CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208232Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208232
Priority or Standard	Standard
Submit Date(s)	12/26/2019
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PDUFA Goal Date	06/26/2020
Division/Office	DGE/OCHEN
Reviewer Name(s)	Sonia Doi, MD, PhD
Review Completion Date	06/08/2020
Established/Proper Name	Octreotide acetate
(Proposed) Trade Name	MYCAPSSA
Applicant	Chiasma
Dosage Form(s)	Oral (capsules) 20 mg/capsule
Applicant Proposed Dosing Regimen(s)	Initial dose of (b) (4) mg/day (b) (4) to a maximum of 80 mg/day
Applicant Proposed Indication(s)/Population(s)	Long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with (b) (4) (b) (4)
Recommendation on Regulatory Action	Approval pending labeling agreement
Recommended Indication(s)/Population(s) (if applicable)	Long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with (b) (4) (b) (4)

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Glossary

AC	advisory committee
AE	adverse event
API	Active Pharmaceutical Ingredient
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRL	Complete Response Letter
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DPC	double-blind placebo controlled
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GH	growth hormone
GI	gastrointestinal
GRMP	good review management practice
ICH	International Council for Harmonization
IGF-1	Insulin-like growth factor-1
IND	Investigational New Drug Application
IR	Information Request

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
QTcF	Fridericia's formula-corrected QT interval
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	System Organ Class
SRL	Somatostatin receptor ligand
SSA	Somatostatin analog
SUSAR	Suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
VAI	Voluntary action indicated

1. Executive Summary

1.1. Product Introduction

Oral octreotide, also referred to as octreotide capsules and Octreolin (trade name Mycapssa), is a long-acting acetate salt of a cyclic octapeptide (octreotide) with pharmacologic properties mimicking those of the natural somatostatin.

The proposed indication is for long-term maintenance treatment of patients with acromegaly who responded to and tolerated treatment with (b) (4)
The Applicant's proposed dosing regimen of oral octreotide is an initial dose of (b) (4) mg/day (b) (4) orally, at least 1 hour before a meal or at least 2 hours after a meal. The doses may be individually (b) (4) or titrated up to a maximum of 80 mg/day (each capsule contains 20 mg of active ingredient).

This application is a re-submission of the original NDA 208232 (submitted 12 June 2015) to address two critical deficiencies listed in the Complete Response Letter (CRL) issued on 15 April 2016. Deficiency number 1 in the CRL was related to Active Pharmaceutical Ingredient (API) manufacturing and deficiency number 2 was related to the clinical program. To address the clinical program deficiency, The Applicant (Chiasma) conducted a new clinical efficacy and safety study, Study OOC-ACM-303, which will be the focus of this clinical review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study OOC-ACM-303 provided substantial evidence of effectiveness of oral octreotide for long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with (b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Acromegaly is a rare disease caused by excess secretion of growth hormone (GH) mostly from pituitary adenoma, which leads to increased production of insulin-like growth factor-1 (IGF-1) from the liver and systemic tissues. The chronic and persistent excess production of GH and IGF-1 leads to acral overgrowth, multiple comorbidities, and premature death mainly due to cardiovascular complications. Guidelines recommend somatostatin receptor ligands (SRLs), also referred to as somatostatin analogs (SSAs) as the first line pharmacotherapy. The currently approved SSAs are only available in injectable formulations.

The Applicant (Chiasma) proposes an oral formulation of octreotide (Mycapssa) for the indication of long-term maintenance treatment of patients with acromegaly who responded to and tolerated treatment with (b) (4) Chiasma conducted a randomized, double-blind, placebo controlled trial (OOC-ACM-303) to provide substantial evidence of effectiveness of the drug in the proposed indication and to demonstrate safety of the drug. The primary efficacy endpoint was the proportion of responders, defined by maintenance of biochemical control at the end of the double-blind, placebo-control (DPC) period in the oral octreotide group *vs*. the placebo group. Biochemical control was defined as IGF-1 ≤ 1 x upper limit of normal (ULN). The study met the primary endpoint: results of the efficacy analysis demonstrated a statistically significant (p=0.008) greater proportion of responders in the group treated with oral octreotide (58%) *vs*. placebo group (19%). Results of the secondary endpoint assessing the proportion of patients who maintained GH response defined as GH < 2.5 ng/mL at the end of DPC period was supportive (78% in the oral octreotide group *vs*. 28% in the placebo group). The observed rate of response based on the normalization of IGF-1 or decrease in GH-levels to less than 2.5 ng/mL is consistent with the response during the treatment with other SSAs.

Safety of oral octreotide was consistent with the known safety profile of approved octreotide acetate. No new or unexpected risks were identified in the review of this NDA. The most frequent clinically relevant adverse events reported in the oral octreotide group during the DPC period of Study OOC-ACM-303 included gastrointestinal disorders (predominantly diarrhea and nausea) in 68% of patients, blood glucose increase in 11% of patients, and cholelithiasis in 7.1% of patients. No PMRs/PMCs are required for this NDA.

Overall, the benefit-risk assessment of oral octreotide (Mycapssa) is favorable in intended population.
Based on the completed clinical assessment of NDA 208232, this Medical Officer recommends approval of the NDA for oral octreotide for the proposed indication with modifications of the proposed labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acromegaly is a rare disease caused by excess secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). • In most patients (>95%), the etiology of acromegaly is due to pituitary adenoma. • The chronic and persistent excess production of GH and IGF-1 leads to acral overgrowth (typical of acromegaly) causing physical deformities and multiple comorbidities (e.g., hypertension, diabetes mellitus, dyslipidemia, hypertrophic cardiomyopathy). • If left untreated, acromegaly has a poor prognosis due to serious complications of pituitary tumor growth and comorbidities due to the elevated GH and IGF-1.	Acromegaly is a rare disease that if left untreated may cause serious complications, including premature death.
Current Treatment Options	• Transsphenoidal surgery is the primary line of treatment, followed by pharmacotherapy for patients with post-surgery persistent disease or for whom surgical treatment is not an option, and radiation therapy in patients with residual tumor following surgery, for which medical therapy is not available, unsuccessful, or not tolerated. • Remission of disease after transsphenoidal surgery is estimated in 50% due to incomplete resection of tumor (macroadenomas). • The current pharmacotherapy includes somatostatin receptor ligands (SRLs), also referred to as somatostatin analogs (SSAs), GH receptor antagonist (pegvisomant), and dopamine agonists (bromocriptine, cabergoline). • The current first line pharmacotherapy recommended is SRLs, followed by pegvisomant and dopamine agonists, which are recommended only for mild forms of disease.	The currently approved SRLs are injectable formulations and require a healthcare professional for administration, which may be a burden for some patients. In addition, patients may develop injection site reactions. An oral formulation of SRL may represent a convenient option for some patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• SRLs are currently only available in injection formulations (deep subcutaneous or intramuscular).	
Benefit	• Efficacy results in Study OOC-ACM-303 showed 53% responders in the oral octreotide group *versus* 19% responders in the placebo at the end of the 36-week double-blind placebo controlled period. Response rate based on maintenance of mean GH <2.5 ng/mL from baseline to the end of the study (78%) measured as a secondary endpoint is supportive.	The analysis of the primary efficacy endpoints is consistent with demonstration of benefit of oral octreotide for maintenance of acromegaly biochemical control
Risk and Risk Management	• The results derived from studies included in this NDA (Study OOC-ACM-303, Study CH-ACM-01, and reports of death from the ongoing Study OOC-ACM-302) provided sufficient information to support safety of oral octreotide in the intended population . • No new or unexpected safety signals were identified in the safety database of oral octreotide reviewed in this NDA re-submission. • No deaths were reported during study OOC-ACM-303; 2 deaths occurred in Study OOC-ACM-302 and 2 deaths were previously reported in Study CH-ACM-01. There were no deaths related to study drug.	The safety profile of oral octreotide is consistent with the known safety profile of octreotide acetate (injectable) and include gastrointestinal, gallbladder-related AEs, glucose abnormalities, TSH abnormalities, cardiac abnormalities. Given the favorable safety profile of this drug, risk evaluation and mitigation strategies (REMS) are not required. Safety signals will be sufficiently communicated in the labeling.

2. Therapeutic Context

2.1. Analysis of Condition

Acromegaly is a rare disease (current estimated annual incidence = 0.2 to 1.1 cases/100,000 people)[1] caused by excess secretion of growth hormone (GH), which leads to increased production of insulin-like growth factor-1 (IGF-1) from the liver and systemic tissues. Etiology of acromegaly is attributed to GH-secreting pituitary adenoma in more than 95% of the cases[2]. The chronic and persistent excess production of GH and IGF-1 leads to acral overgrowth (typical of acromegaly) and physical deformities, multiple comorbidities (*e.g.*, hypertension, diabetes mellitus, dyslipidemia, hypertrophic cardiomyopathy), and premature death mainly due to cardiovascular complications. Neurological symptoms and visual disturbances may occur due to suprasellar and parasellar expansion of the pituitary adenoma. Common symptoms are not specific of acromegaly and include fatigue and weakness, excessive perspiration, joint pain and edema due to musculoskeletal changes and arthropathy, sleep apnea and excessive snoring due to macroglossia, and headache[2,3]. For diagnosis of acromegaly, the Endocrine Society guidelines recommend using measurement of serum IGF-1 and a confirmatory GH-suppression test (oral glucose load) in patients with elevated or equivocal IGF-1 results[4].

2.2. Analysis of Current Treatment Options

The current primary therapy for acromegaly recommended by the Endocrine Society[4] is transsphenoidal surgery, followed by pharmacotherapy for patients with post-surgery persistent disease or for whom surgical treatment is not an option, and radiation therapy in patients with residual tumor following surgery, for which medical therapy is not available, unsuccessful, or not tolerated. The current pharmacotherapy available includes somatostatin receptor ligands (SRLs), also referred to as somatostatin analogs (SSAs), GH receptor antagonist (pegvisomant), and dopamine agonists (bromocriptine), which are only recommended for mild forms of disease[4,5].

There are three long-acting injection formulations of SRLs currently approved for treatment of acromegaly [octreotide (Sandostatin), lanreotide (Somatuline) and pasireotide (Signifor)], and one immediate-acting subcutaneous injection formulation of octreotide. The reported response rate to SRLs varies in clinical trials and depends on multiple factors including the definition of the response (based on IGF-1 alone, GH or GH and IGF-1), levels of GH considered to be normal (< 1, < 2.5 or < 5 ng/mL), tumor characteristics, assay used, etc. Proportion of patients with normalization of IGF-1 levels in clinical trials described in the labels of the approved long-acting SRLs varies from 39% to 67%.

The Endocrine Society recommendation for therapeutic goal in acromegaly is to achieve biochemical control determined by normalization of serum IGF-1, *i.e.*, IGF-1 ≤1 x upper limit of normal (ULN), adjusted for age and gender and serum GH < 1 ng/mL in a random sample[4,5]. Serum IGF-1 reflects an integrated GH secretion and is considered the biochemical marker of acromegaly used for diagnosis and monitoring of treatment. Goals of treatment include biochemical normalization, reduction of mortality risk, attenuation of symptoms, control of tumor mass, and maintenance of pituitary function. However, there is lack of consensus for target GH and IGF-1 levels that correlate with prevention of comorbidities or reversal of mortality risk. IGF-1 levels correlate with comorbidities better than glucose suppressed GH tests[4].

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NDA 208232 was originally submitted on 12 June 2015 and a Complete Response Letter (CRL) was issued on 15 April 2016 at the completion of the review process. The clinical deficiency listed in the CRL issued to the NDA was lack of data to provide substantial evidence of oral octreotide effectiveness in the intended population (See discussion under Section 3.2 of this review), which resulted in the not approval of the product for marketing in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

NDA 208232 was first submitted for review on 06/12/2015, and the application received a Complete Response Letter on 04/15/2016 due to identification of the following 2 deficiencies:

1. Manufacturing deficiency: During an inspection of (b) (4) our field investigator identified deficiencies that required resolution before evaluation of the application for approval.
2. Clinical deficiency: The data in the application did not provide substantial evidence of oral octreotide effectiveness in the intended population. The estimate of efficacy derived from study CH-ACAM-01 does not distinguish the effect of oral octreotide (Mycapssa) from other effects such as inactive disease at the endpoint visit due to the cumulative effect of past therapies, or due to differences in the biological effect of individual tumors, or due to confounding from the residual effects of pre-trial therapy(ies) used to control disease activity. The presence of important biases in the estimate of efficacy derived from study CH-ACM-01 precluded a determination of whether oral octreotide had a clinically important effect on disease control and of the magnitude of the effect attributed to oral octreotide on the efficacy estimate in this study. Satisfactory resolution of this deficiency was required before the application was evaluated for approval.

An End-of-Review meeting was held on 06/08/2016 to discuss the deficiencies outlined in the CRL (Minutes issued on 07/19/2016).

On 09/23/2016 Chiasma requested a meeting to discuss a protocol intended to demonstrate patients that were responders in study CH-ACM-01 had active acromegaly disease and included an additional proposed Phase 3 study (modification of study OOC-ACM-302 that was ongoing to support registration of oral octreotide in Europe) to provide support for NDA approval by FDA. After a teleconference with the Applicant, a Meeting Minutes was issued on 01/06/2017 with the Agency's comments that in summary did not agree that the design of the proposed study OOC-ACM-302-4 addressed the deficiencies highlighted in the CRL.

On 10/31/2016, during a teleconference, Chiasma discussed the design of a randomized, double-blind, placebo-controlled study in patients controlled on SRL injections to resolve the clinical deficiency outlined in the CRL. The FDA provided feedback for the proposed study design and agreed that an Special Protocol Assessment (SPA) request with a full protocol and a statistical analysis plan (SAP) for review would be acceptable.

On 12/16/2016, Chiasma submitted a request for SPA to which a No Agreement Letter was issued. A second SPA request was submitted on 02/17/2017 to which a No Agreement Letter was issued. On 05/08/2017, the FDA granted a Type C meeting (WRO) and the Meeting Minutes was issued on 06/13/2017 with responses to questions regarding clarifications requested in the SPA No Agreement Letter.

SPA was submitted on 06/21/2017 with the protocol of Study OOC-ACM-303 (Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy and Safety of Octreotide Capsules in Patients who Previously Tolerated and Demonstrated Biochemical Control on Injectable SRLs Treatment). The protocol submitted for SPA included revisions discussed in previous meetings with the Agency. An SPA Agreement Letter was issued on 08/04/2017 with response to the Applicant's questions and additional comments summarized below:

- The Agency agreed with the proposed primary endpoint of proportion of patients who maintained an IGF-1 <1.0 x ULN at the end of DPC period (average of 2 IGF-1 values available between week 34 and week 36). We also agreed with the classification of patients as responders (IGF-1 <1 x ULN) and non-responders (IGF-1 ≥ 1 x ULN).
- The Agency agreed that the proposed protocol Version 5.0 and SAP Version 6.0 (reviewed on 08/03/2017) were acceptable.
- The Agency noted that the Applicant had modified the order of the secondary endpoints in protocol version 5.0 and SAP version 5.0, in which the change in GH became the first endpoint in the hierarchy. We strongly recommended enrollment of sufficient number of subjects with baseline GH <2.5 ng/mL in order to perform meaningful analyses of the secondary endpoints.

On 01/26/2018 the Applicant submitted a protocol amendment which was reviewed with no comments on the modifications proposed.

On 02/20/2018 the Applicant requested a meeting to seek clarification of data and information required in the NDA submission and Meeting Minutes (WRO) was issued 05/04/2018 with responses to questions and comments, as summarized below:

- The Agency did not agree that the (b) (4) (b) (4) (b) (4) be included in the Integrated Summary of Safety (ISS) of the NDA, presented separate. Also, data from the Core phase should be presented separately from the Extension phase for each study.
- The Agency accepted that the safety data from study OOC-ACM-302 be provided in blinded manner as part of the NDA, and we informed that the blinded data would be of limited utility in informing the safety profile of oral octreotide.
- The Agency requested that at the time of submission, Chiasma provided graphical visualization of the relationship between adverse events and treatment duration.

On 07/30/2019, Chiasma requested a Pre-NDA meeting which was held on 10/08/2019 and the Meeting Minutes were issued on 11/08/2019. The most relevant issues discussed and comments are summarized below:

- The Agency agreed that Study OOC-ACM-303 was designed, conducted and analyzed as agreed under SPA and was adequate to address the clinical deficiency listed in the CRL.
- The Agency reiterated that we did not agree that 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 and that we did not believe Study CH-ACM-01 is necessary to support resubmission. Chiasma asked for clarification as why Study CH-ACM-01 is not necessary to support resubmission. The Agency reiterated that deficiencies of Study CH-AACM-01 are outlined in the CRL and that the study results don't support the target population indication for disease control, which is IGF-1 ≤1 x ULN. FDA stated that Study DH-ACM-01 and Study OOC-ACM-303 had different population. Chiasma disagreed and stated that the patient baseline demographics in both studies are similar.
- Chiasma proposed a starting dose of (b) (4) (b) (4) We responded that the information ultimately included in the final US prescribing information is determined after review.
- The Agency requested the Applicant to analyze the responders by the previous SRLs dosing regimen required for the disease control during the screening period.
- The Agency noted that 5 patients in the placebo group who maintained their biochemical

response at end of the treatment period were transitioned to oral octreotide in the OLE phase due to active acromegaly symptoms. We asked Chiasma to clarify why these patients required treatment with active drug if their disease was biochemically controlled. (b) (4)

(b) (4)

- Chiasma agreed with the FDA request to include in NDA resubmission a sub-group analysis per dose level of prior SRL injection prior to treatment, as well as other sub-group analyses (i.e., gender, age, region).
- Answering to FDA request for clarification on primary endpoint and the second secondary endpoint in study OOC-ACM-303, Chiasma clarified that the primary endpoint defines a patient as non-responder when the average (week 34 and week 36) IGF-1 is >1.0 x ULN; and the second secondary endpoint was defined as having 2 consecutive IGF-1 values >1.0 x ULN after being treated for at least 2 weeks with 4 capsules per day.
- Chiasma was asked to clarify the results of the analysis of the secondary endpoint, median time to loss of response. Chiasma referred to a Kaplan-Meier curve presented during the meeting 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 oral octreotide arm since less than 50% of patients lost response. The Agency said 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 said that the mean would be helpful to know when patients dropped out. Chiasma said that in their view, the mean is biased estimand and proposed to submit both analyses. FDA also asked Chiasma 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 Chiasma agreed.
- FDA asked for clarification for 5 patients in the placebo group who maintained their biochemical response at end of the treatment and continued treatment with oral octreotide in the OLE phase. The Sponsor reiterated that three patients required further treatment due to persistence of loss of biochemical control during the study due to IGF-1 fluctuation but were responders by the meeting the primary endpoint at the end of the study. The other 2 out of 5 patients were symptomatic during the study and continued into the OLE study. 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.
- FDA agreed with Chiasma not providing BIMO dataset in the NDA resubmission for Study OOC-ACM-302, which was ongoing at the time of this meeting. FDA requested that Chiasma included in the NDA narratives for all deaths, serios adverse events, and adverse events leading to discontinuation. FDA reminded that 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.

- Chiasma asked about their [redacted] (b) (4) FDA responded that was premature to [redacted] (b) (4) FDA reminded the Sponsor that in general FDA considers data derived from well - controlled study(ies) 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), and that uncontrolled extension trials 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.
- The Sponsor was asked to include graphical visualization of relationship between adverse events and treatment duration.
- FDA asked Chiasma to clarify the results of the analysis of the secondary endpoint, median time to loss of response. Chiasma stated that median time to loss of response was not reached for patients treated with oral octreotide; however, 42% of patients on oral octreotide lost biochemical response at the end of DPC period. FDA found these results discordant. Chiasma defines median time to loss of response as "the earliest time when the IGF-1 of 2 consecutive visits was > 1 x ULN after the patients was treated for at least 2 weeks with 4 capsules per day". However, mot all patients were on 4 capsules per day in the fixed dose period (beyond week 24). Chiasma was asked to clarify whether these patients were included in the median time to loss of response analysis, and if so, what definition was applied to this patient cohort. Chiasma responded via email:

Chiasma requested 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 oral octreotide, and the median time to loss of response on oral octreotide has not been reached. Chiasma clarified that the prespecified analysis (protocol and SAP) was that cited by FDA in the request for clarification. Chiasma adds that only one patient was not treated with 4 capsules a day by week 24, was not rescued, and had 2 consecutive IGF-1 values > 1.0 x ULN before the end of the study. They inform that this patient was censored for this secondary endpoint per the SAP and that this patient was considered a non-responder for the primary endpoint analysis. Chiasma added that 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.

3.3. Foreign Regulatory Actions and Marketing History

Oral octreotide has not been approved on any foreign country up to the date of this review.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical Site Inspection

No clinical sites were selected for inspection to support the re-submission of NDA 208232. In the original NDA submission, three foreign clinical sites involved in the pivotal Study CH-ACM-01 and the Sponsor were inspected as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 208232. There were no significant inspectional findings. Two sites were classified NAI (No Action Indicated) and one site and the Sponsor were classified VAI (Voluntary Action Indicated).

To resolve the clinical deficiency listed in the CRL issued to NDA 208232, Chiasma conducted an additional pivotal Phase 3 trial (Study OOC-ACM-303), which was a relatively small study with a total of 56 patients enrolled on a 6-month core study duration. In this study, 34 study sites enrolled at least 1 patient and no more than 4 patients each. Of a total of 119 patients screened, 56 patients were randomized 1:1 to oral octreotide or placebo for the core treatment period. All 56 patients completed the core study and 40 patients enrolled in the extension open-label study.

The decision of no selecting clinical sites for inspection in Study OOC-ACM-303 was supported by the reasons outlined below and in concurrence with OSI:

1. There were no significant issues with sponsor trial implementation and oversight with the original application.
2. There were no relevant deviations in the new pivotal study (OOC-ACM-303) that would require a clinical site inspection.
3. The amount of data generated by the new pivotal study (OOC-ACM-303) is small, with no more than 4 patients enrolled per clinical site, and it is unlikely that any potential deviations at one site in this study would impact the final decision on data supporting approvability of the NDA.

4.2. Product Quality

In the original NDA submission, a CMC deficiency was listed in the CRL and was related to the compliance status of the contract manufacturer facility, (b) (4) where the octreotide acetate drug substance is manufactured. To resolve this deficiency, (b) (4) worked with FDA and Chiasma conducted its own risk assessment. The Applicant's response to the manufacturing deficiency was reviewed by the Office of Pharmaceutical Quality (OPQ) team and the deficiency was considered resolved. OPQ's recommendation for the NDA is approval

Please refer to the OPQ review dated 06/01/2020 for complete information.

4.3. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology data were submitted for review in this re-submission package.

4.4. Clinical Pharmacology

No new clinical pharmacology data were submitted for review in this re-submission package.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical development program included Study OOC-ACM-303 and Study CH-ACM-01 (Table 1).

Table 1: Clinical trials reviewed for assessment of efficacy and safety

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients	Duration	Dose, Route, and Regimen	Primary Endpoint
OOC-ACM-303 A Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL) treatment (DPC period completed; OLE ongoing and not part of ISE) IND 108163 Sequence 0057	Randomized, double-blind, placebo-controlled (DPC) followed by a voluntary open-label extension (OLE) phase	Acromegaly patients currently receiving parenteral somatostatin analogs, who are responders to treatment (IGF-1 ≤ 1 × ULN)	56	Randomized DPC phase – 9 months OLE – up to market availability or study termination	octreotide capsules, 40 mg/day (20 mg bid) up to 80 mg/day (40 mg bid)	The proportion of patients who maintain their biochemical response (average of last 2 IGF-1assessments) ≤ 1 × ULN at end of DPC period (9 months)
CH-ACM-01 Efficacy and safety of oral octreotide in patients with acromegaly who are currently receiving parenteral somatostatin analogs (Completed) NDA 208232 Sequence 0000 REVIEWED FOR SAFETY ONLY	Open-label, baseline-controlled study (core study) followed by a voluntary open-label extension (OLE) phase	Acromegaly patients currently receiving parenteral somatostatin analogs, who are responders to treatment (IGF-1 < 1.3 × ULN and GH < 2.5 ng/mL)	155	Core study – 7 months OLE – 6 months	octreotide capsules, 40 mg/day (20 mg bid) up to 80 mg/day (40 mg bid)	Proportion of responders (IGF-1 < 1.3 × ULN and GH < 2.5 ng/mL), at the End of the Core Treatment (7 months)

Source: Excerpted from the Clinical Overview file submitted in NDA 208232 resubmission package.

5.2. Review Strategy

Study OOC-ACM-303 was conducted to address a clinical deficiency listed in the CRL for the original NDA application. Thus, the primary focus of this review was evaluation of efficacy and safety data of the Phase 3 Study OOC-ACM-303. While the Applicant proposed to use Study CH-ACM-01 submitted in the original NDA to support this re-submission, the FDA did not agree that Study CH-ACM-01 provide substantial evidence of efficacy and safety of the drug in the intended population (See Meeting Minutes dated 11/08/2019). Results of Study CH-ACM-01 have been reviewed in the original NDA submission and will not be discussed under this re-submission review (for reference please see clinical review of original NDA submission by Dr. Smita Abraham dated 04/12/2016). Safety data of Study OOC-ACM-303 was also evaluated together with the safety data from Study CH-ACM-01 and follow-up Study CH-ACM-01-FU. Studies CH-ACM-01 and CH-ACM-01-FU have been discussed earlier in the original submission review and will not be discussed in detail in this current review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study OOC-ACM-303

6.1.1. Study Design

Overview and Objective

Study OOC-ACM-303 is a Phase 3 trial designed to address the clinical deficiency listed in the CRL, i.e., to provide substantial evidence that oral octreotide will have the effect it purports to have under the conditions of use recommended in labeling for patients with acromegaly in a new clinical trial. This study was conducted under Special Protocol Assessment (SPA) agreement (issued on 08/04/2017). See comments under Section 3.2.

The primary objectives of the study was to compare effect of the treatment with oral octreotide *vs*. placebo on maintenance of biochemical control attained by patients with acromegaly treated with SRLs prior to entering the study.

The secondary objectives of the study was to compare effect of the oral octreotide treatment vs. placebo on maintenance of biochemical control, based on GH measurements, and to evaluate the safety profile of oral octreotide compared to placebo.

Trial Design

Study OOC-ACM-303 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter

study design. This study consisted of a screening period, a double-blind placebo controlled (DPC) period (also referred to as Core phase), an open-label extension (OLE) period (also referred to as extension phase), and a follow-up period. This study was conducted under a special protocol assessment (SPA) agreement. See a diagram of the study design provided by the Applicant in Figure 1.

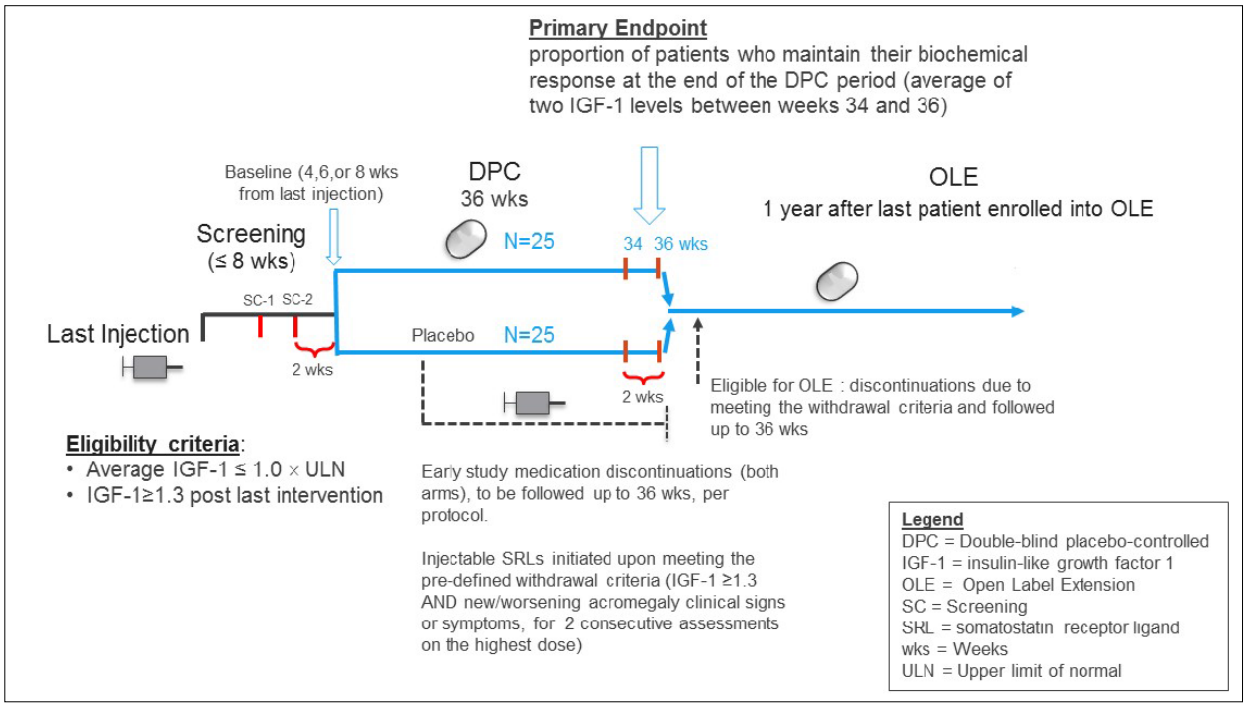

Figure 1: Diagram of Study Design
Source: Excerpted from CSR, Figure 1

Medical Officer comment: It is noted that the trial design figure presented by the Applicant (Figure 1 of the CSR) shows N=25 for the number of subjects in each arm, which in fact is 28 subjects per arm. Also, the eligibility criteria in the figure shows both average IGF-1 ≤ 1.0 x ULN and IGF-1≥ 1.3 post last intervention. This information in the figure is confusing and through the written explanation of the study design, it appears that the "IGF ≤ 1.0 x ULN" refers to the actual IGF-1 value for inclusion in the study and the "IGF-1≥ 1.3 post last intervention" refers to the IGF-1 documented value of acromegaly diagnosis (See Inclusion Criteria).

