this indication before approval of your NDA.

Discussion during FDA meeting: ***No discussion took place; sponsor accepts FDA Response.***

5. Does the Agency agree that the proposed content of the clinical section of the OOA application is sufficient for filing and review (details to be provided in background package)? In particular:
   a) Does the Agency agree with the plan for submitting subject narratives?

FDA Response: Yes.

   b) As the 505(b)(2) application is supported by a single, original clinical study assessing the safety and efficacy of OOA, does the Agency agree with the plan of not including an Integrated Summary of Efficacy (ISE) or an Integrated Summary of Safety (ISS)?

FDA Response: Yes.

   c) Is the proposed plan for submission of Case Report Forms (CRFs), Case Report Tabulations (CRTs), and SAS datasets acceptable to the Agency?

FDA Response: Yes. The proposed SAS datasets are acceptable. Please also see http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm and its related links regarding the preparations of SAS datasets.

   d) Does the Agency have any other comments on the content of the application?

FDA Response: We noted that you plan to include safety data from 155 patients from CH-ACM-01 study in this NDA. Include supporting safety data from all studies conducted with OOA.

Clarify the number of patients in your safety dataset that you expect to have been exposed to the drug for 6 months, 12 months, and > 12 months at the time of NDA submission.

Discussion during FDA meeting: FDA asked how many patients will provide long-term data for the NDA. Genentech stated that 88 patients entered a voluntary extension trial but the information regarding the exact length of exposure was not available. Genentech stated that 12 months of exposure data from the extension phase will be available at the time of NDA submission.

Clinical Pharmacology

6. Does the Agency agree that the drug-drug interaction package, including the requested evaluation of a potential interaction between digoxin and OOA (Studies CHI-005, CHI-006, OCT-02, OCT-03, OCT-04), addresses the request for this information and supports approval of OOA via the 505(b)(2) pathway?

   FDA Response: The proposed studies addressed our request for the evaluation of the potential drug interactions.

   Discussion during FDA meeting: No discussion took place; sponsor accepts FDA Response.

7. Reference is made to the End of Phase II meeting minutes and to the discussion at the FDA meeting related to Question #10 on the use of mannitol as a transcellular permeability marker in Study CHI-004. The pharmacology reviewer cited literature suggesting mannitol is a paracellular permeability marker and requested that Chiasma explain this discrepancy in the NDA submission. Has the information summarized in the PMP addressed this discrepancy?

   FDA Response: Yes, you addressed the discrepancy. However, the interpretation of study results will be a review issue.

   Discussion during FDA meeting: No discussion took place; sponsor accepts FDA Response.

8. Do the completed hepatic-impairment and renal-impairment studies (CH-PHT-01 and CHI-007, respectively) satisfy the Agency's request for this information and support approval of OOA via the 505(b)(2) pathway?

   FDA Response: It is not clear whether the division's request has been fully addressed because brief description of studies in the meeting material did not

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include sufficient information to evaluate the issue. Acceptability of the results will be a review issue.

Discussion during FDA meeting: ***No discussion took place; sponsor accepts FDA Response.***

Nonclinical

9. Does the Agency agree that the available nonclinical pharmacology, DMPK, and toxicology studies support NDA submission and approval of OOA?

   FDA Response: The scope of the nonclinical studies is sufficient to support filing of the NDA application. Whether or not the nonclinical studies are sufficient to support approval of OOA is a matter of review of the NDA application package.

   Discussion during FDA meeting: ***No discussion took place; sponsor accepts FDA Response.***

10. To support drug product (DP) specifications as per ICHQ3B, Genentech intends to conduct an additional 4-week monkey toxicity study, similar to the already submitted 4-week study with DP material representative of the current specifications. Does the Agency agree that a study of this duration would support the DP specifications upon submission of the NDA package?

    FDA Response: The proposed 4-week monkey bridging toxicology study is of duration sufficient to satisfy ICH guideline Q3B(R2) recommendations; however, qualification of the current drug product in the 4-week monkey study is a matter of review. Please clearly indicate the differences in drug product formulation and specifications used in the bridging and original toxicology studies.

    Discussion during FDA meeting: ***No discussion took place; sponsor accepts FDA Response.***

Chemistry, Manufacturing and Controls (CMC)

11. On the basis of the U.S. Food and Drug Administration (FDA) Draft Guidance for Industry "Naming of Drug Products Containing Salt Drug Substances" (December 2013), and considering that the molecular formula of octreotide acetate is C49H66N10O10S2 x C2H4O2 with an acetic acid content between (b) (4)% to (b) (4)% being described in the Draft United States Pharmacopeia (USP) Monograph (published in Pharmacopeial Forum Vol. No. 36 [6], page 1559), the following text is proposed for the product label:

    Trade Name: (to be determined)
    Octreotide capsules
    20 mg
    Each capsule contains: octreotide acetate
    Corresponding to 20 mg octreotide free peptide

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Does the Agency agree?

FDA Response: Your proposed established name "octreotide" that matches the labeled dosage strength "20 mg" is acceptable as discussed in FDA's and USP's guidances. The final text of your product label will be reviewed as part of our NDA review and further comments will be conveyed to you at that time.

***Discussion during FDA meeting:* No discussion took place; sponsor accepts FDA Response.**

12. Does the Agency agree that a (b) (4)-month shelf-life of the commercial-scale product may be proposed based on 18 months of data from the primary stability study at pilot scale available at the time point of NDA submission, and (b) (4)-month data filed subsequently during NDA review? Does the Agency agree that submission of the (b) (4)-month data during the first 3 months of review is acceptable and does not have an impact on review timelines?

FDA Response: Your proposed amendment for the (b) (4)-month primary stability data, to update the 18-month data that will be in the initial NDA submission, will not have an impact on our review timelines. You may propose a shelf life of the commercial product based on the 18-month data. The final shelf life of the commercial product will be determined after our review of all available information in the NDA.

***Discussion during FDA meeting:* No discussion took place; sponsor accepts FDA Response.**

Regulatory/Administrative

13. Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) program will not be required for OOA?

FDA Response: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

***Discussion during FDA meeting:* No discussion took place; sponsor accepts FDA Response.**

14. Given that OOA has been granted orphan drug designation (File # 10-3093), and based on the Pediatric Research Equity Act (PREA) and FDA Draft Guidance for Industry, "How to Comply with the Pediatric Research Equity Act", does the Agency agree with a request for a pediatric waiver for the proposed NDA for OOA, and that no Pediatric

Study Plan (PSP) will be submitted to the Agency in conjunction with this product application?

FDA Response: **Yes.**

Discussion during FDA meeting: ***No discussion took place; sponsor accepts FDA Response.***

15. Does the Agency anticipate reviewing data included in this NDA at an Advisory Committee?

FDA Response: **We do not anticipate a need for an Advisory Committee at the present time. This may change, however, after review of the data.**

Discussion during FDA meeting: ***No discussion took place; sponsor accepts FDA Response.***

Other

16. Would the Agency like Genentech to provide a face-to-face technical walkthrough of the NDA following its submission? Specifically, to provide the Agency with:
    a) A table of contents with document descriptions, as needed.
    b) A walkthrough of the submission in Global Submit, with particular attention to specific constructs in the filing that may be unique.

FDA Response: **A face-to-face technical walkthrough of the NDA is not needed.**

Discussion during FDA meeting: ***No discussion took place; sponsor accepts FDA Response.***

Additional FDA Comments

Please refer to advice from the Office of Scientific Investigations (OSI) attached to the end of this document. (Note: this attachment was included in the FDA preliminary responses and is being included again in the meeting minutes.)

Discussion during FDA meeting: ***No discussion took place; sponsor acknowledges advice from OSI.***

3.0 ADDITIONAL INFORMATION

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*

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4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

- OSI Pre-NDA/BLA Request Document

[Note: the sponsor had one handout (a copy of the clarification responses provided to FDA via email on May 20, 2014). The content of this handout has been incorporated into the responses to Questions 1, 2 and 3 above rather than attaching the handout to the minutes.]

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/contract research organization (CRO) inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Items I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, the Applicant can identify the location(s) and/or provide link(s) to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (*Technical Instructions: Submitting Bioresearch Monitoring [BIMO] Clinical Data in eCTD Format*).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in the submission, describe the location or provide a link to the requested information).

1. Please include the following information in a tabular format in the original NDA/BLA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal Investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA/BLA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued at each site

3. Please include the following information in a tabular format in the NDA/BLA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as

described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

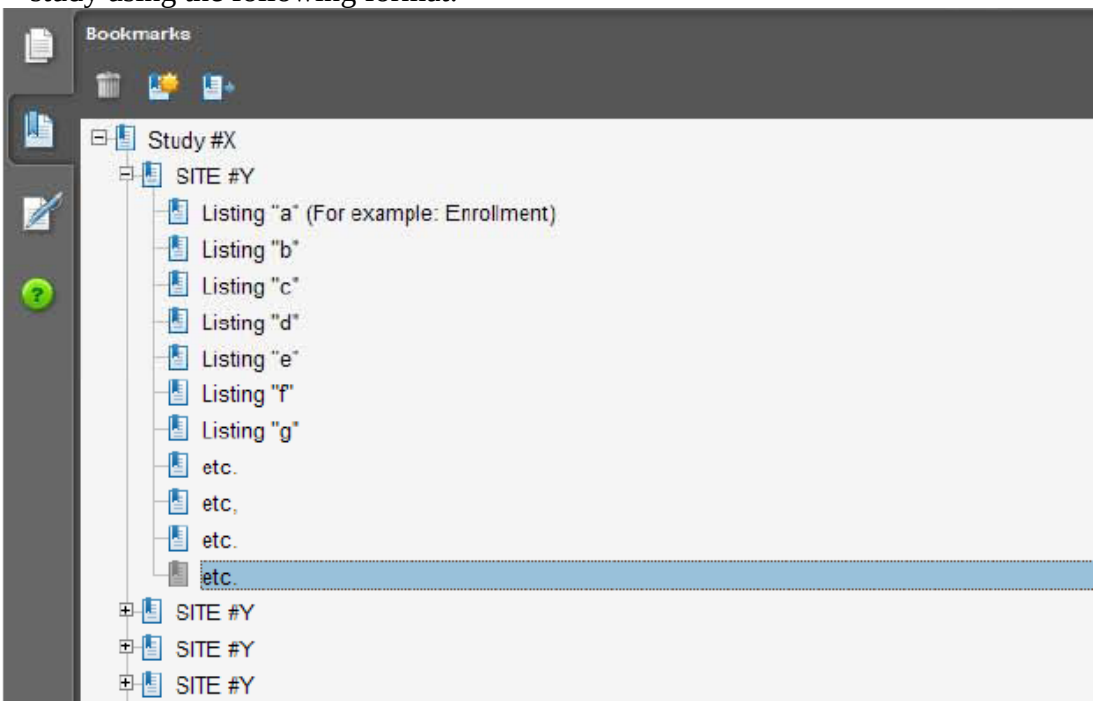
4. For each pivotal trial, provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial, provide the original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per-protocol subjects/ non per-protocol subjects and reason not per-protocol
   e. By subject, listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject, listing of AEs, SAEs, deaths and dates
   g. By subject, listing of protocol violations and/or deviations reported in the NDA/BLA, including a description of the deviation/violation
   h. By subject, listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject, listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject, listing of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

OSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

JEAN-MARC P GUETTIER
06/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108163

MEETING MINUTES

Camargo Pharmaceutical Services, LLC
U.S. Agent for Chiasma, Inc.
Attention: Ruth E. Stevens, Ph.D., MBA
Chief Scientific Officer and Executive Vice President
10151 Carver Road, Suite 200
Cincinnati, OH 45242

Dear Dr. Stevens:

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

We also refer to the meeting between representatives of your firm and the FDA on August 9, 2011. The purpose of the meeting was to discuss your development plans for this product for the treatment of acromegaly.

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) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: FDA End-of-Phase 2 Meeting Minutes for Octreolin (octreotide acetate) Oral

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	Tuesday, August 9, 2011, 1:00 – 2:00 pm
Meeting Location:	CDER, White Oak Campus
Application Number:	IND 108163
Product Name:	Octreolin (octreotide acetate) Oral
Indication:	Treatment of acromegaly
Sponsor/Applicant Name:	Chiasma, Inc. (U.S. Agent: Camargo Pharmaceutical Services, LLC)
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Jennifer Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D.	Director
Dragos Roman, M.D.	Clinical Team Leader
Marina Zemskova, M.D.	Clinical Reviewer
Karen Davis Bruno, Ph.D.	Supervisory Pharmacologist
Parvaneh Espandiari, Ph.D.	Pharmacology/Toxicology Reviewer
Julie Marchick, MPH	Acting Chief, Project Management Staff
Jennifer Johnson	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Jayabharathi Vaidyanathan, Ph.D.	Acting Clinical Pharmacology Team Leader
S.W. Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics II

J. Todd Sahlroot, Ph.D.	Deputy Director and Team Leader
Lee Ping Pian, Ph.D.	Biometrics Reviewer

Office of New Drug Quality Assessment III, Division of Premarketing

Joseph Leginus, Ph.D.	Chemistry Reviewer

Office of Orphan Products Development	
Soumya Patel, Pharm.D.	Pharmacist Reviewer
Omar McMillan	Pharmacy Student
Office of Planning and Informatics, Division of Regulatory Review and Support	
Valerie Gooding	Regulatory Information Specialist, Electronic Submission Support

SPONSOR ATTENDEES
Representing Chiasma, Inc.

Roni Mamluk, Ph.D.	Chief Operating Officer (Drug Development)
Sam Teichman, M.D.	Chief Medical Officer
Shoshie Katz	Director, Regulatory Affairs and Quality Assurance
Ruth E. Stevens, Ph.D., MBA	Chief Scientific Officer, Executive Vice President (Drug Development, Regulatory Affairs), Camargo Pharmaceutical Services, LLC
Lynn Gold, Ph.D.	Vice President, CMC Services, Camargo Pharmaceutical Services, LLC
Patricia D. Williams, Ph.D.	President & CEO (Nonclinical), IND Directions, LLC
(b) (4)	
Shlomo Melmed, M.D., FRCP	Professor of Medicine, Senior Vice President and Dean, Cedars-Sinai Medical Center, Los Angeles, California, USA

1.0 BACKGROUND

Chiasma, Inc. is developing an oral formulation of octreotide acetate (Octreolin), a somatostatin analog, and plans to submit a marketing application via the 505(b)(2) regulatory pathway for the treatment of patients with acromegaly. Currently approved therapies include Sandostatin Injection (subcutaneous/intravenous route), which is administered daily, and Sandostatin LAR Depot Injection (intramuscular route) and Somatuline Depot Injection (intragluteal route), which are administered monthly. Citing the need for a more convenient formulation for acromegalic patients, the sponsor is utilizing Transient Permeability Enhancer (TPE) in its oral formulation (an enteric-coated capsule designed to pass through the stomach intact and disintegrate when it reaches the higher pH of the small intestine where Octreolin is released into the lumen).

The sponsor submitted a Pre-IND meeting request on March 2, 2010. The meeting was denied and written responses were issued on August 30, 2010. Orphan drug designation was granted for Octreolin for the treatment of acromegaly by the Office of Orphan Products Development on June 17, 2010. The sponsor opened its IND 108163 with an original submission on November 9, 2010. The IND was placed on partial clinical hold on December 9, 2010, due to inadequate nonclinical data to support multiple-dose studies. The sponsor submitted a complete response to clinical hold on March 4, 2011, and the hold was removed on March 30, 2011.

The sponsor submitted an End-of-Phase 2 meeting request on May 2, 2011.

Background materials were submitted by the sponsor on June 29, 2011.

Preliminary comments were sent to the sponsor via electronic mail on August 5, 2011.

2.0 DISCUSSION

The sponsor's questions are listed below, followed by the FDA pre-meeting response (bolded), followed by the meeting discussion (bolded/italicized).