Study Population: Trial OOC-ACM-303 involved 60 study sites in 17 countries, and 34 sites enrolled at least one patient. A total of 21 (37.5%) patients were enrolled in US. The study population consisted of adults with active acromegaly, who at screening were receiving parenteral SRL monotherapy for at least 6 months and met both the inclusion and exclusion criteria.

Key Inclusion Criteria:

1. Adults with active acromegaly , defined as documented evidence of GH-secreting pituitary tumor based on MRI/pathology report and documented evidence of IGF-1 levels ≥1.3 x ULN, at least 3 months following pituitary surgery in those patients who had prior pituitary surgery.
2. Received parenteral SRL monotherapy (long-acting octreotide or lanreotide but not pasireotide) for at least 6 months with a stable dose for at least the last 3 months of therapy.
3. Average of plasma IGF-1 of 2 assessments obtained during the Screening period is ≤1 x ULN.

Key Exclusion Criteria:

1. Patients taking injections of long-acting SRLs off label.
2. Patients who previously participated in CH-ACM-01 or OOC-ACM-302.
3. Symptomatic cholelithiasis.
4. Conventional or stereotactic radiotherapy any time in the past.
5. High-risk pattern of pituitary tumor location on pituitary MRI/CT as per medical history or most recent MRI/CT.
6. Treatment with pegvisomant within 24 weeks before the screening visit
7. Treatment with dopamine agonists within 21 weeks before the screening visit
8. Treatment with pasireotide within 24 weeks before the screening visit.

Key Eligibility Criteria for the OLE:

1. Patients complying with any one of the following criteria:
    a. Completed the full 36-week duration of the DPC period on study medication.
    b. Met the predefined withdrawal criteria during the DPC period and completed follow-up per protocol through week 36 of DPC period.
2. Patient not currently having study medication withheld for a study medication-related AE
3. Patient not having a clinically significant or unstable medical or surgical condition detected or worsening during the study, which could preclude safe participation and completion of the OLE period.
4. Patient preference to continue treatment with octreotide capsules.

Dose Selection and Dose Escalation Criteria:

Dose selection for Study OOC-ACM-303 followed that used in Study CH-ACM-01. The starting dose of 40 mg/day was expected to yield serum levels of octreotide similar to that of 0.1 mg of octreotide subcutaneous (sc) injection administered three times daily (tid). The highest dose of 80 mg/day was chosen based on toxicology data and was expected to be safe and well tolerated.

In Study OOC-ACM-303, dose escalation was allowed any time through and including week 24. All patients were started on 40 mg/day (2 capsules of 20 mg in the morning) and escalated to

60 mg (40 mg in the morning and 20 mg in the evening), and to 80 mg (40 mg bid) at the discretion of the study Investigator, who could use the Sponsor's recommended guiding rules. The Sponsor recommended any one of the following guiding rules for dose escalation:

- Significantly increased IGF-1 levels compared to Baseline defined as IGF-1 increase by at least 30% to > 1 × ULN.
- IGF-1 levels > 1 × ULN for 2 consecutive visits.
- New or worsening of any one of the following acromegaly signs/symptoms: headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia, or hypertension, or other signs that in view of the Investigator are related to acromegaly.

Study Endpoints

Primary Efficacy Endpoint: The primary efficacy endpoint was assessed by the proportion of patients who maintain their biochemical response at the end of the DPC period.
Response was defined as an average of two IGF-1 measurements performed on week 34 and week 36. All patients had two IGF-1 measurements at the end of the DPC period. Patients with average IGF-1 ≤1xULN were considered as responders. Patients who discontinued study drug prior to Week 34 for any reason were considered as non-responders.

Secondary Efficacy Endpoints: The secondary efficacy endpoints were assessed by:

- Proportion of patients who maintained GH response (*i.e.*, GH <2.5 ng/mL) at week 36, out of those who were responders (*i.e.*, GH <2.5 ng/mL) on SRL injection at screening. GH response was defined using the mean integrated GH value, based on 5 assessments 30 minutes apart. Patients who discontinued treatment during the DPC period for any reason were classified as non-responders, regardless of their IGF-1 values.
- Time to loss of response: Loss of response was defined as the earliest time when the IGF-1 of 2 consecutive visits was >1xULN after the patient was treated for at least 2 weeks with 4 capsules per day (*i.e.*, 80 mg/day).
- Time to loss of response: Loss of response was defined as the earliest time when the IGF-1 of 2 consecutive visits was >1.3xULN after the patient was treated for at least 2 weeks with 4 capsules per day (*i.e.*, 80 mg/day).
- Proportion of patients who began rescue treatment prior to and including week 36.

The Applicant also included a series of descriptive endpoints and exploratory endpoints, which will not be discussed in this review (for discussion on these endpoints refer to Statistical Review by Dr. Ketterman):

Descriptive Efficacy Endpoints – IGF-1 Levels

- Change from baseline to end of DPC period in IGF-1 (treatment policy estimand)
- Change from baseline to end of treatment in IGF-1 – Exploratory Analysis

Descriptive Efficacy Endpoints – GH Levels

- Change from baseline to end of treatment in growth hormone levels (Treatment Policy Estimand)
- Change from baseline to end of treatment in growth hormone levels – Exploratory Analysis

Exploratory Efficacy Assessments

- Time to loss of biochemical control in the DPC period – Predefined Analysis
- Proportion of patients who were biochemically controlled at the end of the DPC period – Predefined Analysis
- Shift in IGF-1 and GH response categories from baseline of the DPC period to end of treatment in the DPC period – Descriptive Analysis
- IGF-1 change from baseline to end of study in patients rescued – Descriptive Analysis
- Maintenance of response from end of dose titration to end of treatment – Descriptive Analysis
- Response by prior dose of SRL – Post-Hoc Analysis
- Categorical IGF-1 and mean integrated growth hormone suppression at the end of the DPC period – Descriptive Analysis
- Proportion of patients continuing into the OLE – Descriptive Analysis

Statistical Analysis Plan

As described above, SAP was agreed upon SPA (See comments under Section 3.2 of this review).

Protocol Amendments

Study OOC-ACM-303 was initiated with Protocol Version 4 (dated 24 April 2017), which was amended to Protocol Version 5 on 3 August 2017 and subsequently amended to Protocol Version 6 on 29 November 2017.

Country-specific protocol amendments were issued for Canada, Denmark and Sweden and the specific changes are summarized below by country:

- Canada: Clarification of exclusion criterion #7 and addition of 2 safety laboratory assessments (amylase and lipase) in response to specific requests by the Health Canada
- Denmark: Established a set duration of 48-week participation for subjects enrolled in OLE.
- Sweden: Changes were made as per request of the Swedish Medical Products Agency. The Benefit/Risk Assessment initially provided as a standalone document is provided an integral part of the Swedish country-specific protocol addendum. The text under Blinding and Unblinding was modified to add an emergency unblinding option id the IWRS system is not in function. The text under Notification of serious unexpected suspected adverse event was modified to add information concerning Suspected Unexpected Serious Adverse Reaction

(SUSAR) reporting. Text was modified under Retention of Essential Documents to add the Swedish regulatory requirements for retention of essential documents.

Protocol Amendment 1 (Protocol Version 5) changed the order of the secondary objectives and secondary efficacy endpoints; added an exploratory endpoint (i.e., proportion of patients who require rescue medication); and modified the definition of the full analysis set (FAS), from (b) (4) (b) (4) to "all randomized patients".

Protocol Amendment 2 (Protocol Version 6) removed the following (b) (4) (b) (4) (b) (4) added the following secondary endpoint "proportion of patients who begin rescue treatment prior to and including week 36"; recategorized 2 of the endpoints from (b) (4) to descriptive endpoints; removed the following (b) (4) modified the statistical methods for the secondary efficacy analyses; and added statistical methods for the descriptive endpoint analyses. These modifications were agreed to by FDA through a modification of the SPA on 11 May 2018.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study in this NDA was conducted in accordance with the following guidelines:

- ICH-GCP: Consolidated Guideline (International Council for Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, November 2016)
- Declaration of Helsinki: Brazil, 2013
- US Code of Federal Regulations (CFR) Title 21, and/or European Union (EU) Directives; and local country regulations and guidelines.

Financial Disclosure

(b) (6)

Patient Disposition

Out of 119 patients screened, 63 patients (53%) were classified as screen failure. The main reason for screen failure (53 of the 63 patients) was 'not meeting the eligibility criteria'. A total of 56 patients were randomized to either oral octreotide or placebo and all patients completed the 36-week DPC period. Out of the 56 randomized patients, 26 patients (7 randomized to oral octreotide group and 19 randomized to placebo group) discontinued study treatment and were followed up to the end of the DPC period. The Investigator was to discontinue study drug at patient request or if it was determined that continuing study drug would result in a significant safety risk for the patient. The most frequent reason for discontinuation was treatment failure, which included patients who did not meet the pre-defined withdrawal criteria. The second reason was adverse event, in much lower proportion compared with treatment failure.

Pre-defined withdrawal criteria: IGF-1 ≥1.3 x ULN for 2 consecutive assessments while treated for at least 2 weeks with study drug 4 capsules/day (placebo or 80 mg oral octreotide) during the DPC period and exacerbation of acromegaly clinical signs or symptoms defined as headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia, hypertension or other signs assessed by the Investigator as related to acromegaly and recorded as adverse events of special interest (AESIs). New or worsening acromegaly clinical signs or symptoms could be treated while the patient remained in the study as per Investigator's discretion.

Per protocol, all patients meeting the pre-defined withdrawal criteria were to receive rescue medication, *i.e.*, injectable SRL used prior to screening and continued to be followed per protocol until week 36 of DPC period. However, all patients who discontinue study drug received rescue medication regardless of meeting withdrawal criteria. Of the 5 patients on oral octreotide who discontinued treatment due to treatment failure, 2 patients did not meet the withdrawal criteria but received rescue medication. All 18 patients in the placebo group who discontinued study drug due to treatment failure met the withdrawal criteria. Three patients discontinued due to adverse events (2 in the oral octreotide group and 1 in the placebo group) and received rescue medication. Discussion of patients who discontinued study drug due to AE is located in Section 8.4.3 of this review. A summary of individual study drug discontinuation in both treatment arms, with oral octreotide group sub-divided in dosing groups is shown in Table 2.

Table 2: Study drug discontinuation rate and reason for discontinuation for randomized patients during the DPC period.

Discontinuation rate	Oral octreotide			Placebo
	40 mg (N=7)	60 mg (N=2)	80 mg (N=19)	(N=28)
Discontinued study drug/completed DPC	1 (14 %)	0	6 (32 %)	19 (68 %)
Reasons for Discontinuation				
Treatment failure	**0**	**0**	**5 (26 %)**	**18 (64 %)**
Met withdrawal criteria	0	0	3 (11 %)	18 (64 %)
Did not meet withdrawal criteria	0	0	2 (10.5%)	0
IGF-1 >1xULN and <1.3xULN, with acromegaly symptoms exacerbation	0	0	1 (5 %)	0
IGF-1 ≥ 1.3 ULN, no symptoms	0	0	1 (5 %)	0
Adverse Event	**1 (14 %)**	**0**	**1 (5 %)**	**1 (4 %)**

Source: Table generated by the Clinical Reviewer with data obtained from the CSR.

***Medical Officer comment**: It is noted that there was no defined criteria for rescue medication. While all patients who met the withdrawal criteria were to be rescued, patients who were considered treatment failure and did not meet the withdrawal criteria also received rescue medication.*

OLE Period

Data from OLE study were not included in the efficacy analyses of the NDA and safety results were analyzed in the integrated safety summary.

The pre-defined inclusion criteria for OLE period were:

1. Patients who complied with either of the following criteria
    a. Completed the 36-week DPC period on study medication (placebo or oral octreotide)
    b. Met the pre-defined withdrawal criteria during DPC period and completed follow-up through the week 36 of DPC period.
2. Patient not having study medication withheld due to study medication-related AE
3. Patient not having a clinically significant or unstable medical or surgical condition (new or worsening) during the DPC, which would preclude safe participation in the OLE period.
4. Patient preference to continue treatment with oral octreotide

Patients who discontinued the study but did not meet the withdrawal criteria and patients who experienced AEs (2 patients on oral octreotide and 1 on placebo) were not eligible to enter the OLE period (See Table 3).

Table 3: Transition of patients from DPC period to OLE period.

OLE PERIOD	Oral octreotide	Placebo	Total
Subjects who did not qualify to participate in OLE	4/28	1/28	5
Subjects eligible to enter OLE period	24/28	27/28	51/56
Subjects who opted not to participate in OLE	4/24	7/27	11
Eligible patients who entered OLE period	20/24	20/27	40

Source: Table generated by the Clinical Reviewer with data obtained from the CSR.

Protocol Violations/Deviations

There was a report of protocol deviation for randomization error and undo in Medidata Electronic Data Capture (EDC) system at Investigator site number (b) (6) The form describes that Subject (b) (6) was randomized in error in EDC and should have been noted as a screen failure due to meeting an exclusion criterion for the study. The Sponsor, PI and patient remained blinded to the erroneous randomization. The randomization was taken by the next patient randomized. The study biostatisticians reviewed and confirmed that this error does not affect the study randomization scheme. The error happened because after completing the screening procedures the patient was approved for enrolment, the baseline visit was scheduled and the patient was randomized. However, the patient mistakenly had his Sandostatin LAR injection the day before the baseline visit and could not be enrolled in the study at the time. The patient was re-screened as patient number (b) (6) but did not meet the criteria for IGF-1 and was not enrolled. Kit numbers were allocated by the interactive web/voice response system (IWRS) but no drug was ever dispensed to this patient.
Corrective action: Medidata programmers reversed the randomization in the EDC system, undid the kit allocation and released the kits to become available again.

Table of Demographic Characteristics

The demographic data and baseline characteristics for the DPC period were balanced between the oral octreotide and placebo groups (See Demographics Table in Appendix 13.3). The majority of the study population was in the race category of White/Caucasians (91.1%) and in the ethnicity category of Not Hispanic or Latino (94.6%). The mean age of patients was similar between the oral octreotide group (55.3 years) and the placebo group (54.2 years) with a total of 13 patients (23.2%) at age ≥ 65 years.

The only demographic parameter that does not appear to be well balanced is the number of patients enrolled by region. Of the 56 patients enrolled in the DPC period, 21 (37.5%) patients were from US sites and 35 (62.5%) were from non-US sites. The number of patients randomized to each treatment group per region was also imbalanced, *e.g.*, the number of patients randomized to oral octreotide was 6 in the US sub-population *vs.* 22 in the non-US sub-

population (See Table 4). The effect of this difference in number of patients exposed to oral octreotide in the US *vs.* non-US region is discussed in the sub-group analysis for efficacy (Section 7.1.1 of this review) and safety (Section 8.5 of this review).

Table 4: Number (%) of patients on each treatment arm per region.

	Oral octreotide (N=28)	Placebo (N=28)	Total (N=56)
US	6 (21.4%)	15 (53.6%)	21 (37.5%)
Non-US	22 (78.6%)	13 (46.4%)	35 (62.5%)

Source: Table generated with data reported in CSR.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant presented an additional table with a summary of acromegaly baseline characteristics for the DPC period which includes: duration of acromegaly, tumor size at diagnosis, previous treatments for acromegaly, prior acromegaly surgery, time from last surgery, residual tumor size, symptom burden, baseline average IGF-1 (ULN), baseline average IGF-1 (categorical), baseline GH (ng/mL), and baseline GH (categorical) for each treatment group. The most frequent SRL used prior to entering the study was octreotide long acting followed by lanreotide, and the proportion of patients using these medications was similar between oral octreotide and placebo treatment groups. A copy of the table of acromegaly baseline characteristics submitted by the Applicant is placed in Appendix 13.4 of this review.

Numerical imbalances between treatment groups are noted in the following categories:

- Duration of acromegaly: There were more patients with acromegaly duration >10 years in the placebo group (20 patients, 71.4%) than in the oral octreotide group (15 patients, 53.6%). However, acromegaly has a slow and insidious onset, and symptoms are generally non-specific leading to inaccurate data on the actual duration of the disease. Therefore, the small difference in disease duration found in this trial is unlikely to affect the results and conclusion of the study.
- Type of treatment prior to trial: A small numerical imbalance was found with patients using Cabergoline (7 patients in oral octreotide *vs*. 3 patients in placebo) and SRLs plus dopamine agonists (4 patients in oral octreotide *vs*. 1 patient in placebo). However, due to the small number of patients in these sub-categories, it is unlikely that these imbalances can influence the results of this trial.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance: Compliance assessment relied on capsule count on each in-person visit and revealed that most of the patients complied with the study drug regimen. The overall mean compliance was similar between the oral octreotide group and the placebo group (98.2% and 96.9%, respectively) and compliance is unlikely to have played a role in the study results.

Concomitant Medications: Nearly all patients were taking at least 1 concomitant medication while in the DPC period, and the most frequent medications in both groups were non-steroid anti-inflammatory and antirheumatic products (43% of the patients in the oral octreotide group and 39% of the patients in the placebo group). In the listed concomitant medications, the highest difference between the treatment groups was in the drug classes of systemic corticosteroid and lipid lowering agents, showing 2-fold more patients in the oral octreotide group *vs*. placebo group for both drug classes.

Rescue Medication: All patients who discontinued study drug during the DPC period received rescue medication*, i.e.*, the injectable SRL used prior to entering the trial. The proportion of patients who were rescued during DPC was 7 patients (25%) in the oral octreotide group and 19 patients (67.9%) in the placebo group. See Section 6.1.2 of this review for discussion on patient disposition and rescue.

Medical Officer comment: This finding raises no concerns since no drug interaction has been found between octreotide and drugs in these two drug classes[a].

Efficacy Results

This section will present a summary of efficacy results and discussion. Please refer to the Statistical Review performed by Dr. Anna Ketterman, dated 06/01/2020 for complete information on efficacy results.

ANALYSIS OF PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint was the proportion of patients who maintained their biochemical response at the end of the DPC period, defined by the average IGF-1 level of the last 2 available assessments between weeks 34 and 36 in the DPC period. The patients were categorized in relation to the IGF-1 threshold of 1.0 x ULN into:

- Responder: patient with average IGF-1 ≤1 x ULN between week 34 and 36
- Non-responder: patient with average IGF-1 >1 x ULN; patients who discontinued study drug in the DPC period (regardless of their IGF-1 values and the reason for discontinuation).

An IR was sent by FDA (4/2/2020) requesting information regarding timing for IGF-1 collection at each monthly visit and at the end of study visit (for evaluation of primary endpoint) during DPC period. We were particularly interested in whether blood samples for IGF-1 measurement were collected before or after morning or evening dose administration. Chiasma responded that the times of IGF-1 collection in relation to study drug administration was not stipulated in the protocol of Study OOC-ACM-303. The Applicant clarified that for the baseline visit, sample

[a] (*https://www.drugs.com/interactions-check.php?drug_list=1739-0,1929-0*)

for IGF-1 assessment was collected at the site prior to or at drug administration. For IGF-1 assessment at week 36 visit, in 13 of 14 patients receiving oral octreotide the IGF-1 sample was collected approximately 2 hours after study drug administration and in 1 patient sample was collected 4 hours after drug administration. The Applicant's rationale for not stipulating time for IGF-1 sample collection was that the recommendations of the Consensus Guidelines do not specify the timing for IGF-1 collection relative to drug administration.

All patients completed the study and there were no missing data. The Applicant's reported proportion of patients who met the primary efficacy endpoint was 58.2% (16/28 patients) in the oral octreotide group and 19.4% (5/28 patients) in the placebo group. The difference between the two groups was statistically significant (p=0.008) with an odds ratio of 5.77 in favor of the group treated with oral octreotide (See Table 5).

Table 5: Proportion of patients who maintained their biochemical response at the end of the DPC period.

	Octreotide Capsule Treatment Group (Final Dose in DPC Period)				
Parameter	**40 mg (N = 7)**	**60 mg (N = 2)**	**80 mg (N = 19)**	**Total (N = 28)**	**Placebo (N = 28)**
Unadjusted proportions					
Responder	5 (71.4)	1 (50.0)	10 (52.6)	16 (57.1)	5 (17.9)
Non-responder	2 (28.6)	1 (50.0)	9 (47.4)	12 (42.9)	23 (82.1)
Observed	1 (14.3)	1 (50.0)	3 (15.8)	5 (17.9)	4 (14.3)
Early withdrawal [1]	1 (14.3)		6 (31.6)	7 (25.0)	19 (67.9)
Adjusted proportions [2]					
Responder				58.16	19.42
Non-responder				41.84	80.58
Difference in adjusted proportions [2]				38.74	
95% CI				(10.68, 59.90)	
P-value				0.0079	
Odds ratio (octreotide/placebo) [2]				5.7674	
95% CI				(1.4440, 28.2115)	

Note: Maintaining biochemical response was defined as having average IGF-1 (between weeks 34 and 36) ≤ 1 times the ULN.
[1] Patients who discontinued study drug during the DPC period for any reason were classified as non-responders.
[2] Adjusted proportions and odds ratios were obtained from an exact logistic regression model including covariates for treatment group, baseline SRL dose (low versus medium or high) and baseline IGF-1 level (< median, ≥ median). CI for difference in adjusted proportions used Newcombe method.
CI = confidence interval; DPC = double-blind, placebo-controlled
Source: excerpted from CSR, Table 14.

The reported proportion of patients in the oral octreotide who achieved normalized IGF-1 (*i.e.*, IGF-1 ≤1.0 x ULN) at the end-of-treatment was similar to those reported in clinical trials of approved long-acting release SSAs. While results of different trials cannot be used for comparison of efficacy, the following proportions of patients with normalized IGF-1 in clinical trials were extracted from approved long-acting SSA labels for reference:

- Octreotide LAR: average of monthly levels over the course of the trial 51% (27-28 injections) and 67% (12 injections).
- Lanreotide: 58% (52 week-study)
- Pasireotide: 38.6% (12-month study, naïve patients).

The endpoint analysis performed by the Statistical Reviewer (Dr. Anna Ketterman; refer to her review for details) revealed that the Applicant used rounded values of IGF-1 leading to inclusion of patients with IGF-1 values above 1.0 x ULN in the study population and, thus, considered some patients with IGF-1 average slightly above 1.0 x ULN as responders. An Information Request was sent to Chiasma on 4/17/2020 regarding the inclusion of patients with average IGF-1 >1.0 x ULN in the randomized population and in the group of patients classified as responders. Chiasma responded that the calculation of IGF-1 average values was performed as pre-specified in Section 6.1 of the Statistical Analysis Plan (SAP), which the FDA approved, and it states: "No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider digit to right of last significant digit: if < 5, then round down; if ≥ 5, then round up". This Medical Officer has confirmed that Chiasma's information on the rounding rule included in SAP is accurate. This Medical Officer has also recalculated the average IGF-1 values applying the SAP rule for rounding numbers, as shown in Table 6 for screening values and in Table 7 for the last two weeks of DPC period and concluded that the average values as presented by Chiasma are accurate.

Table 6: Serum IGF-1 values of responders on oral octreotide at screening visits and average of screening values.

Patient ID	Oral octreotide Dose (mg/day)	Serum IGF-1 values			
		Screening 1	Screening 2	Average screening	Rounded Average
(b) (6)	40	0.399	0.535	0.467	0.5
	40	0.42	0.657	0.539	0.5
	40	0.604	0.574	0.589	0.6
	40	0.558	0.759	0.659	0.7
	40	0.847	0.841	0.844	0.8
	60	0.777	0.875	0.826	0.8
	80	0.866	0.907	0.887	0.9
	80	1.005	1.077	1.041	1.0
	80	0.691	0.76	0.726	0.7
	80	0.896	0.805	0.851	0.9
	80	0.84	1.027	0.934	0.9
	80	0.762	0.767	0.765	0.8
	80	0.959	0.831	0.895	0.9
	80	0.703	0.698	0.701	0.7
	80	0.948	1.097	1.023	1.0
	80	0.643	0.638	0.641	0.6

Source: Table generated by Medical Officer with data provided in Datasets.

Table 7: Serum IGF-1 values of responders on oral octreotide treatment at week 34 and week 36, and average of week 34-week 36.

Patient ID	Oral octreotide Dose (mg/day)	Serum IGF-1 values			
		Week 34	Week 36	Average week 34-week 36	Rounded Average
(b) (6)	40	0.507	0.656	0.582	0.6
	40	0.599	0.562	0.581	0.6
	40	0.768	0.558	0.663	0.7
	40	0.622	0.658	0.640	0.6
	40	0.655	0.674	0.665	0.7
	60	0.936	0.880	0.908	0.9
	80	0.842	1.219	1.031	1.0
	80	1.061	0.956	1.009	1.0
	80	0.823	0.915	0.869	0.9
	80	0.893	0.751	0.822	0.8
	80	0.852	0.804	0.828	0.8
	80	0.886	0.754	0.820	0.8
	80	0.782	0.720	0.751	0.8
	80	1.172	0.818	0.995	1.0
	80	0.944	0.852	0.898	0.9
	80	0.889	0.929	0.909	0.9

Source: Table generated by Medical Officer with data provided in Datasets.

Based on verification of accuracy of the information presented by Chiasma for the average IGF-1 screening values and the average IGF-1 used to determine response to treatment, this Medical Officer concludes that there was no violation of the rules for enrolment and for determination of the response to treatment based on IGF-1 values.

Dr. Ketterman's point of view is that according to SAP "rounding should occur only after analysis" and therefore patients whose baseline and end-of-treatment IGF-1 values were above 1.0 and lower than 1.5 and were rounded to 1.0, should be excluded from the analyses. She performed detailed statistical analyses considering assumptions of patients who failed to meet inclusion criterion and/or "responder" criterion based on IGF-1 value ≤1.0. Dr. Ketterman concludes that the statistical issues she identified did not change the overall efficacy analyses, and her recommendation is approval of the NDA.

***Medical Officer comment**: The statistical review supports the demonstration that the proportion of patients who met the primary efficacy endpoint in the oral octreotide group is statistically significant higher compared to that of placebo group.*

Analysis of Responders (Oral octreotide) by IGF-1 Values During the DPC Period
The pre-defined criterion to classify patients as responders or non-responders was the IGF-1 average of the last 2 visits (week 34 and week 36) regardless of the IGF-1 values across the DPC period. However, from a clinical perspective the profile of serum IGF-1 during the course of treatment may give a more accurate information on true responders and can help to guide the monitoring schedule of patients on treatment.

To assess IGF-1 profile during the DPC period of the 16 patients classified as responders in the oral octreotide group, this Medical Officer plotted graphs for each patient using data provided in the Analysis Datasets and the JReview analysis tool. This analysis revealed that 4 of the 16 patients classified as responders did not maintain biochemical control (*i.e.*, IGF-1 ≤1.0 x ULN) during the entire DPC period. These 4 patients showed IGF-1 levels above 1 x ULN at various time points across the DPC period before ending with IGF-1 levels at week 34 and week 36, which satisfied the criterion for responders (see graphical illustrations in Figure 2. However, they did not meet pre-defined withdrawal criteria, *i.e.*, IGF-1 ≥1.3 x ULN and exacerbation of acromegaly symptoms on 2 consecutive assessments while treated with 4 capsules/day of study drug in DPC period.