QUESTIONS FOR THE AGENCY

Chemistry, Manufacturing, and Controls

1. Chiasma will qualify multiple suppliers of octreotide acetate for use in Octreolin drug product. Does the Agency agree with the plan as presented?

   FDA Preliminary Response:
   The approach to qualify potential alternate sources of the octreotide acetate drug substance is acceptable. We remind you to include a thorough comparison of impurities/degradants in each batch of drug substance. Be advised that nonclinical studies may be required to qualify any difference in the impurity/degradant profile.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

2. Does the Agency agree that the specifications for in-process controls during the drug product production process are acceptable to support the Phase 3 clinical program?

FDA Preliminary Response:
The specifications for in-process controls during the drug product production process appear adequate to support the Phase 3 clinical program. However, in-process tests that are only used for the purpose of adjusting process parameters within an operating range are not necessarily included in the drug product specification. The final drug product must meet the acceptance criteria in the drug product specifications at release and stability. The in-process controls will be evaluated during the NDA review after the sponsor has had an opportunity to gain more experience with the overall manufacturing process following the manufacture of a larger number of batches at or close to commercial scale.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

3. Does the Agency agree that the current stability program supports the drug product expiration date and clinical study use?

FDA Preliminary Response:
The designs for the long term and accelerated stability studies for the drug product are acceptable for Phase 3 (The clinical supply material will be placed on stability for 36 months stored at the long-term condition of 5 ± 3°C and for 6 months stored at the accelerated condition of 25 ± 3°C/60% RH). The sponsor is reminded that data from stability studies will be considered for batches of the same formulation and packaged in the same container closure system as proposed for clinical use. See ICH Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products (November 2001) for additional details.

Expiration dating will be determined based upon stability findings on drug product according to ICH Guidance for Industry Q1E Evaluation of Stability Data (June 2004).

As you have indicated, during Phase 3 subjects will store (b) (4) **drug product under refrigeration. After opening and during actual use,** (b) (4) **will be kept under refrigeration or at controlled room temperature (25 ± 2°C) for up to 1 month. Incorporate the following in-use stability study as part of an overall stability design for the drug product:**

- **In-use stability studies should include drug product samples at the extreme of their expiration dating. For example, for drug products**

whose expiration is 18 months, in-use stability studies (in your case, samples stored (b) (4) that have been opened and stored at controlled room temperature for up to 1 month) should be initiated using drug product samples having been maintained under recommended storage conditions for as close to 18 months as possible. The approach should provide a reliable indication of in-use stability of the drug product throughout its intended shelf-life.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

4. Does the Agency concur that the CMC plan for the Octreolin drug product is sufficient to support the Phase 3 clinical program?

FDA Preliminary Response:
This is adequate for Phase 3.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

Regulatory Strategy

5. Does the Agency agree with the proposed indication: (b) (4) (b) (4)

FDA Preliminary Response:
The final indication will have to reflect the type of patients that have been studied in the registration trial. Your proposed protocol includes patients who are either partial or complete responders to several acromegaly treatments (immediate acting Sandostatin, Sandostatin LAR, Somatuline) thus suggesting that it is intended as maintenance medical therapy and not as initial therapy in treatment-naïve patients. Please clarify if this is indeed your intent.

Discussion at FDA meeting: ***Refer to slide 3 of sponsor's slide presentation. The sponsor intends to eventually pursue indications for both initial and maintenance therapy of acromegaly. The sponsor confirmed that the current Phase 3 trial will enroll patients eligible for maintenance therapy. At a later date, the sponsor plans to submit additional information to support the use of Octreolin for initial therapy.***

6. Does the Agency agree that studies conducted by Chiasma assessing the comparative BA and pharmacokinetics (PK) of octreotide after administration of Octreolin and Sandostatin (Octreotide; NDA 19-667) Injection, have established an adequate "bridge" between the 2 products, that will enable Chiasma to rely in part on the Agency's findings of efficacy and safety for the LD Sandostatin in a 505(b)(2) NDA submission?

FDA Preliminary Response:
You conducted the following 2 studies in healthy volunteers:

- **Study CHI-001 to assess the relative bioavailability between different doses of oral Octreolin under fasting condition and subcutaneous Sandostatin**
- **Study CHI-002 to assess the food effect on Octreolin bioavailability and the relative bioavailability between oral Octreolin and subcutaneous Sandostatin**

Per these 2 studies, the exposure of oral 20 mg Octreolin under fasting condition seems comparable to the exposure of subcutaneous 0.1 mg Sandostatin. However, the acceptability of Studies CHI-001 and CHI-002's results as an adequate bridge between Octreolin and Sandostatin will be a review issue upon your future NDA submission.

Discussion at FDA meeting:
The sponsor has its own clinical trial to establish Octreolin's efficacy and safety. The sponsor does not seek bioequivalence between Octreolin and Sandostatin. For the 505(b)(2) NDA submission, the sponsor clarifies that the comparative bioavailability studies are to establish the "bridge" between Octreolin and Sandostatin (b) (4)

(b) (4)

7. Does the Agency agree that in addition to relying in part on the Agency's findings of efficacy and safety for Sandostatin Injection (NDA 19-667), the LD identified in the 505(b)(2) submission for Octreolin, Chiasma can also rely in part on the Agency's findings of efficacy and safety, for Sandostatin LAR (NDA 21-008), which was approved more recently by FDA and refers, to a large extent, to the data supporting the Sandostatin Injection product (NDA 19-667)?

FDA Preliminary Response:
In order to rely on Sandostatin LAR's findings of safety and efficacy you will have to establish a "bridge" between your product and Sandostatin LAR. We do not see how this can be easily accomplished given the very different pharmacokinetic profiles of Octreolin and Sandostatin LAR. There is the theoretical possibility of establishing such a bridge via a clinical trial but this requires further discussion.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

8. Does the Agency agree that if favorable results are shown for the proposed Phase 3 clinical study (Study CH-ACM-07), the results of this study in combination with the data from the completed and planned studies to be conducted by Chiasma, and the existing information in the public domain and the Agency's previous findings of efficacy and safety for the LDs Sandostatin and Sandostatin LAR, will be sufficient to satisfy the efficacy and safety data requirements for an NDA for Octreolin (oral octreotide acetate) for the proposed indication?

FDA Preliminary Response:
Yes, assuming that the additional comments and requirements from various disciplines are addressed. Refer also to the response provided for Question 5 regarding the indication. Refer also to the response to Question 7. Unless you are able to establish a "bridge" between Octreolin and Sandostatin LAR, the Agency cannot rely on the findings of efficacy and safety of Sandostatin LAR in support of your application.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

Nonclinical

9. Does the Agency agree that no additional nonclinical safety data will be required for the conduct of the Phase 3 program and for approval of Octreolin using the 505(b)(2) regulatory pathway?

FDA Preliminary Response:
The Agency does not agree that adequate safety information has been provided to support safety of Octreolin for marketing approval. It is acknowledged that Chiasma has performed a comparative 3-month bridging toxicology study in monkey comparing Octreolin (oral capsules) and octreotide (SC). In this study ¾ female monkeys in the Octreolin group had macroscopic findings of black lung pigment deposition and histopathology findings of minimal-mild pleural adhesions/fibrosis that appeared correlative. Chiasma reports that this is a background finding in monkeys; however data to support this claim has not been provided. The control groups as well as the octreotide treated groups do not demonstrate this finding. This finding may be related to inhalation of foreign material; however, the correlation with the presence of the new oral formulation containing permeability enhancers (TPE) elicits concern. Additional safety information is needed to support chronic use of this novel formulation of octreotide containing TPE. Chronic toxicity and a carcinogenicity assessment of the formulation are likely needed to support marketing.

Discussion at FDA meeting: ***Refer to slide 5 of sponsor's slide presentation. Chiasma presented its interpretation of the FDA comments to Question #9 as well as describing its plans to provide additional information to support that the lung findings observed in Octreolin treated monkeys were background lesions. The basis of this conclusion is the study pathologist's conclusions and historical control data from two publications provided by Chiasma. Chiasma plans to evaluate the controls from the 3-month toxicity study for histopathology. Chiasma asked additional clarifying questions:***

1. Pending provision of additional data to the IND as described in the EOP2 meeting presentation, does FDA have additional concerns with the findings?
2. Since the lung findings are not Octreolin-related what is the rationale for additional long-term toxicology studies?

Response: Submission of additional information is encouraged including histopathologic evaluation of the control group tissues from the 3-month monkey toxicity study as this is standard for GLP toxicity studies. However the control group is olive oil treated and therefore a vehicle/formulation (TPE) treated group is not available from this study for comparison. Chiasma clarified that monkeys with black pigment deposition (3/4 females) also had pleural fibrosis/adhesion/inflammation (2/3) but the findings were not correlated to the same histopathologic site. Chiasma also noted that 1/3 Sandostatin female monkeys had black pigment in the lungs. Chiasma plans to submit photographic data to describe this. The published literature provided in response to DMEP preliminary comments includes data from different laboratories other than the (b) (4) ***site which conducted the 3-month Octreolin comparative bridging monkey toxicity study (Exp Anim 41(4):455-469; 1992 and Toxicol Pathol 38:642-657; 2010). The 2010 publication has point estimates for pleural histopathologic lesions in monkeys that are high corresponding to the broad range reported in the incidence pleural fibrosis (0-50%; 0-100% pigment deposition) from 60 studies at*** (b) (4) ***The mean values for pleural pigment deposits are ~26% and for pleural fibrosis 25% in both male and female monkeys. The incidence of these findings is higher in female monkeys from the 3-month comparative bridging toxicology study (at*** (b) (4) ***than the published mean and these incidences exceed the concurrent Sandostatin treatment group. Historical control incidences for these lung findings have not been provided from the study site*** (b) (4)

A comparative bridging toxicology study is pivotal in supporting the planned 505(b)2 development pathway proposed by Chiasma. The results of the 3-month comparative bridging toxicity study in monkeys suggest that the toxicology profiles of Octreolin and octreotide are different. An adequate bridge has not been provided between Octreolin and Octreotide. This difference may be due to the novel oral formulation used in Octreolin; TPE contains (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) ***Characterization of the toxicity profile and carcinogenicity assessment of TPE, particularly for these components for chronic use, has not been established. This is the basis for requesting additional safety information for TPE. Based on this concern the additional information needed to support safety will be needed prior to any clinical dosing beyond 3-months' duration.***

Clinical Pharmacology

10. Does the completed Chiasma Phase 1 study (Study CHI-004) with the lactulose/mannitol (L/M) assay address the Agency's request for information on the duration of increased intestinal permeability in humans and nonabsorbable GI contents?