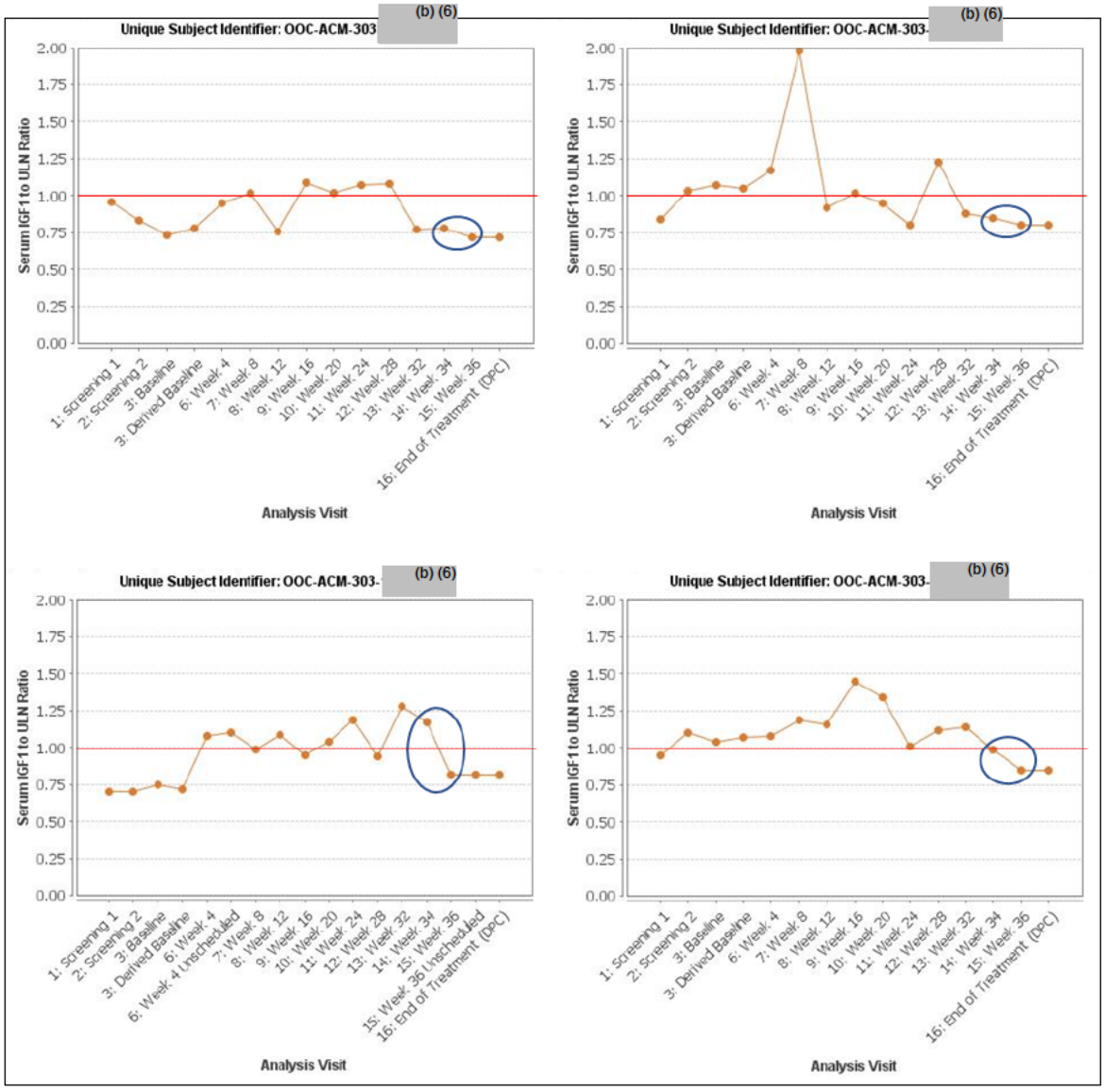

Figure 2: IGF-1 profile of 4 patients classified as responders in the Mycapssa group.
Each point represents a single IGF-1 measurement. All 4 patients ended the study on 80 mg Mycapssa dose. Circles indicate the 2 IGF-1 measurements (week 34 and week 36) used to calculate the average
Source: Graphs generated by the Clinical Reviewer using raw data from the Analysis Dataset and the JReview analysis tool.

IGF-1 blood levels are more stable than GH levels in daily assessments within patients. However, IGF-1 may also fluctuate from day to day during the natural course of the disease. In this study IGF-1 was measured by a central laboratory, which eliminated the variations due to different assay methodologies. While the 4 patients discussed above had several values of IGF-1 above the threshold of normal, their average (week 34 - week 36) IGF-1 values met the criteria for "responders".

Medical Officer comment: The IGF-1 profile of the 4 patients discussed above demonstrate that if the endpoint had been measured at a different time point, perhaps these patients would not have met the criteria for "responders". While this observation does not change the efficacy analysis, it supports a recommendation for monthly measurement of serum IGF-1 after initiating treatment with oral octreotide for dosing adjustment and monitoring of treatment failure.

Analysis of Non-responders to Oral Octreotide Treatment
Of 12 patients on oral octreotide who failed to maintain biochemical response at the end of DPC, 5 patients did not meet the primary endpoint criterion and 7 patients discontinued study drug prematurely. Of the 7 patients who discontinued the study drug, 2 patients discontinued due to AEs and 5 due to treatment failure (see Patient Disposition in Section 6.1.2 of this review). The inclusion of patients who discontinued study drug in the group of non-responders regardless of their IGF-1 values was consistent with the criterion established in the protocol.

Patients from the Placebo Group Included in OLE despite their Classification as Responders
In the Pre-NDA meeting, the FDA review team requested clarification for 5 patients in the placebo group who maintained their biochemical response at the of the DPC period and were transitioned to oral octreotide in the OLE period based on active acromegaly symptoms (see Pre-NDA Preliminary Comments dated 10/04/2019 and comments under Section 3.2 of this review). In the Pre-NDA meeting discussion, the Applicant explained that the reasons for transitioning the 5 patients to the OLE phase were loss of biochemical control during the DPC period in 3 patients and symptoms of acromegaly during the study period in 2 patients. The FDA requested the Applicant to submit case narratives in the NDA for these 5 patients (see Pre-NDA Meeting Minutes dated 11/08/2019).

Per protocol, following availability of study results, the PIs were informed of the treatment allocation of these patients and decided that all 5 patients should be enrolled in the OLE study to receive active medical treatment. The PI's rationale for enrolling patients in the OLE study provided in case narratives was loss of biochemical control and symptoms of acromegaly for 2 patients, loss of biochemical control for 1 patient, and symptoms of acromegaly for 2 patients. See details for each patient in the summary of narratives below.

Summary of Narratives:

1. Patient # (b) (6) 47-year old male, previously treated with lanreotide 120 mg/4 week. During the course of DPC period, his minimum IGF-1 was 0.68 x ULN and his maximum IGF-1 was 1.12 x ULN at week 24. IGF-1 value remained above ULN from week 24 to week 34, thus the patient met the pre-defined criteria for loss of response (2 consecutive IGF-1 values > 1 x ULN). The patient experienced the AEs of diffuse joint pain, increased sweating, fatigue and carpal tunnel syndrome that persisted to the end of DPC. The patient did not meet the criteria for withdrawal and rescue because his IGF-1 values were < 1.3 x UNL. At the end of DPC, the patient elected to enter the OLE period. The PI's rationale to include

this patient in the OLE study was that the patient had symptoms of active acromegaly and required treatment.

2. Patient # (b) (6) 57-year old male, previously on lanreotide 90 mg/4 week. His IGF-1 levels increased from a minimum 0.63 x ULN to a maximum of 1.14 x ULN at week 36 and this was the only measurement of IGF-1 above 1.0 x ULN during the DPC period. This patient was considered a responder because the average IGF-1 of week 34 and week 36 was 1.0 x ULN. The patient experienced AEs of diffuse joint pain (multiple episodes) and knee pain during the course of the DPC period. While the Investigator believed the symptoms were due to acromegaly, the criteria for rescue were not met because of IGF-1 levels <1.3 x ULN and at the end of the DPC period the patient elected to continue in OLE. The PI's rationale to include this patient in the OLE study was that the patient had symptoms of active acromegaly and required treatment.
3. Patient # (b) (6) 59-year old female, previously treated with lanreotide 60 mg/4 week. Her minimum IGF-1 level was 0.29 x ULN and the levels increased consistently up to a maximum of 1.37 x ULN at week 32, but she did not meet the criteria for rescue medication because she had a single IGF-1 value above 1.3 x ULN. The patient reported several AEs including swollen fingers, carpal tunnel symptom (2 episodes), shoulder arthritis (2 episodes), and hip arthritis. The PI's rationale for including this patient in the OLE study was loss of biochemical control and symptoms of active acromegaly.
4. Patient # (b) (6) 59-year old male, previously on treatment with lanreotide 60 mg/4 week. This patient had only one IGF-1 value above 1 x ULN (1.08 x ULN) at week 12, thus did not meet the criteria for loss of control. The patient reported AEs of trace bilateral edema of lower extremity at week 16 that resolved by week 20. The PI rationale to include this patient in the OLE study was because he believed the patient had active acromegaly symptoms and required treatment.
5. Patient # (b) (6) 72-year old male, previously treated with octreotide LAR 30 mg/4 week. The patient's minimum IGF-1 level was 0.52 x ULN at week 4 and his maximum was 1.24 x ULN at week 20. This patient had 8 consecutive IGF-1 values above 1 x ULN but < 1.3 x ULN, therefore he met the criteria for loss of response and did not meet the criteria for rescue. The AE reported was increased fatigue that started between baseline and week 4 and resolved at week 12. The PI's rationale to include this patient in the OLE study was loss of biochemical control.

Medical Officer comments: This Medical Officer does not agree with the Applicant's assessment that Patient # (b) (6) described in narrative 4 had evidence of active acromegaly to justify including this patient in the OLE study. There was one single IGF-1 value above 1 x ULN (1.08 x ULN) and the only AE reported was 'trace bilateral edema in lower extremities', which resolved by the following visit. The Medical Officer also noted that this patient was taking hydrocortisone (5 mg QD) for the treatment of adrenal insufficiency (not described in the narrative provided). An inadequate treatment of the adrenal insufficiency could explain the transient edema.

Analysis of Response by Dose (low or mid/high) of SRL Previously Used
The most frequent long-acting SRLs used prior to entering the study was octreotide long-acting release (LAR) followed by lanreotide, and the proportion of patients using these medications was similar between oral octreotide and placebo treatment groups. Other treatments used less frequently were Cabergoline and SRLs combined with dopamine agonists. Octreotide LAR approved doses are 10 mg, 20 mg, 30 mg and exceptionally 40 mg every 4 weeks via intramuscular injection. Lanreotide approved doses are 60 mg, 90 mg and 120 mg every 4 weeks via deep subcutaneous injection. Patients in the low dose SRL included those receiving octreotide LAR 10 mg/4 weeks and lanreotide 60 mg/4 weeks. Patients in the mid/high dose included those receiving octreotide LAR 20 mg/4 weeks and 30 mg/4 weeks, and lanreotide 90 mg/4weeks, 120 mg/4 weeks, and 120 mg/6 weeks.

The rate of responders and non-responders in each treatment group was analyzed by patients previously using SRLs at low dose and mid/high dose. A comparable number of patients was randomized to oral octreotide and placebo groups from low dose SRLs (6 patients and 5 patients, respectively) and from the mid-high dose SRLs (22 patients and 23 patients, respectively). The proportion of responders in the oral octreotide group previously treated with low dose SRL (66.7%) was slightly higher than that of patients previously treated with mid/high dose SRL (54.5%). See responder vs. non-responder analysis by previous SRL dose in Table 8. While interpretation of the proportion of responders by previous SRL dose should be taken with caution because of the limited number of patients in the low dose SRL, the results of this analysis demonstrate that the severity of the disease and previous dose of SRLs required for the disease control does not affect the efficacy.

Table 8: Patients who attained biochemical control (IGF-1) at the end of DPC period by dose of SRLs previously used

DOSE OF SRL	Octreotide oral treatment group (Final dose in DPC)				
LOW	40 mg (n=3)	60 mg (n=2)	80 mg (n=1)	Total (n=6)	Placebo (n=5)
Unadjusted proportions					
Responder	2 (66.7)	1 (50.0)	1 (100)	4 (66.7)	2 (40.0)
Non-responder	1(33.3)	1 (50.0)		2 (33.3)	3 (60.0)
Observed	1(33.3)	1 (50.0)		2 (33.3)	
Early Withdrawal					3 (60.0)
Adjusted Proportions					
Responder				66.90	27.20
Non-responder				33.10	72.80
Difference in adjusted proportions				39.70	
95% CI				(-24.4, 76.25)	
p-value				0.435	
Odds ratio (octreotide/placebo)				5.409	
95% CI				(0.256, 165.99)	
MID/HIGH	40 mg (n=4)	60 mg (n=0)	80 mg (n=18)	Total (n=22)	Placebo (n=23)
Unadjusted proportions					
Responder	3 (75.0)		9 (50.0)	12 (54.5)	3 (13.0)
Non-responder	1 (25.0)		9 (50.0)	10 (45.5)	20 (87.0)
Observed			3 (16.7)	3 (13.6)	4 (17.4)
Early Withdrawal	1 (25.0)		6 (33.3)	7 (31.8)	16 (69.6)
Adjusted Proportions					
Responder				52.11	16.21
Non-responder				47.89	83.79
Difference in adjusted proportions				35.90	
95% CI				(5.09, 59.53)	
p-value				0.032	
Odds ratio (octreotide/placebo)				5.859	
95% CI				(1.1324, 41.152)	

Source: Table adapted from data presented in CSR, Table 14.2.1.14

Data Quality and Integrity

No evidence of issues regarding data integrity was identified. Data quality was not ideal and led to a number of requests for clarifications sent to the Applicant during the review process.

ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

The analysis of the secondary efficacy endpoints used a pre-specified testing order to adjust for multiplicity and the secondary endpoints are discussed in the testing order. All secondary endpoints have shown statistically significant differences between treatment groups.

1. Proportion of patients who maintained their GH response at Week 36

GH response was defined the mean integrated GH value < 2.5 ng/ml based on 5 measurements 30 minutes apart. Patients who discontinued study drug during the DPC period were classified as non-responders, regardless of their GH values. The proportion of patients who had GH < 2.5 ng/ml at week 36 was 77.7% in the oral octreotide group and 30.4% in the placebo group. The difference between groups was statistically significant (p=0.0007) with an odds ratio of 7.96 in favor of oral octreotide (Table 9).

Table 9: Proportion of patients who maintained GH response at the end of DPC period.

	Octreotide Capsule Treatment Group (Final Dose in DPC Period)				
Parameter	**40 mg (N = 7)**	**60 mg (N = 2)**	**80 mg (N = 19)**	**Total (N = 28)**	**Placebo (N = 28)**
Patients who were responders (mean GH < 2.5 ng/mL) on SRL injections at screening [1]	7 (100.0)	2 (100.0)	18 (100.0)	27 (100.0)	25 (100.0)
Unadjusted proportions					
Responder	6 (85.7)	2 (100.0)	13 (72.2)	21 (77.8)	7 (28.0)
Non-responder	1 (14.3)		5 (27.8)	6 (22.2)	18 (72.0)
Observed					2 (8.0)
Early withdrawal [2]	1 (14.3)		5 (27.8)	6 (22.2)	16 (64.0)
Adjusted proportions [3]					
Responder				77.66	30.40
Non-responder				22.34	69.60
Difference in adjusted proportions vs placebo [3]				47.26	
95% CI				(17.48, 67.67)	
P-value				0.0007	
Odds ratio [3]					
Odds ratio (octreotide/placebo) [3]				7.9584	
95% CI				(2.0671, 36.1539)	

Note: Maintaining GH response was defined as having mean GH (5 measurements 30 minutes apart) < 2.5 ng/mL.
[1] Only patients who were responders on SRL injections at screening were used in the analysis. Percentages used this as the denominator.
[2] Patients who discontinued the study drug during the DPC period for any reason were classified as non-responders.
[3] Adjusted proportions and odds ratios were obtained from an exact logistic regression model including covariates for treatment group, baseline SRL dose (low versus medium or high), and baseline mean GH level (< median, ≥ median). CI for difference in adjusted proportions used Newcombe method.
CI = confidence interval; DPC = double-blind, placebo controlled; GH = growth hormone; SRL = somatostatin receptor ligand

Source: Excerpted from CST, Table 15

The proportion of patients with mean GH <2.5 ng/mL at the end-of-treatment in the octreotide group is consistent with the proportions reported in the label of approved long-acting SSAs which are provided here for reference:

- Octreotide LAR: 47% (27-28 injections) and 66% (12 injections).

- Lanreotide: 51% (52 week-study).
- Pasireotide: 48.3% (12-month study, naïve patients).

All 6 patients in the oral octreotide group classified as GH response failure were patients who discontinued study drug, and of those only 1 patient had GH ≥2.5 ng/mL at the end of DPC period.
In the placebo group, of the 18 patients who failed GH response 16 had discontinued study drug during the DPC period and 2 were observed with GH ≥2.5 ng/mL at the end of the DPC period.

2. Time to loss of response (defined as IGF-1 >1 x ULN)

Time to loss of response was defined as the earliest time when IGF-1 increased to >1 x ULN on 2 consecutive visits after the patient was treated for at least 2 weeks with study drug 4 capsules per day (Oral octreotide equivalent to 80 mg/day) and was summarized using the Kaplan-Meier method. As requested by the FDA, to account for patients who discontinued study drug prior to meeting the definition of loss of response, three different approaches were used:

A) They were counted as having had an event (i.e., met the criteria of loss of response) at the time of treatment discontinuation.
B) They were censored at the time of their last available assessment, when the patient was known to have not lost response. If there was no post-baseline assessment for response status, the patient was censored with a time to loss of response of 0.
C) They were not censored but evaluated for response based on the data collected after discontinuation (i.e., as long as the patient was known to be a responder regardless of adherence to treatment).

Analysis using definition A: The time to loss of response was significantly greater ($p<0.0001$) in the oral octreotide group (median >36 weeks) compared to placebo group (median = 16 weeks). Based on the Kaplan-Meier analysis, 26 of 28 (93%) patients in the placebo group lost response by the end of the DPC period compared to 13 of 28 (46%) patients in the oral octreotide group. The average time to loss of response in the oral octreotide group was 27.3 weeks compared to 15.6 weeks in the placebo group (Figure 3).

Results using Definitions B and C were consistent with results using Definition A.

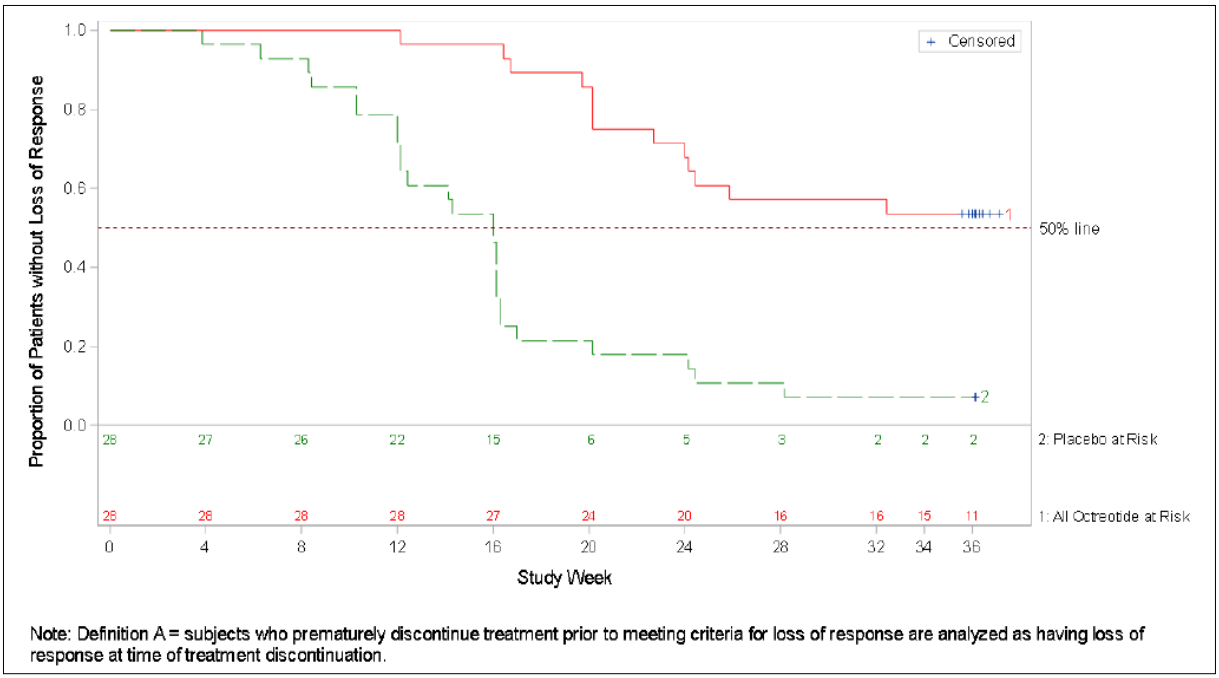

Figure 3: Plot of time to loss of response. Definition A (IGF-1 of 2 consecutive visits >1 x ULN)

Source: Excerpted from CSR, Figure 3.

3. Time to loss of response (based on IGF-1 **≥1.3** x ULN)

The time to loss of response based on IGF-1 ≥1.3 x ULN was determined at the date time of the earliest of the 2 consecutive measurements when the response was lost. To account for patients who prematurely discontinued treatment prior to meeting these criteria, analyses were performed using the 3 approaches used to analyze the secondary efficacy endpoint # 2 as described above.

Using definition A, the time to loss of response was significantly greater in the oral octreotide group *vs*. the placebo group (p <0.0001). The median time to loss of response for the placebo group was 16.2 weeks and for the oral octreotide group was not reached (i.e., >36 weeks). The number of patients who lost response by the end of the DPC period was 26 of the 28 patients in the placebo group and 9 of the 28 patients in the oral octreotide group (Figure 4). The difference between the 2 groups was statistically significant (p<0.0001). The analyses using approaches B and C were consistent with the analysis using approach A.

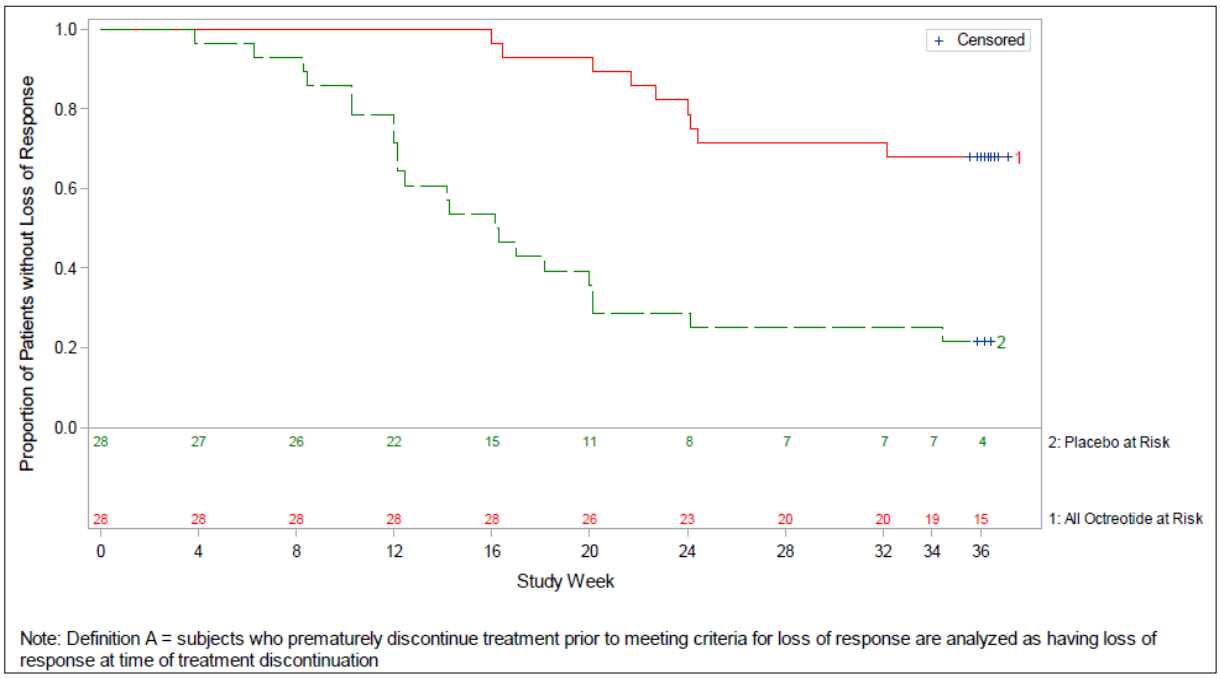

Figure 4: Plot of time to loss of response. Definition A (IGF-1 of 2 consecutive visits >1.3 x ULN)
Source: Excerpted from CSR, Figure 4

4. Proportion of patients who began rescue treatment prior to and including Week 36
All patients who discontinued study drug during the DPC period received rescue medication. Rescue treatment was initiated in 7 patients (25%) of the oral octreotide group and in 19 patients (68%) in the placebo group. The difference between the two treatment groups was statistically significant (p=0.003). A summary of patients who received rescue medication by oral octreotide dose level is shown in Table 10.

Table 10: Proportion of patients who began rescue treatment prior to and including week 36

Parameter	Oral octreotide dose at the end of DPC				Placebo (n=28)
	40 mg (n=7)	60 mg (n=2)	80 mg (n=19)	Total (n=28)	
Rescued patients	1 (14.3)		6 (31.6)	7 (25.0)	19 (67.9)
Non-rescued patients	6 (85.7)	2 (100.0)	13 (68.4)	21 (75.0)	9 (32.1)
Difference in proportion of rescued patients (oral octreotide vs placebo)				-42.86	
95% CI				(-66.4, -19.3)	
P-value				0.0029	

95% CI was based on the Clopper-Pearson exact method and p-value was based on Fisher's exact test.
Source: Table adapted from CSR, Table 18.

Dose Escalation

All patients in the oral octreotide group started at dose 40 mg/day and were allowed to escalate the dose sequentially to 60 mg/day and to 80 mg/day. While the Sponsor recommended guiding rules for dose escalation (See Dose Selection in Section 6.1.1 of this review) the decision to escalate dose was ultimately at the discretion of the study Investigator based on any of the following: IGF-1 >1.3 x ULN, or 2 consecutive values of IGF-1 >1.0 x ULN, or new/worsening acromegaly symptoms.

According to pre-established rules, dose escalation was allowed up to and including week 24 and was done at scheduled or unscheduled visits including telephone visits. Of the 28 patients treated with oral octreotide, 7 patients received 40 mg/day throughout the DPC period and 21 patients underwent dose escalation. Of the 21 patients, 2 escalated to 60 mg and remained on 60 mg to the end of DPC. A plot of time to dose escalation during the DPC period for the 21 patients is shown in Figure 5.

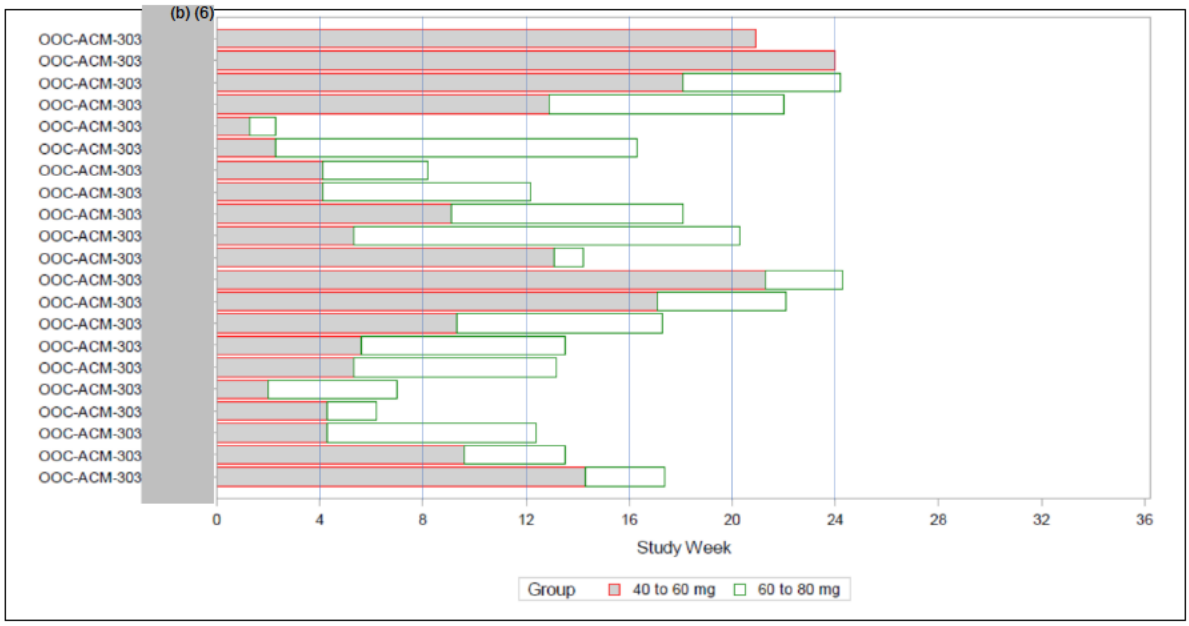

Figure 5: Plot of time to dose escalation during the DPC period
Source: Excerpted from CSR, Figure 14.1.7.3

Interpretation of the plot of time to dose escalation allows for drawing information on the pattern of time within an oral octreotide dose level before escalating to the next higher level.