    FDA Preliminary Response:
    Study CHI-004 assessed the time frame of increased intestinal permeability caused by Octreolin via the lactulose/mannitol test. However, the acceptability of Study CHI-004's results will be a review issue upon your future NDA submission.

    Discussion at FDA meeting: ***Some literature states that mannitol is an intestinal paracellular permeability marker in vitro [Madara et al. J Clin Invest 1989;83:724-7; Collett et al. Pharm Res 1996;13:216-21]. However, Study CHI-004 uses mannitol as an intestinal transcellular permeability marker and lactulose as an intestinal paracellular permeability marker. The sponsor should explain this discrepancy for mannitol as markers of intestinal permeability in its future NDA submission.***

11. Does the completed Chiasma Phase 1 study (Study CHI-004) with Growth Hormone Releasing Hormone (GHRH)-Arginine stimulated GH release address the Agency's request for documentation that the systematic octreotide delivered from Octreolin is associated with a functional response?

    FDA Preliminary Response:
    From a Clinical Pharmacology perspective, the changes of growth hormone as a functional response upon administration of Octreolin seem reasonable.

    Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

12. Do the proposed studies in hepatic-impaired (Study CH-PHT-01) and renal-impaired (Study CHI-007) special populations address the Agency's requests for this information?

    FDA Preliminary Response:
    Your proposed Study CH-PHT-01 will assess the pharmacokinetic profile of single dose Octreolin in patients with cirrhosis and portal hypertension as well as to evaluate the effects of Octreolin on hepatic venous pressure gradient in such patients. However, you should use the Child-Pugh classification system to categorize the patients so as to evaluate the effect of varying degrees of hepatic impairment on the pharmacokinetics of Octreolin per the hepatic impairment guidance:
    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.

Your proposed Study CHI-007 to assess the effect of varying degrees of renal impairment on the pharmacokinetics of Octreolin seems reasonable. You should conduct the study per the draft renal impairment guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response and intends to comply with FDA's recommendations and/or clarify all of the issues raised by FDA in its respective study protocols or statistical analysis plans (refer to slide 4 of sponsor's slide presentation).***

13. Do the completed Study CHI-005 (with proton pump inhibitor [PPI]) and the proposed DDI study (Study number CHI-006) with drugs of low BA and narrow therapeutic window address the Agency's request for this information?

FDA Preliminary Response:
Study CHI-005 assessed the effect of esomeprazole on Octreolin pharmacokinetics upon oral co-administration. However, the acceptability of Study CHI-005's results will be a review issue upon your future NDA submission.

For Study CHI-006, you should provide the rationale for a meal to be taken with the 5 probe drugs 2 hours following Octreolin administration since food may reduce the absorption of drugs such as captopril by 30 – 40%.

You also need to address the potential interaction between digoxin and Octreolin since digoxin is a likely to-be-coadministered narrow therapeutic window drug in acromegalic patients. You may address this interaction via an independent study or add digoxin as another probe drug in Study CHI-006, if feasible as the 6th probe drug.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response and intends to comply with FDA's recommendations and/or clarify all of the issues raised by FDA in its respective study protocols or statistical analysis plans (refer to slide 4 of sponsor's slide presentation).***

14. Does the plan to collect repeat-dose PK data during chronic therapy with Octreolin as part of the proposed Phase 3 study (Study CH-ACM-01) address the Agency's request for this information?

FDA Preliminary Response:
Yes, your proposal to collect repeat-dose pharmacokinetic data during the chronic therapy with Octreolin as part of the proposed Study CH-ACM-01 is acceptable.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response.***

15. Chiasma will accept the current Sandostatin labeling with regard to "Cardiac Function Abnormalities." Chiasma will monitor patients in clinical trials of Octreolin for electrocardiogram (ECG) abnormalities. Does the Agency agree that a thorough QT study of Octreolin is not required for approval?

    FDA Preliminary Response:
    For octreotide alone, a thorough QT study is unnecessary from a Clinical Pharmacology perspective since the approved octreotide product label states QT prolongation during octreotide therapy. For Octreolin, a thorough QT study may be unnecessary at this time pending further safety data from the Phase 3 study (CH-ACM-01).

    Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response and intends to comply with FDA's recommendations and/or clarify all of the issues raised by FDA in its respective study protocols or statistical analysis plans (refer to slide 4 of sponsor's slide presentation).***

16. Does the Agency agree that the clinical pharmacology plan for Octreolin is sufficient to support the conduct of the Phase 3 program and for approval of Octreolin using the 505(b)(2) regulatory pathway?

    FDA Preliminary Response:
    You should address the issue of immunogenicity of Octreolin upon chronic oral administration, via a validated assay for the detection of octreotide antibodies, on the following:
    - **The effect of octreotide antibodies on the bioanalytical assay of octreotide**
    - **The effect of octreotide antibodies on the pharmacokinetics of Octreolin**
    - **The effect of octreotide antibodies on the efficacy and safety of Octreolin**

    In case the clinically tested Octreolin formulation is not identical to the to-be-marketed Octreolin formulation, appropriate bridging study will be necessary before submission of future NDA.

    Enteric-coated dosage form must empty from the stomach before drug absorption can begin, which is a function of gastric emptying. Gastric emptying varies among and within individuals. [M. Gibaldi. *Biopharmaceutics and Clinical Pharmacokinetics.* Chapter 5, 4th ed., (1991); M. Rowland and T.N. Tozer. *Clinical Pharmacokinetics and Clinical Pharmacodynamics: Concepts and Applications* Chapter 6, 4th ed., (2011)]. Since Octreolin is an enteric-coated capsule, understanding the factors that affect gastric emptying is crucial to minimize the variability of Octreolin absorption. We encourage you to explore the effect of the following on gastric emptying for Octreolin pharmacokinetics:
    - **Posture (Queckenberg and Fuhr. *Eur J Clin Pharmacol* 2009;65:109-19)**
    - **Water intake (Shimoyama et al. *Neurogastroenterol Motil* 2007;19:879-86; Karsdal et al. *J Clin Pharmacol* 2011;51:460-71)**

We also encourage you to explore the gastrointestinal motility effect of representative prokinetic drug and anticholinergic drug on the pharmacokinetics of Octreolin.

Discussion at FDA meeting: ***None; sponsor accepts FDA Preliminary Response and intends to comply with FDA's recommendations and/or clarify all of the issues raised by FDA in its respective study protocols or statistical analysis plans (refer to slide 4 of sponsor's slide presentation).***

Clinical

17. Does the Agency concur that the proposed Phase 3 study (Study CH-ACM-01, including target population, overall design, dose-regimen, treatment duration, endpoints, size, and intended analysis) is sufficient to support the NDA for Octreolin for the proposed indication?

FDA Preliminary Response:
The overall plan for the proposed Phase III study is acceptable. Since you propose to submit a single clinical trial under section 505(b)(2) of the Food, Drug and Cosmetic Act, provide in the NDA a summary of efficacy and safety based on available published information obtained with octreotide in patients with acromegaly and indicate how and why these data are relevant to your particular drug product.

Additional clinical comments regarding the proposed Phase 3 trial:

- **Provide a comprehensive medical history description for the patients enrolled in the trial including the type, duration and sequence of prior treatments (surgery, radiotherapy, etc), the criteria used for the diagnosis of acromegaly and how they were applied, the specific criteria used for defining failure of previous therapies, and any additional clinical, radiological, biochemical, or pathological data that is relevant in defining the patient population enrolled in your trial.**
- **Clarify if the patients who are on injections of Sandostatin within the last 3 months prior to enrollment are allowed or not to have any Sandostatin dose adjustments during this period.**
- **We note that for some lanreotide regimens, due to the long half-life of the product, there is a possibility of carryover effect; explain why a longer washout period is not necessary.**
- **Clarify if dose escalation is permitted during the fixed dose phase if the IGF-1 levels are elevated when compared to the previous visit levels or if exit criteria will be used for lack of efficacy.**
- **Clarify if the Octreolin formulation that will be used in the Phase 3 trial is the same as the one you plan to market.**
- **The number of patients you plan to enroll (150) seems reasonable. It is not clear if the number of patients and the duration of exposure at the proposed dose will**

be entirely informative with respect to safety. Although the safety profile of octreotide is reasonably well known, one cannot predict if additional safety signals may or may not be present based on the interaction of the TPE with concomitantly administered drugs; therefore, a this time, we believe the extent and results of the drug-drug interaction package will be important in helping understanding the safety profile of Octreolin.

- **We recommend adding to the list of safety assessments thyroid function tests, vitamin B12 levels, fasting glucose and hemoglobin A1c.**
- **Clarify the timing of IGF-1 and GH measurements (baseline, subsequent visits, etc).**
- **In addition to the proposed responder analyses of patients who normalized GH levels and patients who normalized IGF-1 levels, present an analysis for patients who normalized both GH and IGF-1 levels during the clinical trial.**
- **We suggest that you present descriptive data of within-patient GH and IGF-1 responses at baseline and end-of-treatment using a 4x8 transition table (n and %). There would be 8 end-of-treatment response categories formed by cross-classifications of GH responses (GH >5.0 ng/ml, 2.5 < GH < 5.0 ng/ml, 1.0 < GH < 2.5 ng/ml, GH < 1.0 ng/ml) and IGF-1 responses (normalized, not normalized). The 4 rows of the table would represent responses at baseline (cross-classifications of GH responses (1.0 < GH < 2.5 ng/ml, GH < 1.0 ng/ml) and IGF-1 responses (normalized, not normalized)), the columns responses at the end of treatment.**
- **Clarify the inconsistent statements of "Inferential statistics will not be used to test efficacy results for significance or non-inferiority." and "Unless stated otherwise, two-sided p values<0.05 will be considered statistically significant." in Section 8 of the Statistical Analysis Plan.**

We remind you of the following latter portion of the response to your question #7 as stated in our advice letter issued on August 30, 2010: "For the evaluation of various covariate factors including age, race, gender, as well as renal and hepatic impairment, we recommend that you include a sufficient number of these subjects in your proposed Phase 3 trial for safety and efficacy evaluation."

Discussion at FDA meeting: ***Refer to slide 4 of sponsor's slide presentation, regarding bullet #3 above. The sponsor clarified that there is no formal washout period for any of the subjects enrolled in the Phase 3 study. The sponsor acknowledged that there will be a carryover effect early in the study, but it should not raise any safety concerns because it overlaps with the Octreolin titration period and because of the wide therapeutic index and safety margins of the somatostatin analog utilized in the study (octreotide). The sponsor stated that there is no concern regarding an efficacy carryover effect because the efficacy of Octreolin will be measured at 7 months, long after any effect of the pre-trial somatostatin analogs had disappeared.***

FDA asked why the sponsor chose to evaluate Octreolin's efficacy at 7 months (versus a full year). The sponsor replied that the 7-month time point was chosen as a balance between the shortest time required for the drug development process and a sufficient amount of time for patients to be on Octreolin and to respond to the fixed dose regimen following titration. The sponsor is planning an open-label extension phase (an additional 6 months at the optimum dose for each patient to control hormone levels).