- Before completing 4 weeks of treatment, 3 patients had escalated from 40 mg/day to 60 mg/day and 1 patient escalated sequentially from 40 mg/day to 60 mg/day and from 60 mg/day to 80 mg/day.
- An additional count of 7 patients escalated from 40 mg/day to 60 md/day before completing 8 weeks of oral octreotide treatment.

To clarify the justifications used for dose escalation in each patient, an Information Request (IR) was sent by FDA to Chiasma (dated 04/14/2020) requesting IGF-1 values per visit and justification for dose escalation for patients in the oral octreotide group. Chiasma's response to the IR provided a list of all dose escalation with justification for individual dose escalation per patient. A review of the submitted information confirmed that in several occasions the reason for dose escalation was symptoms experienced by the patient that were deemed by the Investigator based solely on new/worsen symptoms of acromegaly regardless of the IGF-1 value measured at the time. However, since the levels of IGF-1 at the time of each dose escalation remained unclear, an additional IR was sent on 05/08/2020 requesting individual graphs of IGF-1 values per visit for each of the 28 patients who were randomized to oral octreotide, marking the visit when the oral octreotide dose was escalated. Chiasma responded on 5/13/2020 and provided all graphs and short narratives for each patient as requested.

The submitted data was reviewed and the information extracted from the individual graphs and narratives with IGF-1 levels at or immediately before each titration visit by patient ID for each of the 28 patients from the oral octreotide group is summarized in Table 11. The vast majority of oral octreotide up-titrations were decided at the Investigator's discretion based on symptoms only, regardless of normal IGF-1 values. The PI's decision to increase the study drug dose based on IGF-1 increased in most cases did not meet the criteria for dose titration specified in the protocol, i.e., IGF-1 values were not above 1 x ULN, or there was a single IGF-1 between 1.0 and 1.3 x ULN. Several narratives do not describe the reason that led the PI to up-titrated the oral octreotide dose.

Table 11: Summary of reasons and visit (week) for oral octreotide dose titrations and IGF-1 value at or immediately before visit

	Titration 40 mg to 60 mg			Titration 60 mg to 80 mg		
	Week	IGF-1	Reason for dose increase	Week	IGF-1	Reason for dose increase
(b) (6)	18	1.0	PI's discretion: IGF-1 (?)	24	0.9	PI's discretion: symptoms
	12	1.0	PI's discretion	20-24	1.0	PI's discretion
	1	0.9	PI's discretion	2	0.9	PI's discretion
	2	0.9	PI's discretion: symptoms	16	0.8	PI's discretion: symptoms
	4	1.0	PI's discretion	8	1.1	PI's discretion: symptoms
	4	0.6	PI's discretion	12	0.9	PI's discretion
	8-12	0.7	PI's discretion	16-20	0.7	PI's discretion Rescued (headache) – wk 20
	5	1.2	PI's discretion. De-escalated at wk 7 (headache) and re-escalated at wk 11	20	1.0	PI's discretion
	x		Graph shows sequence of IGF-1 >1.3xULN (wk 12-wk 24)	x		Rescued at wk 25 (consecutive elevated IGF-1, GI symptoms)
	12-16	1.2	2 consecutive IGF-1 >1.0xULN and symptoms	12-16	1.2	2 consecutive IGF-1 >1.0xULN and symptoms. Rescued at wk 28 (swelling)
	x			x		
	x			x		
	20-24	1.0	PI's discretion: IGF-1 (?)	24	1.0	PI's discretion: IGF-1 (?)
	16-20	1.1	PI's discretion: IGF-1	20-24	1.0	PI's discretion: IGF-1 (?)
	8-12	1.4	IGF-1 >1.3xULN	16-20	1.1	3 consecutive ≥1.3xULN Rescued at wk 32 (treatment failure)
	4-8	1.1	2 consecutive IGF-1>1xULN	12-16	1.1	PI's discretion: IGF-1
	4-8	1.0	PI's discretion: IGF-1 (?)	12-16	1.1	PI's discretion: IGF-1
	0-4	1.0	PI's discretion	4-8	1.1	PI's discretion: IGF-1
	4	0.6	PI's discretion: symptom	4-8	0.6	PI's discretion: symptom Rescued at wk 24: symptoms
	x			x		
	20-24	1.0	PI's discretion	x		
	x			x		
	4	0.8	PI's discretion: symptoms	12	0.8	PI's discretion: symptoms
	8-12	1.6	IGF-1>1.3xULN	12-16	1.5	IGF-1>1.3xULN
	12-16	1.0	PI's discretion: IGF-1 (?)	16-20	1.3	IGF-1≥1.3xULN
	x				x	
	x				x	
	24	1.1	PI's discretion: symptoms		x	

PI: Principal investigator; wk: week, ULN: upper limit of normal. Escalation on unscheduled visit is shown by the visit number prior and after the escalation; visit number labeled "x" = no escalation;
(?) denotes unsubstantiated PI's justification of IGF-1 increased
Source: Table generated by this Medical Officer with data extracted from response provided by the Applicant (05/13/2020) to information requested by the FDA. Text in blue: rescue information; Text in red: relevant information.

It is also noted from reviewing the graphs, that of the 7 patients who remained at the 40 mg dose, 4 maintained IGF-1 <1 x ULN during the whole DPC period, and 2 patients had values one to a maximum of three values equal or slightly above 1 x ULN. This observation suggests that a dose of 40 mg may be sufficient to maintain biochemical control in some patients and supports a recommendation of 40 mg for initial dose of oral octreotide.

Medical Officer Comment: Overall, the analysis of individual IGF-1 profile through the DPC period for all patients in the oral octreotide group lead to the conclusion that dose up-titration was not warranted based on biochemical control of acromegaly in most patients. The titration based on the symptoms is confusing, since the symptoms are non-specific (e.g., headache, fatigue) and may be due to other factors including underlying disease, concomitant medications, etc. In addition, it is unclear why patient who is biochemically controlled continue to experience symptoms. Lastly, as per Endocrine Society Guidelines[4], the therapeutic goals are to normalize IGF-1 values, which signifies control of acromegaly and to decrease a random GH <1 mcg/L as it correlates with control of acromegaly and to treat comorbidities associated with acromegaly (hypertension, diabetes mellitus, cardiovascular disease, etc.).
The graphs of IGF-1 values provided are also useful to support the recommendation for monthly IGF-1 measurement after initiating treatment with oral octreotide for dose titration and monitoring treatment failure. Analysis of the graphical data submitted showed that dose up-titration based on loss of biochemical control was not necessary in more than half of the patients in the octreotide group and supports 40 mg as initial dose for oral octreotide treatment.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The substantial, evidence of efficacy of oral octreotide in the intended population is obtained from a single Phase 3 trial (Study OOC-ACM-303) that was included in this NDA re-submission.

7.1.1. Subpopulations

Subgroup analyses were performed by the Applicant for the primary efficacy endpoint, i.e., the proportion of patients who maintained their biochemical response at the end of DPC period and was presented by region, age, gender and race.

Analysis by region: There were a total of 35 patients in the non-US subgroup, and 21 patients in the US subgroup. The difference in adjusted proportion of responders between oral octreotide and placebo was 43.58 (95% CI 6.39, 65.88) in the non-US subgroup and 45.15 (95% CI -8.13, 74.06) in the US subgroup.

Analysis by age: There were 43 patients in the age subgroup <65 year and 13 patients in the age subgroup ≥65 years. The difference in adjusted proportion of responders between oral octreotide and placebo was 23.23 (95% CI -7.83, 49.53) for age-group < 65 years and 74.63 (95%CI 11.01, 94.58) for age-group ≥ 65 years.

Analysis by gender: There were a total of 26 males and 30 females enrolled in the study. The difference in adjusted proportions proportion of responders between oral octreotide and placebo was 48.05 (95% CI 4.45, 73.75) in the male subgroup and 37.35 (95% CI -0.13, 63.89) in the female subgroup.

Analysis by race: Of the 56 patients, 51 were Caucasians (white) and since the analysis was performed for this group only the result does not have a meaningful value to the subgroup analysis by race. The incidence of acromegaly has been reported not to vary with race and ethnicity[6], however the study was conducted in regions where there is a predominance of Caucasians. Nevertheless, it is unlikely that efficacy will be significantly different for populations underrepresented in this study.

Overall, the proportion of patients who maintained their biochemical control at the end of DPC period was consistent across all subgroups as illustrated in Figure 6.

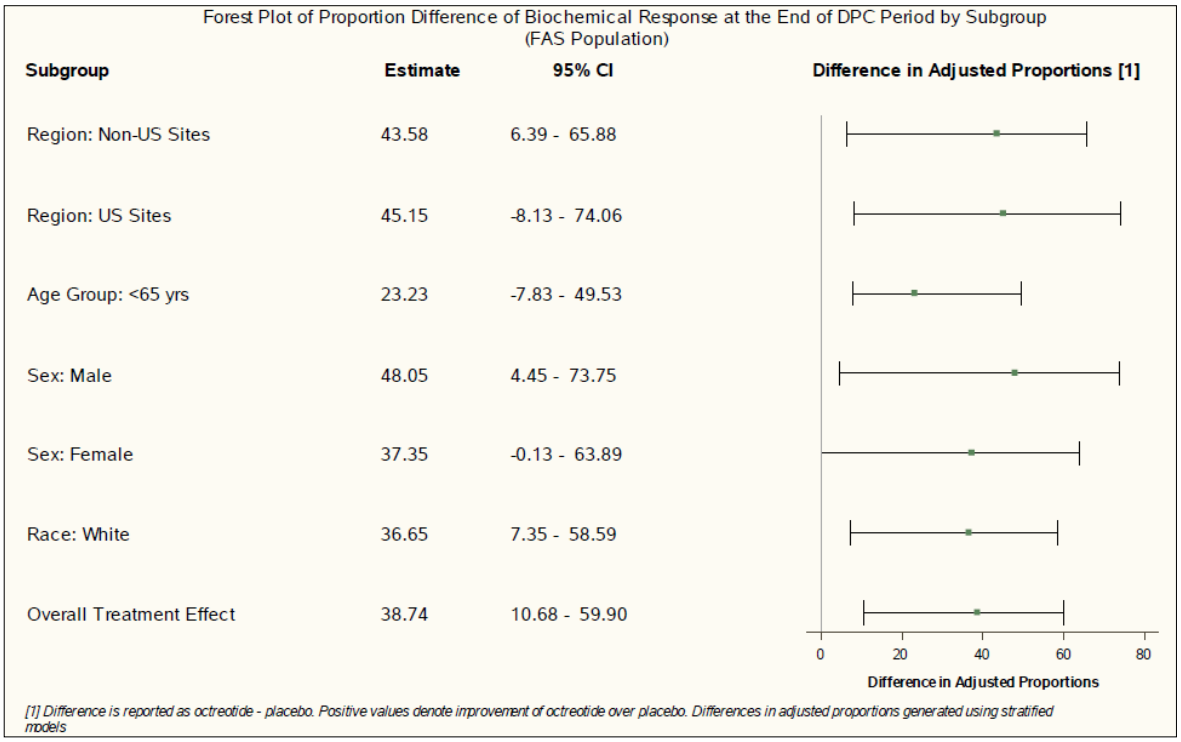

Figure 6: Forest Plot of proportion differences of biochemical response at the end of DPC period by subgroup.
Source: Excerpted from CSR, Figure 5.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The clinical studies conducted with oral octreotide did not include sufficient number of patients aged 65 years and over to determine whether the benefit is significantly different in the geriatric population. A statement in this regard will be included in Section 8 of the label for oral octreotide.

7.2.2. Other Relevant Benefits

The oral octreotide proposed by Chiasma for the maintenance of biochemical control in acromegaly is the first oral SSA formulation proposed for treatment of acromegaly. Currently approved drug therapy for acromegaly includes three classes of drugs: SSAs, GH receptor antagonists, and dopamine agonists. SSAs are the first-line drug therapy recommended and to date is only available in injectable presentation. Octreotide acetate is administered by subcutaneous (sc) injections two or three times daily. The long-acting SSAs formulations are to be administered monthly via intramuscular (octreotide and pasireotide) or deep sc (lanreotide)

injections by a trained healthcare provider. A daily administration of oral octreotide will be an option for patients who develop injection site reactions and for patients who consider inconvenient the requirement of healthcare provider for drug administration.

7.3. Integrated Assessment of Effectiveness

Study OOC-ACM-303 was a pivotal study and met the standards of an adequate and well-controlled trial. The results of Study OOC-ACM-303 provide substantial evidence of effectiveness of oral octreotide in the patient population with acromegaly previously treated with SRL sc injections. The proportion of patients treated with oral octreotide who maintained biochemical control (i.e., IGF-1 ≤1.0 x ULN) at the end of the study period (36 weeks) was approximately 50%, which is consistent with response reported in clinical trials with injectable long-acting SRLs (See Section 2.2 of this review). The results of the secondary analysis were supportive, *i.e.*, the proportion of patients who had GH < 2.5 ng/ml at week 36 (77.66%) was statistically (p=0.0007) higher in the oral octreotide group compared to the placebo group (22.34%). The proportion of responders by GH in Study OOC-ACM-303 is consistent with the proportion of patients who had decrease in GH levels during described with injectable long-acting SRLs (See discussion of secondary endpoints under Section 6.1.2 of this review).

The substantial evidence of oral octreotide effectiveness provided in Study OOC-ACM-303 supports the indication of oral octreotide for maintenance treatment in acromegaly patients who responded to and tolerated treatment with somatostatin analogs. A quarter of the patients treated with oral octreotide met the criteria for rescue medication during the 36-week treatment period and warrants periodic monitoring of IGF-1 in patients treated with oral octreotide switching those who lose biochemical control to injectable SSAs.

8. Review of Safety

8.1. Safety Review Approach

This safety review is primarily focused on safety data of Study OOC-ACM-303 (Core and Extension phases). The safety data from the single-arm, open label study (Study CH-ACM-01 Core and extension phases) were previously reviewed by Dr. Smita Abraham and will be summarized in this section (For complete information refer to Primary Clinical Review submitted to DARRTS on 04/12/2016). The Applicant also included safety data from the ongoing randomized, open-label, active-control Study OOC-ACM-302 up to the cutoff date (7 January 2019). The Applicant remains blinded to the treatment allocation during the randomized phase and only unblinded safety data, *e.g.*, deaths reported in this study will be discussed in review of safety. In review of safety data, Study OOC-ACM-303, Study OOC-ACM-302, and Study CH-ACM-01 will be referred to as Study 303, Study 302, and Study 01, respectively.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

STUDY OOC-ACM-303

The overall mean duration of study drug exposure during the DPC period was 200 days (SD 67.49), median 251 days, minimum of 27 days and maximum of 260 days. Exposure to oral octreotide was balanced across dose groups. A summary of exposure duration with number and proportion of patients at each dose level of oral octreotide compared to placebo for the DPC period is presented in Table 12.

Table 12: Summary of duration of study drug exposure during DPC period (days)

	Oral octreotide (final dose in DPC)				Placebo
	40 mg	60 mg	80 mg	Total	
Duration of study drug exposure (days)					
n	7	2	19	28	28
Mean (SD)	239.1 (35.37)	251.5 (3.54)	232.8 (38.02)	235.8 (35.63)	164.2 (73.18)
Median	252.0	251.5	252.0	252.0	144.0
P25, P75	251.0, 253.0	249.0, 254.0	226.0, 254.0	248.0, 253.5	107.5, 251.5
Minimum, maximum	159, 255	249, 254	141, 260	141, 260	27, 255
Dose level at end of DPC period (n [%])					
40 mg				7 (25.0)	
60 mg				2 (7.1)	
80 mg				19 (67.9)	

Source: Table adapted from Table 26, CSR.

Since there were patients on oral octreotide from the beginning of the study and some patients (on placebo) who were switched to oral octreotide in the OLE period, an IR was sent (dated 05/06/2020) requesting the Applicant to provide total exposure of safety population to oral octreotide in Study 303 (DPC period + OLE period up to cutoff date) by duration (<3 months, 3 to <6 months, ≥6 months, ≥9 months and ≥12 months). Chiasma provided tables with data for Study 303 at the cutoff date for NDA re-submission (July 11, 2019) and for the 120-day safety update cutoff date (October 1, 2019). This Medical Officer summarized the total exposure data for Study 303 in Table 13.

Table 13: Summary of total exposure (combined DPC and OLE periods) in Study OOC-ACM-303

	OOC-ACM-303 Core+EXT (N=48)* Cutoff July 11, 2019	OOC-ACM-303 Core+EXT (N=48)* 120-day safety update
Duration of exposure	Number of patients (%)	Number of patients (%)
< 3 months	8 (16.7)	1 (2.1)
3 to < 6 months	14 (29.2)	18 (37.5)
≥ 6 to < 9 months	6 (12.5)	6 (12.5)
≥ 9 to < 12 months	10 (20.8)	5 (10.4)
≥ 12 months	10 (20.8)	18 (37.5)

*Including patients that were randomized to placebo in DPC and exposed to oral octreotide during OLE.
Source: Table adapted by Medical Officer from tables provided by Chiasma in response to IR (05/06/2020).

The data provided shows that the highest proportion (29.2%) of patients was exposed to oral octreotide for 3 to <6 months and the lowest (12.5%) proportion of patients exposed to the drug was between 6 and 9 months. This dropping in exposure in the time period of ≥ 6 to < 9 months is consistent with patients who discontinued use of oral octreotide during the last 3 months of the DPC period.

Summary of exposure by oral octreotide dose during the DPC period is presented in Table 14.

Table 14: Summary of duration of drug exposure during the DPC period and the number of patients at each dose of oral octreotide at the end of the DPC period

	Octreotide Capsule Treatment Group (Final Dose in DPC)					
Characteristics	40 mg (N = 7)	60 mg (N = 2)	80 mg (N = 19)	Total (N = 28)	Placebo (N = 28)	Overall (N = 56)
Duration of study drug exposure during DPC period (days) [1]						
n	7	2	19	28	28	56
Mean (SD)	239.1 (35.37)	251.5 (3.54)	232.8 (38.02)	235.8 (35.63)	164.2 (73.18)	200.0 (67.49)
Median	252.0	251.5	252.0	252.0	144.0	251.0
P25, P75	251.0, 253.0	249.0, 254.0	226.0, 254.0	248.0, 253.5	107.5, 251.5	142.0, 253.0
Minimum, maximum	159, 255	249, 254	141, 260	141, 260	27, 255	27, 260
Dose level at end of DPC period (n [%])						
40 mg				7 (25.0)		
60 mg				2 (7.1)		
80 mg				19 (67.9)		

[1] Duration of study drug exposure was calculated as date of last dose in the DPC period – date of first dose in the DPC period + 1.
DPC = double-blind, placebo-controlled; P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation
Source: Excerpted from CSR, Table 26.

STUDY CH-ACM-01

The mean (N=155 patients) drug exposure in Study 01 was 42.4 weeks (SD 19.4) and 131.7 patient years. Summary of exposure for Study 01 (Core and Extension phases combined) are presented in Table 15.

Table 15: Summary of total exposure (combined Core and Extension periods) in Study CH-ACM-01

	CH-ACM-01 Core+EXT (N=155)
Duration of exposure	Number of patients (%)
< 3 months	15 (9.7)
3 to < 6 months	24 (15.5)
≥ 6 to < 9 months	28 (18.1)
≥ 9 to < 12 months	6 (3.9)
≥ 12 months	82 (52.9)

Source: Table adapted by Medical Officer from Table 25 presented in the original NDA review.

8.2.2. Relevant characteristics of the safety population:

Study OOC-ACM-303
The safety population of Study OOC-ACM-303 evaluated in this review consists of 56 adult patients with confirmed diagnosis of acromegaly who were previously controlled with SRL injections and tolerated the drugs. All 56 patients completed the DPC study period and 21 of the 28 patients randomized to oral octreotide received treatment to the end of the DPC period. In the placebo group, 19 of the 28 patients met the rescue criteria and received the SRL medication used prior to entering the trial.

Summary of Baseline Characteristics
The full table of disease baseline characteristics of Study 303 is placed in Appendix 13.4 of this review and the relevant baseline characteristics will be presented and discussed in this section, by characteristic category:

- Duration of acromegaly (<10 years, 10 to <20 years, and ≥20 years): The proportion of patients in the placebo group had a predominance (71.4%) of patients with acromegaly duration <10 years, compared to a proportion of 53.6% in the octreotide-treated group. Shorter duration of disease may be associated with lower incidence and severity of acromegaly complications.

- Pituitary tumor characteristics (microadenoma, macroadenoma and other): Tumor was classified by size on magnetic resonance imaging (MRI) in microadenoma (≤10 mm), macroadenoma (>10 mm), and "other" (tumor not visible or undetermined). The proportion of patients in all categories of pituitary tumor was similar across oral octreotide and placebo groups in DPC and patients in the OLE phase. It is noted that the overall proportion of patients with microadenomas was approximately 2-fold higher than that of macroadenomas and the highest proportion (~50%) of patients had pituitary tumors classified as "other" (Table 16).

Table 16: Pituitary tumor characteristics for Studies OOC-ACM-303 (Core and Extension Phases)

Pituitary tumor characteristics n (%)	DPC Period Oral octreotide (N = 28)	DPC Period Placebo (N = 28)	OLE Period Oral octreotide (N = 40)
Microadenoma	10 (35.7)	9 (32.1)	13 (32.5)
Macroadenoma	6 (21.4)	5 (17.9)	6 (15.0)
"Other"	12 (42.9)	14 (50.0)	21 (52.5)

Source: Table generated from data submitted in SCS, Table 6.

Macroadenomas, especially tumors with suprasellar expansion are generally not completely resected in transsphenoidal surgery, resulting in a lower percentage of post-surgical normalization of IGF-1 in patients who have macroadenomas compared to patients who have microadenoma[7]. Patients who have large macroadenomas may present complications due to tumor expansion, *e.g.*, visual field impairment. Patients with evidence of tumor compression of the optic chiasm and invasion of adjacent brain structures (except for sphenoidal sinus and cavernous sinus) were excluded from enrollment. Tumors not visible or undetectable on MRI may represent tumors below the level of MRI resolution, tumors that underwent apoplexy, or poor diagnosis due to low quality images or reader errors, which is the most likely cause for this MRI result.

- Previous treatment for acromegaly at any time (surgery only, radiation only, both, and neither): There were no patients in Study 303 who underwent radiation therapy.

- Prior acromegaly surgery: The proportion of patients who had prior surgery was similar across all groups (DPC and OLE periods) and overall was approximately 90% of patients in Study 303.

8.2.3. Adequacy of the safety database:

The safety database submitted was adequate to allow a thorough review of trial OOC-AC-303 safety.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity and submission quality were identified in the safety database.

8.3.2. Categorization of Adverse Events

AEs for studies OOC-ACM-303 and CH-ACM-01 were coded using MedDRA version 18.1.

8.3.3. Routine Clinical Tests

The routine clinical tests consisted of clinical chemistry, hematology and urinalysis. In addition, ECG and gallbladder ultrasound were included for monitoring the risks of arrhythmia and gallbladder disease, respectively.

8.4. Safety Results

STUDY OOC-ACM-303
DPC Period: The safety population was defined as all randomized patients who received any amount of study medication. In Study 303, all patients randomized received study medication. Of the 56 patients in the safety population, 55 (98.2%) patients experienced at least one TEAE during the DPC period (28 patients in the oral octreotide group and 27 patients in the placebo group). Table 17 shows an overview of the number of patients experiencing treatment emergent adverse events (TEAEs) during the DPC period, which will be further discussed under this section.

Table 17: Overview of the number of patients with treatment emergent adverse events (TEAEs) during the DPC period

Patients with	Oral octreotide (N=28)	Events	Placebo (N=27)	Events
At least one TEAE	28 (100%)	172	27 (96.4%)	219
Treatment-related TEAEs	18 (64.3%)	40	15 (53.6%)	41
One or more severe TEAEs	3 (10.7%)	8	7 (25.0%)	13
At least one SAE	2 (7.1%)	3	1 (3.6%)	1
TEAEs leading to study drug discontinuation	2 (7.1%)	5	1 (3.6%)	1
Treatment-related TEAEs leading to study drug discontinuation	2 (7.1%)	5	0	0
At least one AESI	15 (53.6%)	34	26 (92.9%)	82

Source: Excerpted from CSR, Table 27.

The TEAEs considered by the Applicant as AE of special interest (AESI) were new or worsening acromegaly signs and/or symptoms captured by complaints of headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia, hypertension or other signs assessed by the Investigator as related to acromegaly. The number of patients experiencing at least 1 AESI was 15 (53.6%) in the oral octreotide group and 26 (92.9%) in the placebo. These findings are consistent with untreated clinical manifestations of acromegaly in the placebo group and were not collected as safety signals of the oral octreotide. Therefore, these data will not be included in the safety review.

Medical Officer comments: AESIs are generally used to collect additional information and monitor certain events to better characterize the safety of the study drug. However, the AESIs were defined by the Investigator to capture new or worsening symptoms of acromegaly, not the

adverse events associated with drug. The Applicant's intent to collect the frequency of symptoms of acromegaly during the treatment with the drug vs. placebo targets further characterization of drug efficacy in controlling acromegaly, and not characterization of safety profile of the drug. Thus, I recommend deleting these AESI from section 6 of the label.

OLE Period: Of the 40 patients enrolled in the OLE phase, 22 (55.0%) patients experienced at least 1 TEAE; 9 (22.5%) patients experienced a TEAE that was considered relted to oral octreotide. Most of the events were mild or moderate in intensity and 3 (7.5%) patients experienced a severe TEAE. There were 2 (5%) patients with SAEs. One (2.5%) patient discontinued study drug due to a TEAE, which was assessed as unrelated to study drug. No deaths were reported during the OLE period.

STUDY CH-ACM-01
Of the 155 patients in the Core phase, 134 (86.5%) and of the 88 patients in the Extension phase, 58 (65.9%) experienced at least one TEAE. Patients who experienced SAEs were 17 (11.0%) in the Core phase and 6 (6.8%) in the Extension phase. Patients who discontinued study drug due to TEAE were 22 (14.2%) in the Core phase and 1 (1.1%) in the Extension phase. Two (1.3%) patients died in the Core phase and no deaths were reported in the Extension phase.

8.4.1. Deaths

STUDY OOC-ACM-303
No deaths were reported during Study OC-ACM-303 (core and extension periods).

STUDY CH-ACM-01
In Study CH-ACM-01 (Core phase) two patients died. One patient developed clinical symptoms and laboratory results suggestive of bile duct obstruction and died in sepsis. While the Investigator assessed this death as not related to study drug, Dr. Abraham upon her review assessed this case of death as possibly related to study drug. A second patient developed symptoms and laboratory results consistent with hepatobiliary obstructive disorder and died of cardiac insufficiency. Autopsy revealed tumor of the pancreas. Dr. Abraham's assessed this death as likely unrelated to study drug. See Dr. Abraham's review of the original submission for narratives and complete discussion.

STUDY OOC-ACM-302
Two deaths were reported in the ongoing Study OOC-ACM-302 up to the cutoff date and are summarized together with the deaths reported in Study 01, in Table 18.

Table 18: Deaths during Phase 3 studies in acromegaly patients

Study Number	Patient ID	Age (years)	Sex	Race	Cause of Death	Relationship to Study Drug	Relative Day
CH-ACM-01	(b) (6)	36	M	Caucasian	Sepsis	Not related	179
CH-ACM-01	(b) (6)	60	M	Caucasian	Acute myocardial infarction	Not related	261
OOC-ACM-302	(b) (6)	68	M	Caucasian	Toxicity to various agents	Not related	263
OOC-ACM-302	(b) (6)	70	F	Caucasian	Ischemic stroke	Not related	462

Source: Excerpted from CSR, Table 14.