FDA asked the sponsor if 13 months' total data would be submitted with the original NDA submission (7 months for the pivotal study, and 6 months for the extension study). The sponsor clarified that the data from pivotal Phase 3 study (first 7 months' data) will be submitted in the NDA submission. The extension study will be ongoing at the time of the NDA submission; thus the data from the extension study will be included in the safety update and submitted during the NDA review. FDA acknowledged that the sponsor's plan is acceptable, but recommended that the sponsor encourage patients to continue in the extension trial and collect as much safety and efficacy data as possible. The sponsor asked FDA to clarify the minimum requirements expected (patient numbers, duration of exposure, etc). FDA asked how many completers of the Phase 3 study are expected to be enrolled into the extension phase. The Agency indicated that the patient exposure should be comparable to that obtained with other somatostatin analog programs.

FDA asked for the clarification of the definition of the complete responders versus partial responders used in the trial, and what is the clinical relevance of the 30% ULN IGF-1 threshold planned for the trial. The sponsor stated that IGF-1 values are assay- and lab- dependent and age-dependent and that the 30% ULN threshold was chosen to ensure that any observed IGF-1 levels are clinically relevant changes and not simply due to the inter and intra-assay variability.

FDA expressed the concern that that Octreolin titration in clinical practice may be complicated if the IGF-1 titration criteria in clinical trials are too complex and cannot be followed easily in clinical practice. The sponsor's expert indicated that the decision to change the Octreolin dose if two consecutive IGF-1 levels confirm an increase > 15% is clinically relevant and, in his opinion, can be implemented in clinical practice.

FDA asked why the definition of acromegaly control will use a GH threshold of 2.5 ng/mL and not 1 ng/mL, as per the latest guidelines for cure of acromegaly. The sponsor indicated that the GH threshold of 2.5 ng/mL is still an important criterion of acromegaly control and is also described in the acromegaly labels for the other somatostatin products. Additionally, the sponsor stated that a GH level < 2.5 is associated with reduction in mortality rate to background levels. FDA acknowledged the sponsor's response, but stated that it would like to see data

reported for both GH levels < 2.5 ng/ml and < 1 ng/ml. The sponsor agreed and confirmed that a statistical analysis plan will be submitted for FDA review.

FDA asked if the patient satisfaction is an exploratory endpoint or if the sponsor plans to incorporate the data in the label. The sponsor stated that it would be exploratory and intended for publication only. FDA advised that for label consideration it would have to meet the standard defined in the recent Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

Additional FDA Comments Pertaining to Submission of 505(b)(2) Applications:

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

If you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) (rather than a bioequivalent ANDA product) as the comparator.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. You should establish a "bridge" between your proposed drug product and the listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. The specified listed drug should be used rather than a bioequivalent ANDA product as the comparator. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the

appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

1. In your submission of a 505(b)(2) application, you should clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any of the published literature on which your marketing application relies for approval. If published literature is relied upon, inclusion of copies of the articles would be helpful.

   a. In addition to identifying the source of supporting information in your annotated labeling, your marketing application should summarize the information that supports the application in a table similar to the one below.

   b. We recommend

Source of information (e.g., published literature, name of listed drug)	Information provided (e.g., specific sections of the 505(b)(2) application or labeling)
1.	
2.	
3.	
4.	

   c. We remind you that your labeling must conform to the Physicians Labeling Rule (PLR) format and that 505(b)(2) marketing applications are subject to the Prescription Drug User Fee Act.
   d. Since we have recommended that you conduct clinical studies to support your application, you should submit a Request for Special Protocol Assessment prior to conducting clinical trials to establish safety and efficacy of your product.
   e. We strongly encourage you to request a Pre-NDA meeting to be held two to three months prior to your planned submission date.

<u>Discussion at FDA meeting:</u> Refer to final slide 10 of sponsor's slide presentation regarding clarification sought on 1a and 1c. The sponsor plans to proceed directly to the Phase 3trial without submitting a SPA (as recommended in 1c above). FDA stated that a SPA was not a requirement. Regarding 1a (reliance on literature), the sponsor asked if its presentation as outlined in Table 25 (page 52 of meeting briefing document) was acceptable, as well as the tabular summary included in Appendix 1. FDA reminded the sponsor that approved labeling would be relying upon published clinical data (literature), and that such data has to be summarized and supportive evidence of the clinical trial. FDA also

reminded the sponsor that its product does not have to be bioequivalent in order to submit an NDA via the 505(b)(2) regulatory pathway, but that any data not generated by the sponsor in support of approval of the application would require providing a bridge as to why it would be appropriate to include the information in the label. The sponsor replied that it will state in annotated labeling what is being relied upon.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

- Slides presented by Chiasma, Inc. at End-of-Phase 2 meeting
- Literature references provided by Chiasma, Inc. in support of Nonclinical Question #9
    - Chamanza et al. *Toxicol Pathol* 2010 38:642-657
    - Ito et al. *Exp. Anim.* 1992 41(4):455-469

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/s/

JENNIFER L JOHNSON
09/08/2011