The narratives of deaths that occurred in Study 302 are discussed below:

- Patient (b) (6): 68-year old white male, with a 6-year history of acromegaly and record of transsphenoidal surgery. Relevant medical history includes sleep apnea, degenerative joint disease, bilateral total hip replacement, impaired glucose regulation, hypopituitarism, secondary hypogonadism, seizure, arthritis, hypertension, obesity, left eye blindness due to trauma, leg wound secondary to edema, and intolerance to metoxicam. Concomitant medications at the time of the event included cholecalciferol, cyanocobalamin, testosterone topical gel, naproxen, furosemide, and a multivitamin supplement. The patient initiated oral octreotide at 40 mg dose and the dose was up-titrated to 60 mg dose approximately three and a half months after initiating treatment, and then up-titrated to 80 mg approximately one month after starting the 60 mg dose. On a routine visit at week 30, the patient was reported healthy and the only abnormal laboratory test was a blood urea nitrogen (BUN) of 28 mg/dL (reference range: 5 – 22 mg/dL). Approximately one month later, the patient's wife informed the study coordinator that her husband had suddenly died the previous evening (Study Day 263). The toxicology report findings were positive for ethanol, caffeine, cocaine, benzoylecgonine, and oxycodone. The summarized autopsy findings were hypertensive cardiovascular disease and atherosclerotic cardiovascular disease. Per the autopsy report, the cause of death was "combined drug poisoning" and death was ruled accidental. This death was assessed by the Investigator and Study Medical Monitors as unrelated to study drug. Based on the information provided in the narrative, this Medical Officer agrees with the Investigator's assessment of unrelated to study drug for causality in this case of death.

- Patient (b) (6): 70-year old white female with a 12-year history of acromegaly and record of transsphenoidal surgery. Relevant medical history included coronary artery disease, myocardial infarction, hypertension, hypothyroidism, diabetes mellitus, secondary hyperparathyreosis, gastroduodenitis, and partial stable atrophy of optic nerves. Concomitant medications at the time of the event included levothyroxine, metformin, hydrochlorothiazide, bisoprolol, losartan, aspirin, simvastatin, calcium carbonate and cholecalciferol. The patient initiated oral octreotide at 40 mg dose on (b) (6) but there is no information in the narrative as to the date of last dose of oral octreotide was

administered and when the patient switched to octreotide LAR. The patient experienced an SAE of stroke on (b) (6) (Study Day 462), while receiving octreotide LAR in the safety Follow-up phase of the study. Per the Medical Monitor, the patient received octreotide LAR until (b) (6), *i.e.*, for 138 days before the fatal outcome and 53 days before the SAE start date. The Applicant reported not having information regarding laboratory tests, neurology consultation, or treatment for the period the patient was in the hospital. The patient was discharged from the hospital in (b) (6) (at unspecified day as per narrative) with partial paralysis. On (b) (6), the patient's husband informed the study center that the patient's condition deteriorated after hospital discharge and that she died on that day. The Chiasma Medical Monitor agreed with the Investigator's assessment of death caused by an event of ischemic stroke of severe intensity and with the causality assessment of death as unrelated to study drug, based on the significant risk factors at the time of the event including hypertension and diabetes. Based on the available information provided in the narrative, this Medical Officer agrees with the causality assessment of unrelated to study drug for this case of death.

Medical Officer comment: *As discussed above, this Medical Officer agrees with the PI's causality assessment for these two deaths as unrelated to study drug.*

8.4.2. Nonfatal Serious Adverse Events

STUDY OOC-ACM-303
During the DPC period, there were a total of 3 patients with nonfatal SAEs: 2 (7.1%) patients in the oral octreotide group experienced 3 SAEs (2 events of acute cholecystitis, and 1 event of left hip pain due to worsening of arthritis) and 1 (3.6%) patient in the placebo group experienced an SAE of hip subluxation.

Narratives of SAEs:

1. Patient (b) (6), 61-year old, male, oral octreotide group, hospitalized for let hip pain due to worsening of arthritis (assessed as unrelated to study drug). This patient had a medical history of left hip degenerative arthritis among other comorbidities. On the fourth day of 40 mg oral octreotide, the patient had a hip X-ray showing moderate to severe degenerative changes in left hip. Appproximately 3 months after initiating study drug, the oral octreotide dose was increased to 60 mg. Six days later, due to worsening pain, a total left hip arthroplasty was scheduled and the patient underwent surgery approximately 2 weeks later. No action was taken in regard to study drug.

2. Patient (b) (6), 59-year old, male, oral octreotide group, experienced 2 SAEs of acute cholecystitis. This patient had previous history of asymptomatic cholelithiasis. Concomitant medications included ramipril, atorvastatin, cod liver oil, multivitamins, glucosamine, factor VIII, and paracetamol. The first episode of acute cholecystitis leading to

hospitalization was experienced on Day 123 of study, after the patient had escalated to 80 mg/day of oral octreotide. The patient was discharged with medication and the event was assessed as unrelated to study drug and due to previous history. A second event of acute cholecystitis leading to hospitalization occurred on study day 210 and was assessed as unrelated to study drug because of previous history.

3. Patient (b) (6), 76-year old, male, placebo group, hospitalized on study day 233 for severe increased pain in the right hip due to hip subluxation. This event was assessed as unrelated to study drug.

Medical Officer comment: Both events of acute cholecystitis experience by one patient in the oral octreotide treatment were assessed by the Investigator as unrelated to study drug. While the patient's history of cholelithiasis and dyslipidemia may have contributed to the events of acute cholecystitis in this patient, gallbladder disease is a known potential risk of somatostatin analogs[8-10] and a causal effect of oral octreotide cannot be completely ruled out in this case. This Medical Officer does not agree with the Investigator's assessment that the events of acute cholecystitis were unrelated to oral octreotide and assesses these events as drug-related. This Medical Officer agrees with the Investigator's assessment that hip pain was unrelated to the study drug.

During the OLE period of Study 303, 2 (5.0%) patients experienced an SAE (amaurosis fugax and atrioventricular block complete). No malignancies were reported in the OLE period. Narratives of the patients with SAEs are discusses below:

- Patient (b) (6): 64-year old, white, male with a 4-year history of acromegaly and pituitary surgery. The medical history included hypercholesterolemia, hypertension, diabetes, central hypothyroidism, carpal tunnel syndrome surgery, umbilical hernia surgery, spontaneous left pneumothorax, and liver cyst. Concomitant medications at the time of the event included levothyroxine sodium, amlodipine, aspirin, simvastatin, atorvastatin, and clopidrogel. The patient began the study (DPC period) on placebo and met the pre-defined withdrawal criteria at approximately 4.5 months of treatment. He completed week 36 of DPC and entered the OLE phase with oral octreotide 60 mg daily. Sixteen (16) days after administration of the first dose of oral octreotide, the patient experienced sudden vision loss of the left eye while watching television and was hospitalized. The neurological examination was unremarkable, the ECG and ultrasound of common carotid artery did not show any abnormalities. The patients did not have secondary symptoms of other complaints. He was diagnosed with amaurosis fugax and treated with acetylsalicylic acid and clopidrogel. Simvastatin was changed to atorvastatin. The patient's condition improved and he was discharged on the same day. The Investigator assessed this SAE as not related to study drug and considered atherosclerosis as an alternative etiology. Medical Monitors of the Study agreed with the PI's assessment and no action was taken in regard to

study drug.

- Patient (b) (6): 73-year old, white, male, with a 7-year history of acromegaly and pituitary surgery. His medical history included complete left bundle branch block, intermittent trifascicular block (first degree AV block, right bundle branch block, left anterior fascicular block), bradycardia, arterial hypertonia, dilatative cardiomyopathy with mild to moderate systolic left ventricular (LV) function with ejection fraction (EF) of 44%, which subsequently decreased to 39-40%, circulatory problems with dizziness, electric shock-like pain behind the right eye, headache, numbness of fingers, back pain, sleep apnea, osteoarthritis of large joints, total arthroplasty (right and left hip, and left shoulder), diverticulosis, prostatic hypertrophy without indication of malignancy, calcified inflamed liver cyst, hyperuricemia, cheilognathouranoschisis, vitiligo, hyperchromic macrocytic anemia, cholecystectomy, fibromas on trunk and arms, and blurred vision. During the DPC period, this patient experienced an SAE of hip subluxation. Concomitant medications at the time of the event included amlodipine, acetylsalicylic acid, pantoprazole, tamsulosin hydrochloride, candesartan, allopurinol, dimenhydrinate, ascorbic acid, metamizole , lidocaine, fentanyl, oxycodone, midazolam, esomeprazole, enoxaparin sodium, and ibuprofen. The patient was in the placebo group during DPC period and was enrolled in the OLE phase with oral octreotide 60 mg daily. Two weeks after administration of the first dose of oral octreotide, the patient felt week during routine examination in orthopedic rehabilitation. At this time, his pulse was 25 bpm and he denied chest pain and shortness of breath (patient was observed at rest). The patient was hospitalized and a transthoracic echocardiography (TTE) revealed global moderately reduced systolic left ventricular ejection fraction (LVEF) with EF approximately 40%. Asynchronous contraction patterns were observed, and LV appeared dilated with septal hypertrophy. Mild aortic valve insufficiency, mild mitral valve insufficiency, and mild tricuspid valve insufficiency were also observed. Estimated central venous pressure was 26 mmHg. The patient was diagnosed with third degree AV block (complete block), was transferred to the intensive care unit (ICU) and a temporary pacemaker was placed. Relevant laboratory results showed troponin level of 43 pg/mL (normal reference range <14 pg/mL). A permanent pacemaker was successfully implanted and the patient was discharged home on the fourth day after admission to the hospital. The Investigator assessed the SAE as not related to study drug and most likely related to patient's significant underlying cardiac disease. The Medical Monitors of the Study agreed with the Investigator's assessment. An IR was sent by FDA (05/11/2020) to Chiasma requesting further ECG findings at time of occurrence of the AV block and further information regarding this event of AV block. The Applicant responded that ECG was not available to them because the patient presented to a hospital independent from the PI's site. The Applicant informed that all information available on this event of AV block was provided in the narrative (discussed above).

Medical Officer comment: This Medical Officer agrees with the Investigator's assessment for

both SAEs as not related to study drug.

STUDY CH-ACM-01

In Study 01, the Applicant reported 17 (11.0%) patients who experienced 1 or more SAEs during the Core phase and 6 (6.8%) patients experienced 1 or more SAEs during the Extension phase. Dr. Abraham reviewed all SAE narratives and discussed in detail the SAEs of malignancies and hepatobiliary disorders, which are summarized below.

There were a total of 5 (3.2%) patients who experienced neoplasms, 4 of which were malignant during the Core phase of this study. One patient had a non-malignant neoplasm (meningioma) and 4 patients with malignancies were described as: 1 patient with a recurrence of breast cancer (reported on Study Day 99), 1 patient with colon adenocarcinoma (reported on Study Day 91), 1 patients with a pancreatic carcinoma (reported on Study Day 261), and 1 patient with chordoma (reported on Study Day 77). The patient with colon adenocarcinoma had a medical history suggestive of pre-existing disease (rectal bleeding prior to starting the study). Dr. Abraham's findings were that of the 4 patients with neoplasms, 3 patients had narratives suggestive of undiagnosed malignancy prior to starting oral octreotide, and the narrative for the remaining patient did not have evidence that malignancy was associated with oral octreotide use and no evidence that the patient had uncontrolled acromegaly. Dr. Abraham concluded that there was no evidence for increased signal of malignancy associated with oral octreotide. No new malignancies were reported during the Extension phase of this study.

Hepatobiliary disorders were reported in 4 (2.6%) patients during the Core phase and in 1 (1.1%) patient during the Extension phase of Study CH-ACM-01. This finding is consistent with the rate of hepatobiliary reported for approved SSAs.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

STUDY OOC-ACM-303

The TEAEs leading to study drug discontinuation in the DPC period were reported for 2 (7.1%) patients in the oral octreotide group and 1 (3.6%) patient in the placebo group. All AEs leading to study drug discontinuation were non-serious AEs. The patient in the placebo group experienced multiple episodes of severe intensity headache that were considered unrelated to the study drug. The 2 patients in the oral octreotide group experienced a total of 5 AES as described in the summary of narratives below.

Patient # (b) (6) 30-year old, female, oral octreotide group, with history of acromegaly for 1.5 year, surgical treatment for acromegaly approximately 2 years before trial, hypopituitarism (secondary hypothyroidism, hypogonadism, and adrenal insufficiency), thrombocytosis and diabetes insipidus. Concurrent medications included levothyroxine , hydrocortisone, norethisterone, estradiol, acetylsalicylic acid and desmopressin. The patient began to experience headache of severe intensity on day 16 of oral octreotide (40 mg) and was treated

with metamizole and diclofenac. The AE of headache was assessed by the Investigator as related to study drug. The last dose (80 mg) of study drug was taken approximately 4 months after the event was first recorded and the headache was assessed as resolved approximately 18 days after study drug discontinuation. The patient was rescued and reported as receiving Sandostatin LAR to the end of the DPC period.

Medical Officer comment: The narrative provided by the Aplicant is limited to the information described above. This Medical Officer analyzed the graphical profile of patient # (b) (6) *using the JReview analysis tool to obtain information relevant for complete assessment, as described below:*

- *IGF-1 levels were within normal range (<1 x ULN) during the whole DPC period. Mean GH was 0.8 ng/mL at baseline, 1.2 ng/mL at day 141 and 1.3 ng/mL at day 253.*
- *An additional AE of mild diarrhea was recorded from day 47 to day 84.*
- *Oral octreotide dose escalated from 40 mg to 60 mg at day 64 and from 60 mg to 80 mg at day 126*
- *The study drug was discontinued at day 141 (information consistent with the narrative provided).*
- *The AE of severe headache was recorded from day 16 to day 160 (information consistent with the narrative provided).*

Headache is a frequent symptom of acromegaly. However, this patient maintained biochemical (control based on IGF-1 and GH values), and the headache was of severe intensity and only subsided after oral octreotide was discontinued and the patient began to receive rescue medication. Based on the overall information, this Medical Officer agrees with thePI's assessment that the AE of headache was related to the oral octreotide.

Patient # (b) (6) 45-year old, female, oral octreotide group, with history of acromegaly (19 years), surgical treatment of acromegaly (approximately 15 years prior to trial), fatty liver disease, hypercholesterolemia, gestational diabetes, cholelithiasis/cholecystectomy, and osteopenia. No concomitant drugs were reported. The patient began experiencing nausea and vomiting (mild severity) at study day 5 while on 40 mg oral octreotide, and at study day 68 (still on 40 mg oral octreotide) the patient began experiencing abdominal discomfort and heartburn (moderate intensity). The nausea, vomiting and abdominal discomfort resolved by study day 145. Oral octreotide was discontinued on day 159, but heartburn persisted to the end of DPC period. The Investigator assessed the AEs of nausea and vomiting as possibly related to study drug, and both abdominal discomfort and heartburn as related to study drug.

Medical Officer comment: The narrative provided by the Aplicant is limited to the information described above. This Medical Officer analyzed the graphical profile of patient # (b) (6) *using*

the JReview analysis tool and assessed the compliance data provided by the Applicant to obtain relevant information as described below:

- *IGF-1 levels were within normal values from screening to study day 61 (visit 7, IGF-1 of 0.97 x ULN), and then increased progressively from IGF-1 1.25 x ULN at day 92 (visit 8) up to a maximum IGF-1 1.42 x ULN at day 145 (visit 10) decreasing to IGF-1 1.3 x ULN at day 175 (visit 11) and normal levels thereafter to the end of the DPC period.*
- *The mean GH level was 0.2 ng/mL at baseline, 0.7 ng/mL at day 175, and 0.3 ng/mL at the end of treatment (day 267).*
- *The records of drug accountability demonstrate poor compliance, showed by consistent and progressive decreased in the number of capsules taken over the number of capsules expected to be taken. The calculated compliance was 94% on week 4, 91% on week 8, and 60% on week 12. Study drug was discontinued before completion of week 16 and the reason stated was patient not taking medication every day due to adverse events.*

The period of loss of biochemical control (IGF-1 >1.0 x ULN) observed from study day 92 to study day 175 occurred a few weeks later in relation to the period of gastrointestinal AEs, ending a few weeks after discontinuation of study drug. This observation together with the evidence of poor compliance suggest that the loss of biochemical control was due to drug intolerance leading to missing doses. Poor compliance may also explain the symptoms of nausea, vomiting and abdominal discomfort resolving prior to study drug discontinuation. The Investigator assessed nausea and vomiting as possibly related and headache and abdominal discomfort as related to study drug. This Medical Officer <u>disagrees</u> with the Investigator's assessment for nausea and vomiting and assesses nausea and vomiting as <u>related</u> to study drug (oral octreotide).

In the Extension (OLE) phase, 1 (2.5%) patient discontinue study drug due to a TEAE of headache.

<u>STUDY CH-ACM-01</u>
In the Core phase, 22 (14.2%) patients were reported by the Applicant as experiencing TEAEs leading to drug discontinuation. However, Dr. Abraham's review of Study 01 revealed that one patient classified by the Applicant as drug discontinuation by "Subject request" was actually a discontinuation due to a TEAE, and after reclassification of this patient, the final proportion of patients with TEAEs leading to discontinuation was raised to 23 (14.8%). The TEAEs leading to drug discontinuation in 2 or more patients were nausea [7 (4.5%) patients], diarrhea [4 (2.6%) patients], abdominal pain [2 (1.3%) patients], dyspepsia [2 (1.3%) patients], vomiting [2 (1.3%) patients], and pyrexia [2 (1.3%) patients]. In the Extension phase, one patient discontinued study drug due to a TEAE of gastritis erosive.

8.4.4. Significant Adverse Events

The Applicant reported significant AEs under the following categories:

- Discontinuation of study drug due to a TEAE – discussed in Section 8.4.3 of this review.
- Adverse events of special interest – discussed in 8.4.5 and 8.8 of this review.

8.4.5. Treatment Emergent Adverse Events Related to Study Drug

STUDY OOC-ACM-303

All patients, except 1 patient in the placebo group experienced at least 1 TEAE during the DPC period. The proportion of patients with common (≥5%) TEAEs was similar within each System Organ Class (SOC) category between the oral octreotide and the placebo groups in the DPC period. Among the most common TEAEs with higher numerical incidence by SOC in the oral octreotide group *vs*. the placebo group were GI Disorders, Infections and Infestations, and Hepatobiliary Disorders. GI symptoms and cholelithiasis are common AEs associated with medical treatment of acromegaly and are described in the labels of approved injectable SSAs. Common (incidence ≥5%) TEAEs reported during the DPC period with incidence in oral octreotide > placebo are combined with the respective incidence in the OLE period in Table 19. A full table of common TEAEs is placed in Appendix 13.5.

Table 19: Common TEAEs (incidence **≥5%** by PT) in DPC (with oral octreotide incidence > placebo) and OLE listed in descending order (first column) by SOC and PT.

System Organ Class Preferred Term	Study OOC-ACM-303 DPC period		Study OOC-ACM-303 OLE period
	Oral octreotide N=28	Placebo N=28	N=40
Patients with at least 1 TEAE	28 (100%)	27 (96.4%)	22 (55.0)
Gastrointestinal disorders	19 (67.9%)	17 (60.7%)	13 (32.5)
Diarrhea	8 (28.6%)	6 (21.4%)	4 (10.0)
Nausea	6 (21.4%)	3 (10.7%)	5 (12.5)
Abdominal discomfort	4 (14.3%)	3 (10.7%)	1 (2.5)
Vomiting	4 (14.3%)	0	2 (5.0)
Dyspepsia	3 (10.7%)	1 (3.6%)	0
Large intestinal polyp	2 (7.1)	0	0
Infections and Infestations	13 (46.4)	8 (28.6)	9 (22.5)
Sinusitis	3 (10.7%)	0	0
Urinary tract infection	2 (7.1%)	1 (3.6%)	3 (7.5)
Musculoskeletal and connective tissue disorders	11 (39.3%)	21 (75%)	5 (12.5)
Osteoarthritis	3 (10.7%)	0	1 (2.5)
General disorder and admistration site conditions	10 (35.7%)	15 (53.6%)	9 (22.5)
Pain	2 (7.1%)	0	1 (2.5)
Investigations	9 (32.1%)	10 (35.7%)	5 (12.5)
Blood glucose increased	3 (10.7%)	1 (3.6%)	1 (2.5)
Hepatobiliary Disorders	3 (10.7%)	2 (7.1%)	0
Cholelithiasis	2 (7.1%)	1 (3.6%)	0

Source: Table generated by the Clinical Reviewer with data extracted from the CSR, Table 28.

Analysis of the TEAEs by PTs shows that the most common TEAEs in the oral octreotide treatment group cluster into GI symptoms, which are consistent with the known safety profile of somatostatin analogs. The AE of nausea was 2-fold more frequent in the oral octreotide group and led one patient to discontinue treatment (See Section 8.4.3 of this review). Large intestinal polyp was reported in 2 patients in the oral ocreotide group *versus* 0 (zero) patients in the placebo group (See discussion below under Neoplasms).

This Medical Officer considered hepatobiliary disorders and neoplasms as AEs of special interest for acromegaly.
Hepatobiliary Disorders: A total of 3 (10.7%) patients in oral octreotide group *vs*. 2 (7.1%) patients in placebo group experienced AEs of hepatobiliary disorders. Two (2) of the 3 patients in the oral octreotide group and 1 of the 2 patients in placebo group had cholelithiasis, which has a high prevalence in patients with acromegaly and can worsen with somatostatin analog treatment (See comments in Section 8.4.2 and Section 8.4.6 of this review, gallbladder ultrasound).

Neoplasms: A total of 2 (9.5%) patients experienced TEAEs coded by the SOC of "Neoplasm benign, malignant and unspecified (including cysts and polyps)" and were not included in the Table 19 above because their individual incidence rate was below the cutoff of 5%. One (3.6%) patient was reported with malignant neoplasm (basal cell carcinoma) in the oral octreotide group (subgroup of 80 mg final dose) during the DPC period and this TEAE was assessed by the PI as unrelated to study drug. One (3.6%) patient in the placebo group experienced an acrochordon that was assessed by the Investigator as unrelated to study drug. Both patients were in the age-group < 65 years.

Two (7.1%) patients in the oral octreotide group (DPC period) vs. 0 (zero) patient in placebo group experienced TEAEs of large intestinal polyp and were reported under the SOC of Gastrointestinal Disorders. An IR was sent to the Applicant to provide narratives and any relevant clinical information available for these 2 patients (including but not limited to age, medical history, concomitant medications, doses and duration of treatment, and outcome), as well as their assessment of causality. Chiasma response (dated 06/02/2020) included narratives for 2 patients reported in Study 303 and 1 patient reported in Study 01 with intestinal poplyps. See a summary of the narratives below:

Patient (b) (6) (Study 303), 66 year-old male who received oral octreotide 40 mg dose through the entire DPC period. His medical history included hypertension, osteoarthritis, history of myocardial infarction, hyperlipidemia, bladder dysfunction, basal cell carcinoma, hypothyroidism, hypogonadism, and gastritis. Concomitant medications were aspirin, clopidrogel, atorvastatin, bisoprolol, levothyroxine, pivmecillinam, pantoprazole, and intramuscular testosterone. This patient was reported with "large intestinal polyp" at day 196 after his first dose of study drug. No action was taken regarding the study drug. The event was considered resolved after the patient underwent colonoscopy and four benign polyps were removed. The event was mild in intensity and assessed by the PI and Applicant as unrelated to the study drug.

Patient (b) (6) (Study 303), 63-year-old female, who received oral octreotide 40 mg dose through the entire DPC period. Her medical history included diabetes mellitus, nodular goiter/hypothyroidism, iron-deficiency anemia, vitamin D deficiency, dyslipidemia, osteoarthritis, hemangioma of the liver, nephrolithiasis, and carotid artery aneurysm. Concomitant medications included atorvastatin, cholecalciferol, codeine, dexketoprofen, metformin, iron fumarate, folic acid, levothyroxine, paracetamol, and vildagliptin. This patient was reported with "polyp of colon transversum" (PT of large intestinal polyp) at day 170 after her first dose of study drug. The event was considered mild in intensity and no action was taken regarding the study drug. The event was considered resolved after the patient underwent polypectomy. No pathology report is included in the narrative by the Applicant. Both, the Investigator and the Applicant assessed the event as unrelated to study drug.

Patient (b) (6) (Study 01), 63-year old male with a medical history of "polyposis colon" who underwent polypectomies in 3 occasions prior to entering the study. Other medical history included dyslipidemia, thyroid hyperplasia/primary hypothyroidism, renal cysts, benign prostatic hypertrophy, arterial hypertensionm cholelithiasis, hemorrhoids, and osteonecrosis of the femoral head. Concomitant medications included atorvastatin, levothyroxine, ramipril/hydrochlorothiazide, ursodeoxycholic acid, vitamin B12 injections, and ferrous sulfate. This patient was reported with colonic polyp on day 153 (of Core Phade) after his first dose of study drug (final dose 80 mg). The event was considered moderate in intensity and no action was taken regarding study drug. The event was considered resolved after the patient underwent polypectomy. No result of pathology reported is included in the narrative. Both, PI and Applicant assessed this event as unrelated to study drug.

Medical Officer comment: Without results of colonoscopy at baseline in both groups and presence of confounding factors (e.g., 'polyposis colon' in one patient, age of patients), it is dificult to draw a conclusion regarding relationship between the drug and the event. In addtion, it is well known that acromegaly itself is associated with increased risk of developing colonic polyps. Overall, based on the narratives provided by the Applicant, this Medical Officer agrees with the assessment of "large intestinal polyps" reported in patients who received oral octreotide in Study 303 and Study 01 as AEs unrelated to study drug.

S/TUDY CH-ACM-01

In Study 01, overall the most frequently reported AEs were in the SOC of GI disorders [88 (56.8%) patients] and the PT of headache [52 (33.5%) patients]. A summary of common TEAEs (incidence ≥5%, by PT) in the Core phase is presented in Table 20.

Table 20: Summary of most common **(≥5%)** adverse events by PT in Core phase of Study CH-ACM-01

System Organ Class Preferred Term	Core Phase (N=155)	
	n (%)	Events
Patient with at least 1 TEAE	134 (86.5)	1085
Gastrointestinal disorders	89 (57.4%)	225
Nausea	46 (29.7%)	61
Diarrhea	28 (18.1%)	37
Dyspepsia	13 (8.4%)	16
Flatulence	9 (5.8%)	14
Abdominal distension	10 (6.5%)	13
Abdominal pain upper	12 (7.7%)	13
Abdominal pain	8 (5.2%)	10
Vomiting	9 (5.8%)	10
Nervous system disorders	61 (39.4%)	200
Headache	51 (32.9%)	156
Dizziness	8 (5.2%)	13
Musculoskeletal and connective tissue disorders	57 (36.8%)	140
Arthralgia	40 (25.8%)	85
Back pain	9 (5.8%)	9
General disorders and administration site conditions	53 (34.2%)	126
Asthenia	34 (21.9%)	56
Peripheral swelling	24 (15.5%)	38
Fatigue	8 (5.2%)	9
Infections and infestations	52 (33.5%)	87
Nasopharyngitis	11 (7.1%)	16
Influenza	10 (6.5%)	11
Upper respiratory tract infection	8 (5.2%)	9
Skin and subcutaneous tissue disorders	41 (26.5%)	79
Hyperhidrosis	33 (21.3%)	56
Vascular disorders	13 (8.4%)	19
Hypertension	8 (5.2%)	13

Source: Table adapted from Table 10, CSC.

It is noted that some of the TEAEs reported in high incidence in Study 01, *e.g.*, headache were reported in much lower rate or not experienced in Study 303. This finding may be due to different populations, *i.e.*, in Study 01 (single-arm, open label study), the population consisted of patients who were not biochemically controlled.

Analysis of AEs by Relationship to Study Drug

The TEAEs assessed by the Investigator as related to the study drug were reported in 18 (64.3%) patients in the oral octreotide group and 15 (53.6%) patients in the placebo group (DPC period). During the OLE phase, 9 (22.5%) patients experienced drug-related TEAEs. Most of the TEAEs were classified as mild or moderate in intensity. Common TEAES (incidence ≥2.5% by PT)

assessed by the Applicant as drug-related with incidence in oral octreotide group > placebo group (DPC period) and corresponding incidence in the OLE phase are presented in Table 21.

Table 21: Common drug-related TEAEs **(≥2.5%** by PT) with incidence in oral octreotide > placebo (DPC period) and corresponding incidence in the OLE period (Study OOC-ACM-303), in descending order by first column.

Preferred Term	DPC Period				OLE period	
	Oral octreotide (N = 28)		Placebo (N = 28)		Oral octreotide (N = 40)	
	n (%)	Events	n (%)	Events	n (%)	Events
Any related TEAE	18 (64.3)	40	15 (53.6)	41	9 (22.5)	26
Nausea	5 (17.9)	5	2 (7.1)	2	3 (7.5)	3
Diarrhea	5 (17.9)	5	4 (14.3)	4	4 (10.0)	4
Headache	3 (10.7)	6	0	0	0	0
Dyspepsia	2 (7.1)	2	1 (3.6)	2	0	0
Vomiting	2 (7.1)	2	0	0	1 (2.5)	1
Abdominal pain	2 (7.1)	2	1 (3.6)	1	2 (5.0)	2
Cholelithiasis	2 (7.1)	2	1 (3.6)	1	0	0
Pain	1 (3.6)	1	0	0	0	0
Hyperglycemia	1 (3.6)	1	0	0	2 (5.0)	2
Blood glucose increased	1 (3.6)	1	0	0	0	0
Lipase increased	1 (3.6)	1	0	0	0	0
Anxiety	1 (3.6)	1	0	0	0	0

Source: Table adapted by Medical Officer from Table 11, SCS

STUDY CH-ACM-01

It is noted that while almost all drug-related TEAEs experienced during the Core phase were reported in <2.5% during the Extension phase, cholelithiasis was experienced in 4 (4.5%) patients in the Extension phase *vs*. 3 (1.9%) patients in the Core phase. A summary of the most common (≥2.5% by PT) drug-related TEAEs in Study 01 (Core and Extension phases) is presented in Table 22.

Table 22: Summary of most common **(≥2.5%** by PT) drug-related TEAEs in Study CH-ACM-01 (Core and Extension phases) by PT, in descending order by first column.

Preferred Term	Core Phase (N = 155)		Extension Phase (N = 88)	
	n (%)	Events	n (%)	Events
Nausea	36 (23.2%)	44	0	0
Headache	17 (11.0%)	29	< 2.5%)	2
Diarrhea	14 (9.0%)	18	< 2.5%)	2
Dyspepsia	10 (6.5%)	13	< 2.5%)	1
Asthenia	10 (6.5%)	10	0	0
Arthralgia	9 (5.8%)	10	0	0
Flatulence	7 (4.5%)	9	< 2.5%)	1
Abdominal pain upper	7 (4.5%)	7	< 2.5%)	1
Abdominal distention	6 (3.9%)	7	< 2.5%)	1
Peripheral swelling	6 (3.9%)	9	0	0
Vomiting	5 (3.2%)	6	0	0
Fatigue	5 (3.2%)	5	0	0
Constipation	4 (2.6%)	6	0	0
Abdominal pain	4 (2.6%)	5	< 2.5%)	1
Gastroesophageal reflux	4 (2.6%)	5	< 2.5%)	1
Dizziness	4 (2.6%)	5	< 2.5%)	1
Cholelithiasis	3 (1.9%)	3	4 (4.5%)	4

Source: Table adapted from Table 11, SCS.

8.4.6. Laboratory Findings

STUDY OOC-ACM-303

Clinical Laboratory tests: The overall results of the clinical laboratory tests (chemistry, hematology, and urinalysis) performed during the DPC period compared to the baseline values do not suggest any drug-related pattern.

Chemistry :

- Serum glucose: Serum glucose values were used to assess shift from baseline to end-of-treatment (EOT) and to report patients developing hypo- or hyperglycemia during the DPC period, which were terms defined as disease-related AEs. One of the withdrawal criteria was exacerbation of an AE related to acromegaly. In the oral octreotide group, 14 patients (50%) had glucose levels within normal values at baseline and EOT; 3 (10.7%) patients improved glucose levels; 6 (21.4%) patients remained within the same range; and 5 (17.9%) patients worsened from normal range at baseline to mildly elevated at EOT. In the placebo group, 21 patients (75.0%) had glucose levels within normal limits at baseline and EOT; 3 patients improved , 2 patients maintained glucose levels in the same range of baseline; and 1 patient worsened from an already elevated baseline level (glucose >ULN – 8.9 mmol/L) to

a higher level (glucose >13.9 – 27.8 mmol/L) at EOT. Data from 1 patient in the placebo group was missing.

In the oral octreotide group, a TEAE of blood glucose increased was reported for 3 patients and hypoglycemia was reported for 1 patient. In the placebo group, TEAE of hyperglycemia and HbA1c increased were reported for 1 patient each. A shift in HBA1c from normal at baseline to high at EOT was observed in 1 patient in the oral octreotide group and no shifts from normal to high HbA1c occurred in the placebo group.

In the OLE phase, 6 (16.2%) patients had a shift from normal or low glucose at baseline to high glucose at end of treatment (EOT) and 1 (7.7 %) patient had a shift in HbA1c from low or normal at baseline to high at EOT.

- Liver enzymes: Notable elevations in more than one liver enzyme were reported for 2 (0.7%) patients in the oral octreotide group (described below) in DPC period. None of them was consistent with Hy's law. See case description below:

  Patient # (b) (6), exhibited a level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 x ULN at week 32, while receiving oral octreotide 80 mg. His transaminase levels measured in 2 unscheduled visits between week 32 and week 34 declined to normal levels within 2-7 days. Serum gamma-glutamyl transferase (GGT) also peaked at week 32 and normalized at week 36. Total bilirubin remained within normal limits. There is no information on PI's causal assessment for this event. Since no additional information was provided by the Applicant for complete assessment of this case, this Medical Officer analyzed the graphical patient profile (GPP) using the JReview tool. The GPP revealed that this patient had a history of cholelithiasis and presented with abdominal pain at week 32 assessed by gallbladder ultrasound, which showed a diagnosis of biliary sludge. Based on the overall information, this Medical Officer assessed the event of increased liver enzymes in this patient as resulting from biliary sludge, which is a described class-effect of SSAs.

  Patient (b) (6), exhibited asymptomatic transaminase increased beginning at week 16 (while receiving oral octreotide 40 mg) with ALT > 3x ULN, aspartate aminotransferase (AST) slightly increased (1.3 x ULN) and bilirubin value within normal limits. Despite interruption of study drug, both ALT and AST peaked 5 days later. The Investigator suspected Atorvastatin as a cause of the liver enzymes serum level elevation. The patient's liver enzymes promptly normalized after atorvastatin withdrawal and remained within normal limits after the patient was re-challenged with the study drug. The Investigator assessed the event as related to atorvastatin.

- Thyroid stimulating hormone (TSH): No shifts from baseline to EOT values were observed

and no thyroid-related TEAEs were reported in either treatment group during the DPC period.
In the OLE phase, a shift from high or normal TSH at baseline to low TSH at EOT occurred in 3 (8.3%) patients and a shift from normal or low free T4 at baseline to high free T4 at EOT occurred in 1 (2.7%) patient.

Medical Officer Comment: Risks for hypo and hyperglycemia, hypothyroidism and increased liver enzymes associated with cholelithiasis and biliary sludge are known class effects associated with SSAs and are described in the label of approved somatostatin analogs (octreotide, lanreotide and pasireotide). The proposed label of oral octreotide includes these risks under Section 5 (Warnings and Precautions). The description of these events should be also included in Section 6. See discussion on Gallbladder ultrasound below.

Hematology:
No clinically meaningful differences were observed in hematologic shifts between treatment groups. No hematology laboratory abnormalities were reported as TEAEs in the oral octreotide group. In the placebo group, 4 hematologic abnormalities were reported as TEAEs, all with a single patient each: hematocrit decreased, hematocrit increased, hemoglobin decreased, and white blood cell increased.

Gallbladder ultrasound
Only patients with both baseline (BL) and end of treatment (EOT) data on gallbladder ultrasound were included in the analysis of shifts in gallbladder ultrasound results. Over half of the patients in both treatment groups had an abnormal gallbladder ultrasound at both BL and EOT, and 2 patients in the oral octreotide group shifted from normal to abnormal gallbladder ultrasound. No shifts were observed in the placebo group (See Table 23).

Table 23: Results of gallbladder ultrasound at baseline and end-of-treatment, DPC period.

Results of gallbladder ultrasound	Oral octreotide	Placebo
Abnormal at BL and at EOT	11/20 (55%)	12/18 (67%)
Normal at BL and EOT	6/20 (30%)	6/18 (33%)
Abnormal at BL and normal EOT	1/20 (5%)	0
Normal at BL and abnormal at EOT	2/20 (10%)	0

Source: Table generated by Clinical Reviewer with data from CSR, Section 12.5.4.

In the oral octreotide group, 1 patient with cholelithiasis at BL improved during DPC and 2 patients without cholelithiasis at BL worsened during the DPC period. In the placebo group 1 patient with cholelithiasis at BL worsened and 1 patient without cholelithiasis at BL worsened during the DPC period. Three (10.7%) patients in the oral octreotide group and 2 (7.1%) patients in the placebo group experienced a TEAE of the biliary tree.

A summary of narratives for patients with TEAEs of biliary tree in the oral octreotide group is presented below:

- Patient (b) (6), 57-year old female, experienced cholelithiasis in study day 256. Gallbladder ultrasound was normal at BL abnormal at week 36 due to presence of biliary sludge. The TEAE was assessed by the Investigator as study drug-related.
- Patient (b) (6), 59-year old male, experienced 2 episodes of acute cholecystitis and acute hepatitis. Gallbladder ultrasound was abnormal at BL due to the presence of multiple stones. At week 36, the gallbladder ultrasound was reported as abnormal because the gallbladder had been surgically removed during the study.
- Patient (b) (6), 52-year old male, experienced moderate cholelithiasis approximately at study day 200. Gallbladder ultrasound was abnormal at BL and at week 36 due to the presence of biliary sludge.

Medical Officer Comment: Development and worsening of gallbladder disorders have been reported in clinical trials with octreotide, pasireotide and lanreotide, and is included in the Warnings & Precautions (W&P) of all approved somatostatin analogs. The proposed label for oral octreotide has appropriately included gallbladder abnormalities in the W&P section.

STUDY CH-ACM-01
Abnormal laboratory findings in Study CH-ACM-01 were previously discussed by Dr. Abraham in her review of the original NDA. In summary, there were no clinically significant findings of laboratory abnormalities that raised a concern in Study 01.

8.4.7. Vital Signs

STUDY OOC-ACM-303
There were no clinically meaningful findings in vital sign changes in patients treated with oral octreotide during the DPC period or OLE periods.

STUDY CH-ACM-01
In the Core phase of Study 01, vital sign-associated TEAEs included hypertension in 8 (5.2%) patients, pyrexia in 3 (1.9%) patients, and hypotension in 2 (1.3%) patients. In the Extension phase, vital sign-associated TEAEs reported were hypertension in 3 (3.4%) patients and pyrexia in 1 (1.1%) patient.

8.4.8. Electrocardiograms (ECGs)

STUDY OOC-ACM-303
Patients with acromegaly treated with octreotide injection and other somatostatin analogs have been reported to develop bradycardia, conduction abnormalities, arrhythmias and other ECG changes including QT prolongation. In this study, during the DPC period, no shifts from normal to abnormal findings on PR interval, QRS interval, or heart rate were observed in the

oral octreotide group. One patient in each treatment group exhibited a shift from normal to abnormal Fridericia's formula-corrected QT interval (QTcF). A TEAE of atrioventricular block was reported for 1 patient in the placebo group. No ECG-related TEAEs were reported in the oral octreotide group.

Medical Officer Comment: While changes in the ECG parameters in the oral octreotide treatment group appear to be sparse, this study involved a small number of patients. Bradycardia and conduction abnormalities have been included as potential risks in the label of octreotide injection and other SSAs and are considered a drug class effect. The proposed label for oral octreotide includes bradycardia, arrhythmia and conduction abnormalities in the W&P section.

STUDY CH-ACM-01
No significant ECG abnormal patterns or signals were identified in this Study.

8.4.9. Immunogenicity

Immunogenicity was assessed in Study CH-ACM-01 under SPA by a hierarchical testing scheme and summarized in Study OOC-ACM-303, Module 2.7.1, under Section 2.7.1.7 (Bioanalytical Methods for Immunogenicity Studies). For complete information refer to Clinical Pharmacology Review by Dr. Sista Suryanarayana (dated 06/01/2020)

In summary, results of the immunogenicity study with oral octreotide revealed that:

- No anti-octreotide antibodies were detected in the Core and Extension phases of Study CH-ACM-01.

8.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were submitted for review.

8.6. Safety Analyses by Demographic Subgroups

Safety Analysis by Age-group
Study OOC-ACM-303: The overall incidence of TEAEs was balanced between the age-group < 65 years and age-group ≥ 65 years. Both SAEs reported in the octreotide group were patients under 65 years of age, while the patient in the placebo group with SAE was in the age-group ≥ 65 years.

Study CH-ACM-01: There were no significant imbalances in the incidence of TEAEs or SAEs between age-group < 65 years and age-group ≥ 65 years in any phase of Study 01.

Safety Analysis by Gender
Study OOC-ACM-303: While most common TEAEs were balanced between males and females,

two TEAEs were more frequent in females: diarrhea [7 (43.8%) in female patients *vs*. 1 (8.3%) in male patient] and vomiting [4 (25%) in female patients *vs*. 0 male patients].

Study CH-ACM-01: The overall incidence of common TEAEs was similar between males and females in the Core phase. In the Extension phase, two TEAEs were more frequent in females than in males: arthralgia [8 (15.7%) females *vs*. 3 (8.1%) males] and hyperhidrosis [8 (15.7%) females *vs*. 1 (2.7%)].

Safety analysis by geographic region

Study OOC-ACM-303: The overall incidence and types of TEAEs, including SAEs reported in patients of the US region were similar to those reported in patients of non-US region (Australia, Canada, EU, Israel, Mexico, New Zealand, Russia, and Turkey). While the proportion of patients from US region was smaller than the proportion of patients from non-US region, the overall incidence of TEAEs was balanced between US and non-US regions. This Medical Officer did not find evidence of factors that would preclude extrapolation of data of non-US patients treated with oral octreotide to the US population.

Study CH-ACM-01: This study was conducted entirely with patients from outside the US.

8.7. Safety in the Postmarket Setting

Oral octreotide is not currently marketed in any of the countries.
However, of the adverse reactions that have been identified during the postapproval use of the injectable octreotide acetate formulations and are listed in the octreotide acetate [Long-Acting Release (LAR) formulation], this Medical Officer listed below the clinically relevant adverse reactions associated with octreotide acetate that should be included in the label:

- *Cardiac:* myocardial infarction, cardiac arrest, atrial fibrillation
- *Endocrine:* diabetes insipidus, adrenal insufficiency in patients 18 months of age and under, pituitary apoplexy
- *Gastrointestinal:* intestinal obstruction, peptic/gastric ulcer, abdomen enlarged
- *Hepatobiliary:* gallbladder polyp, fatty liver
- *Laboratory abnormalities:* increased liver enzymes
- *Metabolism and nutrition:* diabetes mellitus
- *Nervous System:* migraines
- *Renal and urinary:* renal failure, renal insufficiency

8.7.1. Expectations on Safety in the Postmarket Setting

Oral octreotide is not currently marketed in any country.

8.7.2. Additional Safety Issues From Other Disciplines

None.

8.8. Integrated Assessment of Safety

The clinical studies included in the oral octreotide safety database are of different design, different drug dosing and regimen, and different population. Therefore, integrated assessment of safety will not be presented by pooled data, and rather by an overall assessment of safety of Study OOC-ACM-303, Study CH-ACM-01 and deaths reported in Study OOC-ACM-302.

It is noted that the proportion of patients who discontinued study drug due to a TEAE was 2-fold higher in the Core phase of Study 01 [23 (14.8%) patients] compared to the Core phase of Study 303 [2 (7.1%) patients]. However, due to different study designs (*e.g.*, single arm *vs*. randomized placebo control, different IGF-1 cutoff), no definitive conclusion can be drawn from this finding.

There were a total of 4 deaths reported in the clinical program, 2 in Study 01 and 2 in the ongoing Study 302. While Dr. Abraham assessed one death in Study 01 as possibly related to study drug, there is no clear evidence of an increased risk of death related to oral octreotide.

Overall, the most frequent AEs were in the SOC of Gastrointestinal (GI) Disorders and with similar incidence rates in Study 303 and Study 01. A lower incidence of GI disorders and other AEs in general was observed in the Extension phases compared to the respective Core phases of Study 303 and Study 01 and is likely due to the eligibility criteria for the Extension phases that selected against patients with drug intolerance and against patients who failed treatment with oral octreotide during the Core phase. In the SOC of Nervous System Disorders, headache appears with a higher incidence rate in Study 01 (both phases) compared to Study 303.

It is also noted that certain common TEAEs reported during the Core phase of Study 01 were not reported in any patient in Study 303. These differences in incidence of reported AEs may be due to study size, how the AE was captured and reported by the Investigator. Also, patient had uncontrolled disease during the study, i.e. the IGF-1 cutoff (1.3 x ULN) established for enrollment in the single-arm Study 01 is not consistent with biochemical control of acromegaly and symptoms of uncontrolled disease may have been a confounding factor in safety reporting.

Rather than discussing the AESIs proposed by the Investigator, this Medical Officer considered events of hepatobiliary disorders and neoplasms as events of special interest. Regarding hepatobiliary disorders, in Study 303, 1 patient experienced 2 SAEs of acute cholecystitis during the DPC period that this Medical Officer assessed as drug-related (contrary to the Investigator's assessment). Cholelithiasis occurred at a similar rate in Study 303, oral octreotide arm and in the single-arm Study 01. This Medical Officer concludes that there is no evidence in the overall

safety database of Study 01 and Study 303 that suggests an increased risk of hepatobiliary disorder associated with oral octreotide and considers these events as class effects.

Regarding malignancies, in Study 303, there was no imbalance in malignancies between oral octreotide group and placebo group. Two patients were reported with large intestinal polyp in the oral octreotide treatment group and were assessed by Investigator as unrelated to study drug. In Study 01, 3 of the 4 malignancies reported were assessed by Dr. Abraham as having evidence suggestive of pre-existing disease. This Medical Officer's assessment based on the overall findings is that there is no sufficient evidence to support an increased risk of malignancy associated with the use of oral octreotide.

In summary, the safety profile of oral octreotide appears consistent with the known safety profile of octreotide acetate (injectable). No new or unexpected safety signals were identified in the data reviewed by this Medical Officer.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was conducted for trial OOC-ACM-303.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling recommendations for oral octreotide (Mycapssa) include:

1. In Section 2
   - Change initial dose recommended by the Applicant from 60 mg daily to 40 mg daily
   - Recommend titration dosage by 20 mg daily, based on IGF-1 levels and patient's signs and symptoms
   - Add recommendations for monitoring loss of biochemical control with IGF-1 measurements; and to discontinue Mycapssa and switch patient to another SSA if IGF-1 > 1 x ULN
   - Add recommendation for periodic withdrawal of Mycapssa to assess disease activity.
   - Add recommended dosage in patients with end stage renal disease
   - Add recommendation for dosage modifications with concomitant use of proton pump inhibitors, H2-receptor antagonists, or Antacids
2. In Section 5 (W&P)
   - Add a statement that 'gallbladder-related AEs have been reported in clinical trials in patients treated with Mycapssa'; and a recommendation for monitoring patients

periodically for cholelithiasis and complications of cholelithiasis.
- Add language for monitoring blood glucose levels when Mycapssa treatment is initiated or when dose is altered.
- Add language to warn that Mycapssa may alter absorption of Vitamin B12.

3. In Section 6
   - List important AEs as bullets (cholelithiasis and complications of cholelithiasis, hyperglycemia and hypoglycemia, thyroid function abnormalities, cardiac function abnormalities, and decreased vitamin B12 levels and abnormal Schilling's Tests
   - Clinical Trial 1 and Clinical Trial 2 were changed to placebo-controlled study and open-label study, respectively.
   - Add sub-section 6.3 for Postmarketing Experience
4. In Section 7
   - Drug interactions (Effect of other drugs on Mycapssa and Effects of Mycapssa on other drugs) were inserted under Section 7 in a table format.
5. In Section 8, and Section 9
   - Language was updated
6. In Section 12
   - A paragraph was added with information on titration management in the placebo-controlled trial.
7. In Section 14
   - Demographics data and results of primary efficacy endpoint of the placebo-controlled trial were updated by the Statistics Reviewer.
   - Add language for patient counseling information

11. Risk Evaluation and Mitigation Strategies (REMS)

No Risk and Mitigation Strategies are required for this NDA.

12. Postmarketing Requirements and Commitments

No Postmarketing Requirements and Commitments are required for this NDA.

13. Appendices

13.1. References

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4 Katznelson L, Laws ER, Jr., Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99(11):3933-3951.
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8 Brighi N, Lamberti G, Maggio I, et al. Biliary stone disease in patients receiving somatostatin analogs for neuroendocrine neoplasms. A retrospective observational study. *Dig Liver Dis.* 2019;51(5):689-694.
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10 Fraquelli M, Bardella MT, Peracchi M, Cesana BM, Bianchi PA, Conte D. Gallbladder emptying and somatostatin and cholecystokinin plasma levels in celiac disease. *Am J Gastroenterol.* 1999;94(7):1866-1870.

13.2. Financial Disclosure

Covered Clinical Study: Study OOC-ACM-303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 201		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: none Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in S none Sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Lists of Investigators who have financial disclosures was provided by the Applicant with payments broken by year (See Table 1, Table 2 and Table 3 below):

Table 1 Payments Made to the Listed Investigators for Consulting Services per Year

PI \ Year	US$	(b) (6)										Total
(b) (6)	US$	-	6,712	-	19,566	-	19,317	6,825	6,120	-	-	**58,540**
	US$	28,150	-	-	-	-	-	-	-	-	-	**28,150**
	US$	-	3,520	3,520	-	-	-	-	-	-	-	**7,040**
	US$	9,388	14,060	40,812	31,400	32,229	77,000	-	-	-	-	**204,889**
	US$	-	-	-	-	-	-	4,200	1,400	-	-	**5,600**
	US$	-	-	-	-	-	-	3,000	-	-	-	**3,000**
	US$	**37,538**	**24,292**	**44,332**	**50,966**	**32,229**	**96,317**	**14,025**	**7,520**	-	-	**307,219**

(b) (6)

Table 2 Payments Made to the Listed Investigators as Honorarium Fees for Participation in Advisory Meetings

PI \ Year	US$											Total
(b) (6)	US$	-	-	-	2,500	-	2,500	-	-	-	-	5,000
	US$	-	-	1,000	2,554	-	-	-	-	-	-	3,554
	US$	-	-	1,000	-	-	2,500	750	-	1,250	-	5,500
	US$	-	-	-	-	-	-	4,250	1,250	3,250	1,984	10,734
	US$	-	-	-	-	-	-	-	500	400	-	900
	US$	-	-	-	-	-	-	3,000	-	-	-	3,000
	US$	-	-	-	-	-	-	-	-	400	-	400
	US$	-	-	-	-	-	-	-	-	-	500	500
	US$	-	-	-	-	-	-	1,000	-	-	-	1,000
	US$	-	-	-	-	-	-	1,750	-	500	750	3,000
	US$	-	-	-	-	-	-	3,500	1,250	3,000	750	8,500
	US$	-	-	-	-	-	-	-	-	400	-	400
	US$	-	-	-	-	-	-	1,000	-	5,000	-	6,000
	US$	-	-	-	-	-	-	-	300	-	-	300
	US$	-	-	-	-	-	-	1,500	1,250	1,750	1,000	5,500
	US$	-	-	-	-	-	-	-	-	400	-	400
	US$	-	-	-	-	-	-	3,000	-	-	-	3,000
	US$	-	-	-	-	-	-	1,000	-	400	-	1,400
	US$	-	-	-	-	-	-	1,500	1,750	500	750	4,500
	US$	-	-	-	-	-	-	2,250	750	2,000	750	5,750
(b) (6)	US$	-	-	2,000	5,054	-	5,000	24,500	7,050	19,250	6,484	69,338

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Table 3 Information with Respect to Stock Options Granted to Investigators

Name	Grant Date	Options granted	Exercise price	Fair Value (on grant date)
(b) (6)		6,045	$1.92	$16,684
		27,353	$1.92	$35,012
		4,853	$8.13	$31,933
		4,853	$8.13	$31,933

	Octreotide Capsule Treatment Group (Final Dose in DPC Period)					
	40 mg	60 mg	80 mg	Total	Placebo	Overall

Table 24: Summary of Patient Demographic and Baseline Characteristics for the DPC Period

Gender (n [%])						
Male	3 (42.9)	1 (50.0)	8 (42.1)	12 (42.9)	14 (50.0)	26 (46.4)
Female	4 (57.1)	1 (50.0)	11 (57.9)	16 (57.1)	14 (50.0)	30 (53.6)
Missing	0	0	0	0	0	0
Race (n [%]) [1]						
American Indian or Alaskan Native	0	0	0	0	0	0
Asian	1 (14.3)	0	0	1 (3.6)	2 (7.1)	3 (5.4)
Black/African or African American	0	0	0	0	1 (3.6)	1 (1.8)
Native Hawaiian or Pacific Islander	0	0	0	0	0	0
White/Caucasian	6 (85.7)	2 (100.0)	19 (100.0)	27 (96.4)	24 (85.7)	51 (91.1)
Other	0	0	0	0	1 (3.6)	1 (1.8)
Missing	0	0	0	0	0	0
Ethnicity (n [%])						
Hispanic or Latino	0	0	0	0	3 (10.7)	3 (5.4)
Not Hispanic or Latino	7 (100.0)	2 (100.0)	19 (100.0)	28 (100.0)	25 (89.3)	53 (94.6)
Not reported	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Region						
US sites	0	0	6 (31.6)	6 (21.4)	15 (53.6)	21 (37.5)
Non-US sites	7 (100.0)	2 (100.0)	13 (68.4)	22 (78.6)	13 (46.4)	35 (62.5)
Age (years) at screening [2]						
n	7	2	19	28	28	56
Mean (SD)	57.1 (9.92)	39.0 (1.41)	56.3 (12.26)	55.3 (11.97)	54.2 (10.96)	54.7 (11.38)
Median	61.0	39.0	57.0	57.0	54.5	57.0
P25, P75	46.0, 66.0	38.0, 40.0	47.0, 65.0	46.5, 64.5	45.5, 63.0	46.0, 63.5
Minimum, maximum	45, 69	38, 40	30, 79	30, 79	38, 73	30, 79
Age (categorical) (n [%])						
< 65 years old	5 (71.4)	2 (100.0)	14 (73.7)	21 (75.0)	22 (78.6)	43 (76.8)
≥ 65 years old	2 (28.6)	0	5 (26.3)	7 (25.0)	6 (21.4)	13 (23.2)
Missing	0	0	0	0	0	0
Weight (kg) at screening						
n	7	2	19	28	28	56
Mean (SD)	82.9 (20.75)	75.6 (22.06)	84.4 (16.33)	83.4 (17.22)	91.6 (20.48)	87.5 (19.19)
Median	82.0	75.6	81.8	81.9	95.5	84.1
P25, P75	71.0, 99.5	60.0, 91.2	74.2, 94.0	72.6, 92.6	75.8, 106.9	73.6, 102.0
Minimum, maximum	48, 113	60, 91	57, 127	48, 127	56, 126	48, 127
Height (cm) at screening						
n	7	2	19	28	28	56
Mean (SD)	167.0 (7.00)	176.1 (8.63)	169.7 (7.74)	169.5 (7.65)	171.3 (8.44)	170.4 (8.03)
Median	167.0	176.1	168.8	169.4	173.8	170.0
P25, P75	163.0, 173.0	170.0, 182.2	163.3, 177.0	163.7, 176.0	166.4, 176.8	164.6, 176.8
Minimum, maximum	154, 175	170, 182	158, 185	154, 185	154, 187	154, 187
Body mass index (kg/m^2) at screening						
n	7	2	19	28	28	56
Mean (SD)	30.1 (9.21)	24.1 (4.74)	29.2 (5.12)	29.1 (6.26)	31.0 (5.58)	30.0 (5.96)
Median	28.1	24.1	28.2	27.8	31.2	28.8
P25, P75	24.6, 42.0	20.8, 27.5	26.2, 31.1	26.1, 30.4	26.5, 35.1	26.2, 34.0
Minimum, maximum	17, 43	21, 27	23, 44	17, 44	22, 43	17, 44

[1] Patients could have selected multiple race categories.
[2] Age (years) = year of study day 0 – year of birth.
DPC = double-blind, placebo-controlled; P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation

13.3. Demographics Table

Source: Excerpted from CSR, Table 11

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13.4. Acromegaly Baseline Characteristics

Table 25: Summary of Acromegaly Baseline Characteristics for the DPC Period

	Octreotide Capsule Treatment Group (Final Dose in DPC Period)					
Characteristics	40 mg (N = 7)	60 mg (N = 2)	80 mg (N = 19)	Total (N = 28)	Placebo (N = 28)	Overall (N = 56)
Duration of acromegaly						
< 10 years	3 (42.9)	2 (100.0)	10 (52.6)	15 (53.6)	20 (71.4)	35 (62.5)
10 to < 20 years	3 (42.9)	0	5 (26.3)	8 (28.6)	5 (17.9)	13 (23.2)
≥ 20 years	1 (14.3)	0	4 (21.1)	5 (17.9)	3 (10.7)	8 (14.3)
Missing	0	0	0	0	0	0
Tumor size at diagnosis (n [%])						
Microadenoma (≤ 10 mm)	2 (28.6)	1 (50.0)	7 (36.8)	10 (35.7)	9 (32.1)	19 (33.9)
Macroadenoma (> 10 mm)	0	0	6 (31.6)	6 (21.4)	5 (17.9)	11 (19.6)
Other	5 (71.4)	1 (50.0)	5 (26.3)	11 (39.3)	12 (42.9)	23 (41.1)
Missing	0	0	1 (5.3)	1 (3.6)	2 (7.1)	3 (5.4)
Previous treatments for acromegaly (n [%]) [1]						
Octreotide daily injection	0	0	0	0	3 (10.7)	3 (5.4)
Octreotide long acting	6 (85.7)	2 (100.0)	13 (68.4)	21 (75.0)	18 (64.3)	39 (69.6)
Lanreotide	3 (42.9)	0	6 (31.6)	9 (32.1)	12 (42.9)	21 (37.5)
Pasireotide	0	0	0	0	4 (14.3)	4 (7.1)
Bromocriptine	1 (14.3)	0	2 (10.5)	3 (10.7)	3 (10.7)	6 (10.7)
Cabergoline	2 (28.6)	0	5 (26.3)	7 (25.0)	3 (10.7)	10 (17.9)
GH receptor antagonist – pegvisomant	0	0	0	0	2 (7.1)	2 (3.6)
SRLs plus dopamine agonists	1 (14.3)	0	3 (15.8)	4 (14.3)	1 (3.6)	5 (8.9)
SRLs plus pegvisomant	0	0	0	0	1 (3.6)	1 (1.8)
Other	0	0	0	0	0	0
Prior acromegaly surgery						
Yes	6 (85.7)	2 (100.0)	17 (89.5)	25 (89.3)	24 (85.7)	49 (87.5)
No	1 (14.3)	0	2 (10.5)	3 (10.7)	4 (14.3)	7 (12.5)
Time from last surgery (years)						
N	6	2	17	25	24	49
Mean (SD)	12.0 (7.23)	5.0 (1.15)	9.3 (8.28)	9.6 (7.75)	8.7 (5.64)	9.1 (6.74)
Median	12.1	5.0	6.2	6.2	7.4	7.1
P25, P75	5.0, 17.1	4.1, 5.8	3.8, 11.9	3.8, 12.7	4.4, 10.9	3.8, 11.9
Minimum, maximum	3, 22	4, 6	1, 32	1, 32	1, 20	1, 32

(Cont.)

	Octreotide Capsule Treatment Group (Final Dose in DPC Period)					
Characteristics	40 mg (N = 7)	60 mg (N = 2)	80 mg (N = 19)	Total (N = 28)	Placebo (N = 28)	Overall (N = 56)
Residual tumor size (mm) (n [%])						
< 5 mm	1 (14.3)	0	4 (21.1)	5 (17.9)	4 (14.3)	9 (16.1)
5-10 mm	1 (14.3)	1 (50.0)	3 (15.8)	5 (17.9)	5 (17.9)	10 (17.9)
> 10 mm	0	0	6 (31.6)	6 (21.4)	5 (17.9)	11 (19.6)
Not visible	5 (71.4)	1 (50.0)	5 (26.3)	11 (39.3)	12 (42.9)	23 (41.1)
Undetermined	0	0	1 (5.3)	1 (3.6)	2 (7.1)	3 (5.4)
Missing	0	0	0	0	0	0
Symptom burden [2]						
≥ 1	6 (85.7)	1 (50.0)	16 (84.2)	23 (82.1)	24 (85.7)	47 (83.9)
≥ 2	3 (42.9)	0	15 (78.9)	18 (64.3)	19 (67.9)	37 (66.1)
≥ 3	2 (28.6)	0	8 (42.1)	10 (35.7)	14 (50.0)	24 (42.9)
Baseline average IGF-1 (ULN) [3]						
n	7	2	19	28	28	56
Mean (SD)	0.70 (0.141)	0.85 (0.071)	0.83 (0.159)	0.80 (0.157)	0.84 (0.210)	0.82 (0.185)
Median	0.70	0.85	0.80	0.80	0.90	0.80
P25, P75	0.60, 0.80	0.80, 0.90	0.70, 1.00	0.70, 0.90	0.75, 1.00	0.70, 1.00
Minimum, maximum	0.5, 0.9	0.8, 0.9	0.6, 1.1	0.5, 1.1	0.3, 1.1	0.3, 1.1
Baseline average IGF-1 (categorical) (n [%]) [3]						
≤ 1 ULN	7 (100.0)	2 (100.0)	18 (94.7)	27 (96.4)	23 (82.1)	50 (89.3)
> 1 to < 1.3 ULN	0	0	1 (5.3)	1 (3.6)	5 (17.9)	6 (10.7)
≥ 1.3 ULN	0	0	0	0	0	0
Baseline GH (ng/mL) [4]						
n	7	2	19	28	28	56
Mean (SD)	0.41 (0.308)	0.40 (0.141)	0.77 (0.869)	0.66 (0.745)	0.90 (1.009)	0.78 (0.887)
Median	0.40	0.40	0.40	0.40	0.60	0.50
P25, P75	0.10, 0.70	0.30, 0.50	0.10, 1.00	0.15, 0.90	0.20, 1.05	0.20, 0.90
Minimum, maximum	0.1, 0.9	0.3, 0.5	0.1, 3.5	0.1, 3.5	0.1, 3.9	0.1, 3.9
Baseline GH (categorical) (n [%]) [4]						
≤ 1 ng/mL	7 (100.0)	2 (100.0)	14 (73.7)	23 (82.1)	21 (75.0)	44 (78.6)
> 1 to < 2.5 ng/mL	0	0	4 (21.1)	4 (14.3)	4 (14.3)	8 (14.3)
≥ 2.5 ng/mL	0	0	1 (5.3)	1 (3.6)	3 (10.7)	4 (7.1)
Prior injectable treatment octreotide LAR dose (n [%]) [5]						
Low	2 (28.6)	1 (50.0)	0	3 (10.7)	2 (7.1)	5 (8.9)
Middle	0	0	7 (36.8)	7 (25.0)	7 (25.0)	14 (25.0)
High	3 (42.9)	0	6 (31.6)	9 (32.1)	8 (28.6)	17 (30.4)
Prior injectable treatment lanreotide dose (n [%]) [5]						
Low	1 (14.3)	1 (50.0)	1 (5.3)	3 (10.7)	3 (10.7)	6 (10.7)
Middle	0	0	1 (5.3)	1 (3.6)	4 (14.3)	5 (8.9)
High	1 (14.3)	0	4 (21.1)	5 (17.9)	4 (14.3)	9 (16.1)
Prior injectable treatment overall (n [%]) [5]						
Low	3 (42.9)	2 (100.0)	1 (5.3)	6 (21.4)	5 (17.9)	11 (19.6)
Middle	0	0	8 (42.1)	8 (28.6)	11 (39.3)	19 (33.9)
High	4 (57.1)	0	10 (52.6)	14 (50.0)	12 (42.9)	26 (46.4)
Prior injectable treatment overall (n [%]) [5]						
Low	3 (42.9)	2 (100.0)	1 (5.3)	6 (21.4)	5 (17.9)	11 (19.6)
Middle and high	4 (57.1)	0	18 (94.7)	22 (78.6)	23 (82.1)	45 (80.4)

[1] Previous treatment anytime in the past. Patients could have had multiple previous treatments for acromegaly.
[2] Symptom burden reflects the number of ongoing acromegaly symptoms at Screening on the acromegaly history form.
[3] Based on the average of the 2 assessments within 2 weeks prior to randomization.
[4] Screening Visit 1. If Screening Visit 1 data were missing, then Baseline data were used.
[5] Low dose: octreotide 10 mg every 4 weeks; lanreotide 60 mg every 4 weeks or 120 mg every 8 weeks. Medium dose: octreotide 20 mg every 4 weeks; lanreotide 90 mg every 4 weeks or 120 mg every 6 weeks. High dose: octreotide 30 mg every 4 weeks; lanreotide 120 mg every 4 weeks.
DPC = double-blind, placebo-controlled; P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation; SV1 = Screening Visit 1; SV2 = Screening Visit 2
Source: Post-text Tables 14.1.4.1 and 14.1.4.4.1

Source: Excerpted from CSR, Table 12.

13.5. Common TEAEs during the DPC period

Table 26: Incidence of common TEAEs **(≥5%** in either treatment group) by SOC and PT during the DPC period

System Organ Class Preferred Term	Octreotide Capsules (N = 28) n (%)	Placebo (N = 28) n (%)	Overall (N = 56) n (%)
Patients with at least 1 TEAE	28 (100.0)	27 (96.4)	55 (98.2)
Gastrointestinal disorders	19 (67.9)	17 (60.7)	36 (64.3)
Abdominal discomfort	4 (14.3)	3 (10.7)	7 (12.5)
Abdominal pain	2 (7.1)	2 (7.1)	4 (7.1)
Abdominal pain upper	1 (3.6)	3 (10.7)	4 (7.1)
Constipation	3 (10.7)	4 (14.3)	7 (12.5)
Diarrhoea	8 (28.6)	6 (21.4)	14 (25.0)
Dyspepsia	3 (10.7)	1 (3.6)	4 (7.1)
Flatulence	1 (3.6)	2 (7.1)	3 (5.4)
Large intestinal polyp	2 (7.1)	0	2 (3.6)
Nausea	6 (21.4)	3 (10.7)	9 (16.1)
Tongue disorder	0	2 (7.1)	2 (3.6)
Vomiting	4 (14.3)	0	4 (7.1)
General disorders and administration site conditions	10 (35.7)	15 (53.6)	25 (44.6)
Fatigue	2 (7.1)	7 (25.0)	9 (16.1)
Influenza-like illness	0	2 (7.1)	2 (3.6)
Oedema peripheral	2 (7.1)	3 (10.7)	5 (8.9)
Pain	2 (7.1)	0	2 (3.6)
Peripheral swelling	3 (10.7)	4 (14.3)	7 (12.5)
Hepatobiliary disorders	3 (10.7)	2 (7.1)	5 (8.9)
Cholelithiasis	2 (7.1)	1 (3.6)	3 (5.4)

(Cont.)

System Organ Class Preferred Term	Octreotide Capsules (N = 28) n (%)	Placebo (N = 28) n (%)	Overall (N = 56) n (%)
Infections and infestations	13 (46.4)	8 (28.6)	21 (37.5)
Nasopharyngitis	3 (10.7)	4 (14.3)	7 (12.5)
Sinusitis	3 (10.7)	0	3 (5.4)
Upper respiratory tract infection	1 (3.6)	2 (7.1)	3 (5.4)
Urinary tract infection	2 (7.1)	1 (3.6)	3 (5.4)
Investigations	9 (32.1)	10 (35.7)	19 (33.9)
Blood glucose increased	3 (10.7)	1 (3.6)	4 (7.1)
Gamma-glutamyltransferase increased	1 (3.6)	3 (10.7)	4 (7.1)
Insulin-like growth factor increased	0	2 (7.1)	2 (3.6)
Weight increased	2 (7.1)	2 (7.1)	4 (7.1)
Metabolism and nutrition disorders	3 (10.7)	4 (14.3)	7 (12.5)
Hypercholesterolaemia	0	2 (7.1)	2 (3.6)
Musculoskeletal and connective tissue disorders	11 (39.3)	21 (75.0)	32 (57.1)
Arthralgia	9 (32.1)	16 (57.1)	25 (44.6)
Arthritis	2 (7.1)	2 (7.1)	4 (7.1)
Back pain	2 (7.1)	4 (14.3)	6 (10.7)
Musculoskeletal pain	1 (3.6)	2 (7.1)	3 (5.4)
Osteoarthritis	3 (10.7)	0	3 (5.4)
Pain in extremity	0	3 (10.7)	3 (5.4)
Soft tissue swelling	1 (3.6)	3 (10.7)	4 (7.1)
Nervous system disorders	10 (35.7)	13 (46.4)	23 (41.1)
Carpal tunnel syndrome	4 (14.3)	4 (14.3)	8 (14.3)
Headache	4 (14.3)	9 (32.1)	13 (23.2)
Hypoaesthesia	0	2 (7.1)	2 (3.6)
Paraesthesia	0	2 (7.1)	2 (3.6)
Psychiatric disorders	2 (7.1)	4 (14.3)	6 (10.7)
Anxiety	1 (3.6)	2 (7.1)	3 (5.4)
Skin and subcutaneous tissue disorders	8 (28.6)	11 (39.3)	19 (33.9)
Hyperhidrosis	6 (21.4)	7 (25.0)	13 (23.2)
Night sweats	1 (3.6)	2 (7.1)	3 (5.4)

DPC = double-blind, placebo controlled; PT = preferred term: SOC = system organ class; TEAE = treatment-emergent adverse event
Note: TEAEs were defined as all adverse events (AEs) that occurred after randomization (ie, date of onset was on or after the date of randomization) and on or before the end of treatment (last dose of blinded study drug) in the DPC period. A patient could have been counted only once within each category. AEs were coded using MedDRA Version 18.1.
Source: Excerpted from CSR, Table 28.

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/

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MARINA ZEMSKOVA
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I concur

Cross-Discipline Team Leader Review

Date	April 14, 2016
From	Marina Zemskova, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208232
Applicant	Chiasma
Date of Submission	June 15, 2015
PDUFA Goal Date	April 15, 2016
Proprietary Name / Established (USAN) names	Mycapssa/ octreotide acetate
Dosage forms / Strength	Capsule/ 20 mg
Proposed Indication(s)	Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)
Recommended:	*Complete Response*

1. Introduction

On June 15, 2015 Chiasma submitted a New Drug Application (NDA) for Mycapssa (oral octreotide acetate) under Section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act in support of the following indication:

Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)

Published literature and nonclinical studies conducted under approved NDA 19677 for use of Sandostatin Immediate Release (IR) in treatment of acromegaly are relied upon by the applicant as permitted under 505(b)(2).

Mycapssa is octreotide acetate formulated with Transient Permeability Enhancer (TPE) system for the oral administration. The oral formulation is an enteric-coated capsule designed to pass through the stomach intact and disintegrate in the small intestine to release octreotide with TPE into the lumen. TPE represents an (b) (4) (b) (4)

In this CTDL review I will summarize the findings from primary reviews and discuss issues identified by each discipline. This review will also discuss the main efficacy and safety findings from the single pivotal clinical study, focusing on the design of the study (i.e. open label, single arm, uncontrolled study in patients with acromegaly treated with injectable and oral octreotide formulations) and results of the primary analysis (i.e. percentage of patients who were able to maintain the control of the disease at the end of the study defined as insulin-growth factor (IGF-1) level < 1.3 X upper limit normal (ULN) and growth hormone (GH) < 2.5 ng/ml).

2. Background

Acromegaly is a chronic, rare disease with the annual incidence of approximately 3 per million[1]. The etiology of acromegaly is a GH-secreting pituitary tumor in majority of the cases. Elevated GH levels cause the symptoms of the disease, directly and indirectly, by stimulation secretion of IGF-1. Patients with acromegaly suffer from many disease complications and have higher mortality rates than an age-matched control population[2]. If the disease is not controlled by surgery or radiation treatment or patients are not surgical candidates, control of GH and IGF-1 concentrations can be achieved by medical treatment.

Somatostatin analogues (octreotide) are the first-line medical therapy of acromegaly. Somatostatin is an endogenous peptide produced in the hypothalamus; it inhibits synthesis and release of GH from the pituitary gland. The inhibitory action of somatostatin is achieved through five identified G protein-coupled somatostatin receptor subtypes. Three injectable synthetic analogues of somatostatin (SSA) are currently available for medical treatment of acromegaly in USA (lanreotide, octreotide and pasireotide).
Since all somatostatin analogs are injectable drugs, the oral delivery of the drug might be more convenient route of administration. Indeed, short-acting octreotide, Sandostatin IR, requires three times a day injections; the use of this formulation might be associated with inconvenience of using needles and daily injections. However, long acting SSAs formulations have more extended duration of action and can be administered monthly or every three months (Sandostatin LAR (octreotide), Somatuline Depot (lanreotide) and Signifor LAR (pasireotide)), thus, the use of long acting formulations decreases inconvenience of daily injections and improves compliance.
It should be also noted, that all approved somatostatin analogs reduce GH and IGF-l levels in up to 80% of patients who are sensitive to somatostatin analogs and in 40 % of patients with acromegaly who are treatment-naïve and do not have proven sensitivity to the drugs[3].

Thus, central to this application is not only whether the oral administration of octreotide is more convenient to the patients, but also whether the Sponsor provided convincing evidence that oral octreotide can maintain the disease control in a considerable proportion of patients who have proven sensitivity to somatostatin analogs.

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[1] Melmed S. Acromegaly. N Engl J Med. 2006 Dec 14; 355(24):2558-73
[2] Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-1 on mortality in acromegaly. Eur J Endocrinol. 2008 Aug;159(2):89-95.
[3] Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab. 2008 Aug;93(8):2957-68.

Regulatory Background

The following are the major regulatory interactions that took place between DMEP and Chiasma regarding the Mycapssa development program for the acromegaly indication:

1) Pre-IND meeting (March 2, 2010).

Retrospectively, this meeting was very important because it set the overall direction of the Mycapssa development program. The Agency indicated, that, in support of 505 (b)(2) application for NDA for Mycapssa, the Sponsor have to establish a "bridge" between Mycapssa and each listed drug upon which the Sponsor proposes to rely to demonstrate that such reliance is scientifically justify. The Agency also advised that the size of pivotal Phase III trial(s) should be the similar to the trial used in other somatostatin analogs clinical programs (e.g. Sandostatin LAR and Somatuline Depot) in order to establish the safety profile of the drug.

2) IND 108163 was opened on December 17, 2010 with a protocol for a Phase 1 clinical trial (CHI-004) to evaluate the duration of drug-induced intestinal permeability in healthy volunteers.

The Sponsor was allowed to proceed with a single dose study. However, the partial clinical hold was issued for the multiple dose studies, because the nonclinical data did not support the administration of the multiple doses. Chiasma submitted a complete response to the partial clinical hold letter on March 4, 2011 that included an amended report of the 28-day repeat-dose toxicity study of Octreolin in monkeys. The Agency lifted the partial clinical hold on March 30, 2011.

3) Mycapssa was granted Orphan Drug designation for "the oral treatment of acromegaly" on May 11, 2010 by the Office of Orphan Products Development.

4) End-of-Phase 2 meeting (August 9, 2011)

The Agency provided multiple comments regarding overall development program for Mycapssa:

- Regarding of the adequacy of the bridge between Sandostatin IR and oral octreotide.

The Division agreed that the exposure of a single dose 20 mg Mycapssa under fasting condition seemed comparable to s.c. 0.1 mg Sandostatin (Sandostatin IR) based on the results of two Phase 1 studies in healthy volunteers (CHI-001 and CH-002), however, the Division emphasized that the acceptability of these studies results as an adequate bridge between Mycapssa and Sandostatin IR will be a review issue. The Sponsor clarified that for the 505(b)(2) NDA submission the comparative bioavailability studies were to establish the "bridge" between Mycapssa and Sandostatin (b) (4) (b) (4) and not to demonstrate bioequivalence between these two products. The Sponsor indicated that the Company has its own clinical trial to establish Mycapssa efficacy and safety.

- Regarding the proposed plan for Phase 3 study.
- Overall, the Division accepted the proposed plan for Phase 3 study (single study, open label, single arm). However, the Division also asked the Sponsor to provide a summary of efficacy and safety based on available published information obtained with octreotide in patients with acromegaly and to indicate how these data are relevant to Mycapssa.
- The Division agreed that the planned number of patients (150) to be enrolled in the study was reasonable to evaluate the efficacy of the drug. However, the Division recommended again that the patient exposure should be comparable to that obtained with other somatostatin analogs program in order to evaluate the safety of the new octreotide formulation (refer to Pre-IND discussion above).
- The definition of the responder and the selected IGF-1 and GH threshold was further clarified during the meeting:
  The Division asked to clarify the clinical relevance of the selected IGF-1 threshold. The Sponsor stated that IGF-1 values are assay and lab dependent and the 30% ULN threshold was chosen to ensure that any observed IGF-1 levels are clinically relevant changes and not simply due to the intra- and inter-assay variability.
  The Sponsor also clarified that the GH threshold of < 2.5 ng/mL versus < 1 ng/mL for the responder definition was chosen because it is associated with reduction in mortality rate to background levels and is also used in the acromegaly labels for the other somatostatin products. The Division recommended to submit data for GH levels < 2.5 ng/mL and < 1 ng/mL.
- It was agreed that the evaluation of patient satisfaction is an exploratory endpoint.
- It was agreed that dedicated QTc study is unnecessary for octreotide alone and might be unnecessary for Mycapssa too pending the safety data from the Phase 3 study.

5) Pivotal Phase 3 study CHI-001

Although the design of the study was extensively discussed during the EOP2 meeting, only 2 versions of the study protocol were submitted to the Agency for the review (the original version #1, prior to EOP2 meeting and version #5, after the study database was locked):

- The first draft of the protocol was finalized on June 30, 2011 and submitted to the Agency within EOP2 meeting briefing package. In the first version, the proposed primary endpoint was IGF-1 levels at the completion of the Treatment Period; the proportion of the patients with normalized IGF-1 levels and GH levels < 2.5 ng/mL was the secondary endpoints.
- The subsequent versions of the protocol were not submitted to the Agency for the review prior to the NDA submission (version #2 from 8/26/2011, version # 3 from 5/22/2012, and version # 4 from 12/7/2012).
- The only version of the protocol that was submitted to the Agency was version #5 of the protocol (12/6/2013). Some of the proposed changes in version #5 were: addition of 6-month extension period and an analysis of proportion of subjects with both normalized IGF-1 levels and mean GH levels< 2.5 ng/ml as a secondary endpoint. However, the primary endpoint in this version remained the same as in the original version #1 (IGF-1 levels at the completion of the study)
- (b) (4) (b) (4) however,

this version was also never submitted to the Agency for the review prior to the NDA submission.

6) The Statistical Analysis Plan (SAP) for the pivotal study CH-ACM-01 submitted by the Sponsor on October 18, 2013.

- The Agency disagreed with the proposed SAP and sent comments to the Sponsor on 21 February 2014. The major points of this disagreement were: (b) (4) (b) (4) (b) (4) However, the Agency's feedback on the SAP was received after the study database was locked and the analyses had been performed. Therefore, the Sponsor agreed to provide a post-hoc analysis using the population and imputation method specified by the Agency.
- It should be noted, that version #5 of the protocol (from 12/6/2013, after the SAP submission) still contained IGf-1 levels at the end of the trial as primary endpoint; (b) (4) (b) (4) (b) (4) It is not known, when the Sponsor changed the primary efficacy endpoint.

6) Sponsorship of IND 108163 for Mycapssa was transferred to Genentech from Chiasma on March 10, 2014.

7) Pre-NDA meeting between the Agency, Genentech and Chiasma (May 1, 2014).

During this meeting, the results of Phase 3 pivotal study (CH-ACM-01) and multiple Division's concerns regarding Mycapssa clinical program were extensively discussed:

- Genentech was asked to provide multiple clarifications regarding the observed results and overall design of the study (criteria for the selection of patients with acromegaly, duration of washout period, decrease in percentage of responders at the end of the study compared to baseline, etc.).
- The Division expressed a concern that a Phase 3 study is a single arm trial and interpretability of efficacy and safety data from such a trial is challenging.
- The Division also expressed a concern regarding the durability of the response and whether the response observed in the trial is due to the effect of the drug and not to other factors such as lack of disease progression or spontaneous improvement. However, the Sponsor argued that the spontaneous remission is rare in patients with active acromegaly and indicated that the low response rate to the oral octreotide formulation at the end of the trial compared to the rate of the disease control with injectable SSAs at the baseline might be explained by other factors (early treatment discontinuation due to adverse events, food effect, etc.).
- The Division indicated again that in the absence of established bioequivalence between Sandostatin IR and Mycapssa through a bridging PK study, the Sponsor has to demonstrate that difference in exposure do not affect safety and/or efficacy.
- The Division indicated again that it will be a review issue whether or not an adequate bridge between Mycapssa and Sandostatin has been established in PK studies.

6) Second Pre-NDA meeting between the Agency and Chiasma (December 8, 2014)

After the first Pre-NDA meeting, the IND for Mycapssa was transferred back to Chiasma from Genentech on July 24, 2014. Thus, the new Sponsor (Chiasma) requested the second pre-NDA meeting in order to gain clarity on outstanding issues from previous interactions with the Agency (including the response rate determined in the Phase 3 study and adequacy of the bridge between Mycapssa and Sandostatin IR) and to discuss the overall plans for the NDA submission for Mycapssa.

- The Division agreed with the Sponsor's plan to submit a 505(b) (2) application for Mycapssa based upon the data collected in the Phase 3 study, clinical pharmacology studies, and existing information in the published literature for Sandostatin IR. However, the Division reiterated again that acceptance of the efficacy and safety data generated in the Phase 3 study and whether the bridge between MYCAPSSA and Sandostatin IR has been established will require full review of the data following the NDA submission.
- The Division continued to have serious concerns regarding a reduction of almost 50% in the number of responders when patients were switched from injectable SSAs to oral Mycapssa and stated that the information submitted in the second Pre-NDA meeting background document has not allayed these concerns. The Division inquired the input from the Sponsor what would be the acceptable rate of loss of biochemical control in patients controlled on the currently approved therapy. The Sponsor indicated that this issue was discussed during the Global Advisory Board Meeting in 2012, and experts in acromegaly field stated that the drug with a 50% responder rate would be acceptable. It was unclear to the Sponsor why the higher response rate was expected. However, the Division clarified that the concern was mostly with the loss of biochemical control when switching from an approved product to oral octreotide, and not with the response rate itself. Finally, the Division indicated that all submitted data has to be reviewed and evaluated in order to determine whether the substantial evidence of effectiveness of the drug was met in the pivotal trial.
- The Division also indicated that the efficacy evaluation will use the 7- month time point data (b) (4) which was prospectively designated as the primary analysis time point in the analysis plan.
- The Division asked the Sponsor if it would be ethical to do a placebo-controlled trial. The Sponsor agreed that such studies were conducted in the past, and that it is common for patients to go on drug holidays with no resulting harm.
- Lastly, the Division also indicated that the (b) (4) cannot be used as supportive evidence of the efficacy of Mycapssa since (b) (4) .

5) NDA submission: June 12, 2015.

6) Amendment – Safety Update Report (4 month): October 14, 2015.

3. CMC/Device

The Office of Pharmaceutical Quality (OPQ) review recommends Complete Response because of the multiple deficiencies identified at (b) (4) facility during the inspection (refer to the review from 4/12/2016). Satisfactory resolution of these deficiencies is required before this application may be approved.

There are no other deficiencies identified by the other review members of the OPQ team. The active ingredient in Mycapssa, octreotide, has a molecular weight of 1019.3.

Details on the drug substance are obtained from (b) (4) DMF (b) (4) and (b) (4) DMF (b) (4) The information was reviewed and found to be acceptable. CMC reviewer indicated that the physical and chemical characteristics of the drug substance from (b) (4) were comparable to those of the drug substance from (b) (4)

Mycapssa is manufactured as delayed-release capsules and formulated to contain 20 mg of octreotide. An enteric coated capsule contains (b) (4)

(b) (4)

An expiry of 36 months was granted when stored at 36^0- 46^0F and of 1 month when stored at room temperature.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Drs. Jessica Hawes and Ronald Wange, the pharmacology/toxicology reviewers, that that there are no outstanding nonclinical toxicology issues precluding the approval. Please see Dr's. Jessica Hawes review dated February 23, 2016, for details of the nonclinical program supporting approval of this NDA. Pharmacology/toxicology reviewers do not make any recommendations for additional studies.

Nonclinical studies conducted by the applicant under this NDA focused on the characterization and development of the TPE formulation and on comparability of toxicological profile of Mycapssa to the Listed Drug (LD, Sandostatin IR); the active ingredient (octreotide) is already well characterized. Pharmacodynamic (PD) parameters of Mycapssa were not evaluated in the nonclinical program. Dr. Hawes indicated that the Sponsor relied on the assumption that similar exposure levels to the active component would have the similar PD effects.

The nonclinical studies conducted by the Sponsor included pharmacokinetic (PK) studies in rats, pigs and monkeys and four toxicology studies in cynomolgus monkeys (28-day study, 13-week study, a chronic 9-month study comparing toxicological profiles of Mycapssa and LD and a 28-day bridging study that evaluated Mycapssa final drug product). The results of these studies were reviewed by Dr. Hawes who concluded that these studies did not reveal any new drug-related toxicity, and toxicology profile of Mycapssa was considered to be comparable to Sandostatin IR. The 28-day bridging study evaluated Mycapssa final drug product formulation stored under stress conditions; the same lot was used in acromegaly patients in pivotal Phase 3 study (CH-ACM-01). Dr. Hawes concluded that he bridging study successfully qualifies the Mycapssa final drug product formulation and the increase in stress-induced impurities and degradation products, supporting the increase in Mycapssa specification to ≤ (b) (4)% for total degradation products and impurities.

Because toxicological profiles of Mycapssa and Sandostatin IR were considered to be comparable, the applicant was not required to conduct the full battery of nonclinical studies including acute, subchronic, chronic toxicity, reproduction, mutagenicity studies. The Sponsor is referencing the nonclinical data in Sandostatin IR label (Novartis) instead. As per pharmacology/toxicology review, the formulation used in Mycapssa does not result in a chemical or physical change in the active component octreotide and the reliance on Novartis's data was found to be scientifically valid.

The Sponsor also did not conduct any carcinogenicity studies. Based on the lack of relevant carcinogenic potential for the Sandostatin injection, coupled with findings from the 9-month toxicity study and available data for human use of sodium caprylate and glyceryl tricaprylate, a waiver for the conduct of carcinogenicity studies was granted for Mycapssa.

Lastly, the Mycapssa drug product contains 4 novel excipients (sodium caprylate, glyceryl tricaprylate, magnesium chloride and Opacode (b) (4) black ink) that are not included in the FDA Inactive Ingredient Guide (IIG) for oral administration and one excipient (Acryl-EZE) that was presented above the current maximal approved levels for oral administration; these excipients were characterized in the sponsor's toxicology studies in monkeys. Dr. Hawes reviewed the safety of all excipients, degradation products and impurities (including the above mentioned 5 excipients) contained in Mycapssa enteric-coated capsule and considered all these components to be safe.

Dr. Hawes concluded, since the Sponsor was not required to demonstrate PD activity of the active ingredient in the nonclinical studies and the sponsor's hazard assessment is considered to be complete, the nonclinical data support long-term oral administration of the TPE formulation and the Mycapssa drug product.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was completed by Dr. Sury Sista and Dr. Jayabharathi Vaidyanathan. Both reviewers recommended Complete Response. The recommendations are based on the following deficiencies: 1) the bioequivalence between single dose of Mycapssa

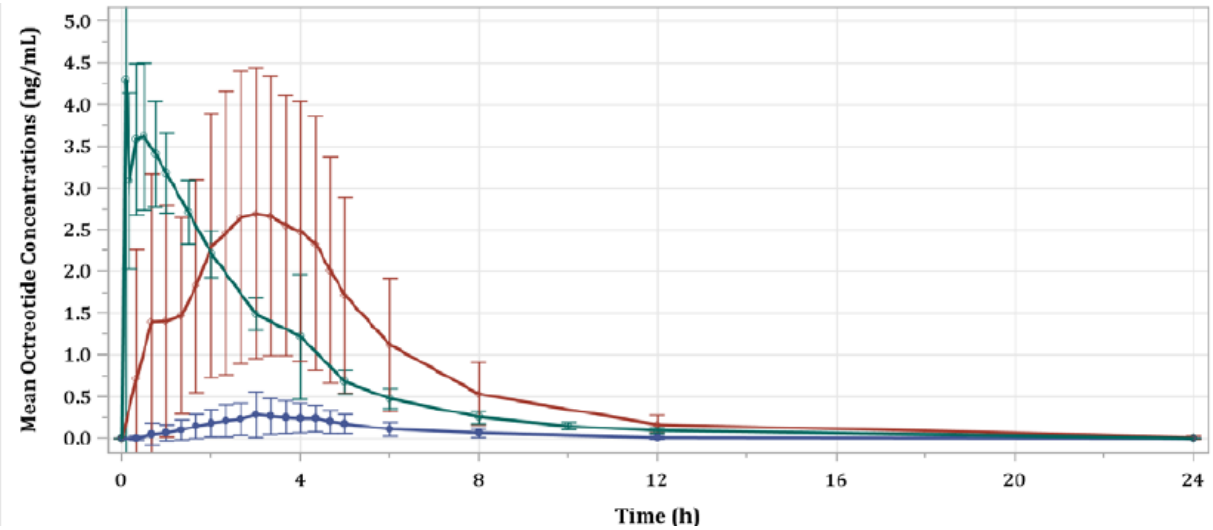
and Sandostatin IR has not been established; 2) Mycapssa dose-response or PD comparability between Mycapssa and Sandostatin IR was not established in clinical program; 3) a comparative PK study evaluating the proposed twice daily (BID) dosing regimen of Mycapssa and the three times daily (TID) dosing regimen of Sandostatin IR was not conducted. The reviewers recommend to evaluate dose-response or PD comparability between Mycapssa and Sandostatin IR and to characterize the PK/PD relationship of Mycapssa on GH over at least 12 hours in future study(s). For detailed discussion, please refer to their Clinical Pharmacology review in DARRTS (April, 2016).

I agree with Clin.Pharm reviewers' recommendations for Complete Response. I agree that without well-established PK/PD characteristics of Mycapssa the meaningful interpretation of Phase 3 study results is complicated.

PK characteristics of Mycapssa (Clin.Pharm review, Table 1)
The PK characteristics of Mycapssa were obtained in healthy volunteers (after single dose in four Phase 1 studies) and in patients with acromegaly (in Phase 3 study):

- Linear pharmacokinetics in the dose range studied (in healthy volunteers and in acromegaly patients)
- Median $T_{max:}$ 1.67 – 2.5 hours
- Relative bioavailability following single-dose (oral compared to s.c.) : 0.5%
- Bioavailability decreased:
  - when Mycapssa is administered 1 hour before high-fat meal, 30 minutes before reduced size meal or 1 or 2 hours after high-fat meal (proposed dosing regimen in Phase 3 study) - by 80%
  - when Mycapssa is administered 1 hour before a reduced-size high-fat meal
  - by 12%, when administered with 75 ml of water - by 60%
  - in standing position compared to the semi-sitting position
- C_{max}:
  - healthy volunteers (20 mg dose): 0.4 ng/mL under fed and 3.6 ng/mL under fasting conditions
  - acromegaly patients: 2.51 ng/mL after 40 mg, 3.83 ng/mL after 60 mg, and 5.30 ng/mL after 80 mg (the drug had to be taken under fasting conditions as described above, however, clear liquids including juice were allowed)
- AUC_{last}:
  - healthy volunteers: 1.3 ng·hr/mL under fed and 15.2 ng·hr/mL under fasting conditions
  - acromegaly patients: 8.41 ng·hr/mL after 40 mg, 14.7 ng·hr/mL after 60 mg, and 19.6 ng·hr/mL after 80 mg (under the same conditions as described above for C_{max})
- $T_{1/2}$ ~ 2-4 h in healthy subjects, and ~3.2 – 4.5 hours at steady state in acromegaly patients
- High intra-subject variability in octreotide concentrations after single dose administration of Mycapssa (Figure 1)

Figure 1. Single-dose, food effect and comparative bioavailability study of octreotide from Mycapssa capsules (Study CHI-002)



Green: Mycapssa 20 mg capsule (Fed); Red: Mycapssa 20 mg capsule (Fasted); Blue: 0.1 mg Sandostatin IR injection
Source: Clin.Pharm review, Figure 6, page 31

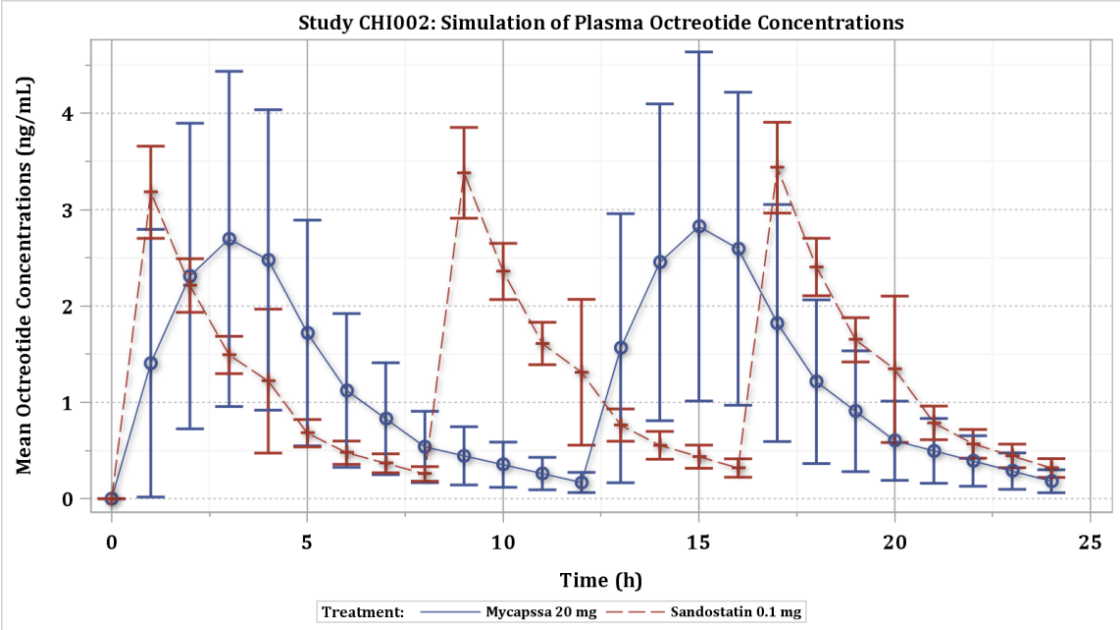
Lack of bioequivalznce between single dose of Mycapssa 20 mg and single dose of Sandostatin 0.1 mg s.q.
The studies CHI-001 and CHI-002 were conducted by the Sponsor to demonstrate a "comparative bioavailability" between Mycapssa and Sandostatin IR that will support the bridge between these two drug products.
Dr. Sista analyzed the results of both studies and concluded that two products are not bioequivalent as demonstrated by the least squares means (LSM) ratio between the two products that failed to meet bioequivalence criteria (80-125% for the AUC_{0-t} and C_{max}):

- **AUC_{0-t}:** 0.97 (90% CI 73.03% - 128.37%)
- **C_{max}:** 0.64 (90% CI 45.29% - 89.78%)

Additionally, as demonstrated above (Figure 1), high intra-subject variability in octreotide concentrations with single-dose Mycapssa compared to single dose Sandostatin IR leads to wide confidence intervals for AUC_{0-t} that makes it more difficult to show bioequivalence between two products in such small study (14 subjects). Dr. Sista indicated that larger study (at least 40 subjects) is required for a proper bioequivalence determination.
There were other deficiencies in study design including a lack of crossover (single dose comparison) and a lack of PD comparison; these deficiencies complicate further the assessment of "PK comparability" and the adequacy of the bridge between the two products. There is also a difference between dosing regimens of Mycapssa and Sandostatin IR (BID vs. TID, respectively). Dr. Sista pointed out that dosing duration was also inadequately assessed in the trial and entire dosing duration, i.e. Sandostatin TID, vs. Mycapssa BID should have been compared so that a measure of the comparative AUCs during the duration (TID or BID) would have been obtained. Dr. Sista simulated single dose PK data from study CHI-002 to a twice daily regimen for Mycapssa and three times daily regimen for Sandostatin IR (Figure 2 and

Table 2). The results of this simulation demonstrated again the lack of bioequivalence between two products.

Figure 2. Simulated mean plasma concentrations time profile of octreotide following oral Mycapssa BID and Sandostatin s.q TID.



Source: Clin.Pharm review, Figure 12.

Table 1. Statistical Comparison of PK parameters for Octreotide after s.q administration of octreotide 0.1 mg and administration of Mycapssa 20 mg to healthy volunteers-simulated data

PK Parameter	Units	Ratio (%)	90%CI
AUC(0-24) for Octreotide	ng·h/ml	77.01	58.19-101.92
Cmax for Octreotide	ng/ml	80.93	62.57-104.67

Source: Clin.Pharm review, Table10.

Lack of well-established PD characteristics of Mycapssa

As stated above, no PD characteristics of Mycapssa were evaluated and established in healthy volunteers in the earlier clinical program. The Sponsor's selection of the 20 mg dose of Mycapssa was based on the assumption that it is equivalent to the 0.1 mg of Sandostatin IR. However, as discussed above, due to the lack of PK bioequivalence between two products, PD effects of Mycapssa are not expected to be the same as PD effect of Sandostatin IR. Lastly, Dr. Sista reviewed the PK/PD data obtained from Phase 3 PK/PD substudy and concluded that the PD profile was not characterized in acromegaly patients, the profile was evaluated for a limited time period only, 2-4 hours post dose, and the limited GH response obtained during this evaluation had no clear relationship with octreotide AUC_{2-4} at all three dose levels.

Other aspects of clinical pharmacology of Mycapssa

- Drug-drug interaction (DDI)

The Sponsor conducted 5 Phase 1 studies evaluating drug-drug interactions. Dr. Sista reviewed the results of these studies and concluded that the data supporting the drug interaction of Mycapssa with warfarin, HCTZ, metformin, and levonorgestrel/ethinyl estradiol may be inadequate due to the insufficient PK sampling. These data has to be regenerated with a full PK sampling included in the study design.

- Other intrinsic factors that could influence exposure and activity of Mycapssa

Dr. Sista reviewed the results of other PK studies submitted in NDA and found that the data supporting other aspects of clinical pharmacology (eg. studies in renal/hepatic impairment, drug-interaction studies, food effect) of Mycapssa is adequate:

- Weight, age, race or gender
  A formal evaluation of such intrinsic factors as weight, age, race or gender that could influence exposure and activity was not performed. Dr. Sury concluded that based on analysis of pooled data from studies in healthy volunteers and on analysis of acromegaly patients from PK substudy of the Phase 3 study these factors had no clinically relevant effect on the PK of Mycapssa.
- Renal impairment
  The Sponsor did not evaluate PK of Mycapssa in patients with mild and moderate renal impairment. In patients with severe renal impairment AUC was increased by 14% and C_{max} was decreased by 14%, clearance was decreased by 13%. This was not substantially different from those in matched controls. Thus, no dose adjustment is recommended in patients with mild, moderate or severe renal impairment. Subjects on hemodialysis had higher total exposure (87%) and lower clearance of the drug consistent with an effect of renal impairment on octreotide clearance; thus the starting dose of Mycapssa is recommended to be adjusted in these patients (20 mg QD).
- Hepatic impairment
  Hepatic impairment was evaluated in Mycapssa clinical program (study CH-PHT-01). Dr. Sury concluded that PK of Mycapssa in patients with hepatic impairment appears to be similar to PK in healthy volunteers and no dose adjustment is required in patients with hepatic impairment.

6. Clinical Microbiology

Not applicable. No Clinical Microbiology information is included in this NDA.

7. Clinical/Statistical- Efficacy

Drs. Anna Kettermann (biostatistician) and Smita Abraham (clinical reviewer) reviewed efficacy results in details. A single open label, single arm study CH-ACM-01, to support the claim of long-term maintenance treatment in acromegaly patients (b) (4) (b) (4) was submitted in this application. As stated in the background section of the memorandum, the Agency disagreed with the Sponsor's original SAP, thus, the efficacy results were analyzed using the originally proposed SAP and the SAP recommended by the Agency.

Both, the clinical and the statistical reviewers recommend Complete Response. The statistical and clinical reviewers concluded that the results of the Phase 3 program do not provide enough evidence to support the efficacy claims proposed in this NDA, i.e. long-term maintenance treatment in acromegaly patients (b) (4) (b) (4) Both reviewers underline the need for a confirmatory randomized, controlled study in the intended patient population.

Since the above recommendations are based on the results of study CH-ACM-01, I will briefly summarize the design and the results of this trial below. All other studies will be referenced as needed.

Study CH-ACM-01

Study CH-ACM-01 was a single-arm, open label, baseline-controlled, withdrawal, multicenter (37 non-US sites), 7-month study that investigated the use of Mycapssa for the maintenance of acromegaly control in adult patients who previously responded to the treatment with SSAs.

Retrospectively, the efficacy and safety of Mycapssa should have been evaluated in randomized controlled study using an active comparator or placebo. A single-arm study is not as informative as a controlled study:

- As per CFR, the data from the baseline controlled study to demonstrate the efficacy of the drug might be acceptable to support the efficacy of the drug in the rare situations such as when the conduct of randomized controlled trial is not possible due to the ethical concerns or the response rate to the new drug is expected to be robust[4].

In my opinion, such situations are not applicable to the studies evaluating the efficacy of octreotide formulations in patients with acromegaly, in general, and to Mycapssa study, in particular:

- First, the conduct of randomized control trials is ethically acceptable in acromegaly patients (even with placebo arm). Endocrine Society (2014) states that "considering the prolonged nature of the course of most patients with acromegaly, interruption of medical therapy for 9-12 months should not have a particularly adverse effects on the long-term outcome "[5]. The Sponsor also confirmed that such studies have been conducted in past (refer to the second Pre-NDA meeting minutes). Lastly, the efficacy and safety of the approved octreotide formulations (e.g. Sandostatin LAR, lanreotide) were evaluated in randomized, placebo controlled trials[6].
- Next, the Sponsor did not select and did not demonstrate that the response rate to Mycapssa was robust in patients with acromegaly (refer to the Efficacy Results section below). The Sponsor claimed that the selected response rate of 50% will be clinically meaningful and acceptable. However, the selected response rate is comparable to the response rate reported in the mixed patient population with unknown sensitivity to octreotide (treatment-naïve patients and treatment-responsive patients); the response rate in patients with proven sensitivity to octreotide formulations is usually expected to be higher (approximately 80%)[7].

[4] 21 CFR §314.126

[5] Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA. Acromegaly: an endocrine society clinical practice guideline. Endocrine Society. JCEM. 2014 Nov;99(11):3933-51.

[6] https://www.accessdata fda.gov/scripts/cder/drugsatfda/

- Lastly, the results of treatment with Mycapssa cannot be compared with historically derived data because dose-response relationships and PD characteristics of the drug were not established in earlier studies and PK characteristics between Sandostatin IR and Mycapssa are not comparable (refer to Clin.Pharm section). Thus, one cannot predict the response to Mycapssa based on the knowledge of the response to the other SSAs.

- There is always concern in interpreting data from a single arm trial wherein some patients may improve spontaneously. The Sponsor's selection of the open label single arm trial was based on the assumption that all patients enrolled in the trial had an active disease, thus adding of a comparator arm was not necessary and would not add scientific value to the study due to the following reasons: 1) there is no spontaneous remission in such patients and thus, the observed effect is due to the treatment itself; 2) the duration of residual IGF-1 and GH suppression after injectable SSAs in patients with active disease is not expected beyond 8-12 weeks, thus, the effect of Mycapssa evaluated at 7 months should be due the drug itself and not to the residual effect of prior SSAs; 3) in order to exclude treatment effect of the previous therapeutic modalities, the study protocol excluded all patients who received pituitary radiotherapy within 10 years prior to screening and patients who underwent surgery within six month prior to screening. However (as discussed below), the presence of active disease has not been confirmed in these patients. Thus, in the absence of the control group and the confirmatory evidence of the disease status (i.e. active disease) prior to the drug administration it is complicated to discriminate the response caused by the drug itself from the response caused by the other factors such as an absence of the active disease or the residual effect of the long acting SSAs.

- Lastly, no hypothesis testing was proposed in this trial. With no apparent hypothesis testing the protocol appeared to be more descriptive than confirmatory, and would be more appropriately regarded as a pilot study evaluating responses to Mycapssa in various subpopulations. Such responses could be further tested in a confirmatory trial that would prespecify the response rate to Mycapssa compared to the other SSA(s) or placebo and power the study adequately.

The primary objective of the study was to evaluate the effect of Mycapssa therapy on IGF-1 and GH levels as measure of the response at the end of 7-month treatment period.

The secondary objectives of the study were to evaluate safety and tolerability of Mycapssa and to compare the effect of Mycapssa therapy on IGF-1 and GH levels with that of parenteral therapy with SSAs in the intended population.

Patient population

Patients > 18 years old with evidence of acromegaly who were treated with stable doses of injectable SSAs for at least 3 months prior to the study enrollment and who were responders to the treatment with injectable SSAs (defined as IGF-1< 1.3 x ULN and GH< 2.5 ng/ml) were eligible to participate in the study. The "evidence" of acromegaly was defined as documented (i.e. retrospectively obtained from the patient's chart) evidence of GH-secreting pituitary tumor that was abnormally responsive to OGTT. However, the activity of the disease did not have to be reconfirmed at the beginning of the study. Thus, the status of the disease prior to the

[7] Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. JCEM. 2008 Aug;93(8):2957-68.

administration of the first dose of Mycapssa remains in question.
Patients who received pituitary radiotherapy within 10 years or underwent pituitary surgery within 6 months prior to the screening were excluded from the study in order to eliminate the residual effect of these therapeutic modalities on the response rate. However, as stated above, it is unknown whether status of the disease was reconfirmed at any time in the past in these patients (as per Endocrine Society Guideline[8] or according to Sandostatin LAR label[9]).
Patients treated with pegvisomant within last 3 months, proton pump inhibitors or histamine 2 receptor blockers within last 1 month and patients with chronic gastrointestinal conditions were also ineligible to participate in the study.

Study design
The study was comprised of a screening period (up to 4 weeks after the last dose of SSAs), baseline visit, a 7-month core treatment period (consisted of up to 2-5 months dose escalation period and 2-5 months fixed dose period) and an optional 6-month fixed dose extension treatment period.

No washout period from long-acting SSAs was required during the study. As per Sponsor, the residual effect of SSAs was expected to washout within 8-12 weeks from withdrawal, and, thus, would not influence the response rate at month 7 (end of the trial). However, even though, 8-12 weeks is a minimum expected washout period, Clin.Pharm reviewer noted that the residual effect of Sandostatin LAR may last up to 4-5 months after the last dose administration (due to the long t/1/2). Additionally, the biological duration of IGF-1 and GH suppression after SSAs are withdrawn is not known and might be delayed even after these drugs are washed out completely (up to 12 months)[10]. Lastly, washout period would be also helpful to confirm presence of the active disease in the eligible patients (as discussed above). Thus, retrospectively, washout period of appropriate duration is required in order to eliminate multiple confounding factors including residual effect of other SSAs and inactivity of the disease (due to the temporary suppression of biomarkers after prolong SSAs treatment, delayed effect of surgery or/and radiation treatment, tumor insult, spontaneous resolution, etc.).

The starting dose of Mycapssa was 40 mg daily (20 mg BID).
The dose was allowed to be increased every month during dose escalation period to 60 mg and 80 mg daily if the following criteria had been met on two consecutive visits (2 weeks apart): 1) there was an increase in IGF-1 > 20% compared to level of IGF-1 during the prior visit or 2) there was a "smaller" increase in IGF-1 levels (i.e. < 20% compared to prior IGF-1 levels) plus emergence of typical symptoms and "less" suppression of IGF-1 levels compared to baseline levels. It should be noted that "smaller" increase in IGF-1 levels, "less" suppression of IGF-1 levels and "typical" acromegaly symptoms were not prespecified by the Sponsor. It should

[8] Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA. Acromegaly: an endocrine society clinical practice guideline. Endocrine Society. JCEM. 2014 Nov;99(11):3933-51.
[9] Sandostatin LAR label recommends to withdraw the drug yearly to assess the disease activity in patients who received pituitary radiation
[10] Vilar L, Fleseriu M, Naves LA, Albuquerque JL, Gadelha PS, dos Santos Faria M, Nascimento GC, Montenegro RM Jr, Montenegro RM. Can we predict long-term remission after somatostatin analog withdrawal in patients with acromegaly? Results from a multicenter prospective trial. Endocrine. 2014 Aug;46(3):577-84.

also be noted that titration regimen did not asses the use of GH for dose escalation purposes; the dose escalation was based on the single biomarker (IGF-1). However, the efficacy evaluation of the drug at the end of the trial was based on two biomarkers, IGF-1 and GH. The approved SSAs also recommend evaluation of both biomarkers in order to escalate the dose. Overall, it seems that the proposed dose escalation regimen was based not on the achievement of the predefined response (IGF-1 < 1.3 XULN and GH< 2.5 ng/ml), but rather on the demonstration that treatment with Mycapssa induces some decrease in IGF-1 levels. All these facts complicate (b) (4) the accurate dosing regimen for Mycapssa and overall evaluation of the response to Mycapssa during the trial.

Patients were allowed to enter the fixed dose phase when IGF-1 levels were < 1XULN or < were increased < 20% compared to baseline values. These criteria are based on only IGF-1 levels again and not on the normalization of both biomarkers. This discrepancy might be due to the fact that the primary end point was changed from IGF-1 levels to the proportion of patients with normalized IGF-1 and GH levels in the later versions of the protocol (refer to the Regulatory Background section above).

Lastly, Mycapssa was administered twice daily and at least 1 hour before a meal or at least 2 hours after a meal. The subjects were allowed to have clear liquids (juice, tea, coffee) during the drug administration. However, as described in Clin.Pharm section above, the absorption of the drug is significantly decreased by food, water intake and even posture. Thus, in the absence of the established PD characteristics of the drug and without controlling for these factors the efficacy assessment of the drug is further complicated.

Primary efficacy outcome

The primary efficacy endpoint was a responder analysis examining the number of subjects in the modified Intent-To-Treat (mITT) population who experienced IGF-1 level < 1.3XULN and mean GH levels over 2 hours < 2.5 ng/ml obtained during two consecutive visits at the end of 7-month treatment period. Mean GH levels were calculated from 3-5 samples collected 2-4 hours after the dose administration; if more than 2 samples of GH were missing, the mean GH values were not calculated and the value was considered to be missing. In patients who discontinued the study drug preliminary the last concentrations of IGF-1 and GH was imputed as the end of the treatment concentrations (last observation carried forward; LOCF). The mITT was defined as all enrolled patients who any amount of the drug during the study, and had at least one measurement of IGF-1 and GH post first dose. The Sponsor's considered a response rate of 50% on Mycapssa with two-sided 95% CI of 42 to 58% to be clinically meaningful.

There are multiple concerns with the proposed primary analysis and evaluation of primary endpoint in the study:

- Response rate of 50%

As per Sponsor, 50% response rate was established based on the expert opinion (the Global Advisory Board Meeting in 2012) who considered this rate to be clinically acceptable. However, as discussed in the above sections of this memorandum, this 50% response rate is more acceptable in the mixed population of patients with acromegaly (naïve, with unknown sensitivity to SSAs, and treated with SSAs), but the response rate in patients with acromegaly and established sensitivity to SSAs is expected to be higher (approximately 80%). Of note, the

Sponsor also admits that the maintenance of response is "well established…and is reported to range between 80-100%" (2.5 Clinical Overview, p.40).

- IGF-1 threshold of < 1.3XULN

Retrospectively, the use of IGF-1 threshold of < 1.3XULN is unclear. The proposed threshold was discussed during the EOP2 meeting. As per Sponsor, the proposed threshold was selected to ensure that any observed IGF-1 levels are clinically relevant changes and not simply due to the intra- and inter-assay variability, since IGF-1 values are assay and lab dependent. However, it should be noted that scientific society guidelines (AACE[11], Endocrine Society[12]) recommend using an age normalized serum IGF-1 values as a therapeutic goal, as this correlates with control of acromegaly. Additionally, all currently marketed SSAs were approved for the treatment of acromegaly based on their effect to achieve IGF-1 within normal limits and/or GH< 2.5-5 ng/mL. Lastly, in the current study, the IGF-1 levels were evaluated by a single central laboratory; the evaluation of biomarkers by central laboratory is expected to minimize inter-assay and intra-assay coefficients of variation of IGF-1.

- GH threshold < 2.5 ng/mL

The use of GH threshold < 2.5 ng/mL is acceptable. This GH threshold was used in order to demonstrate the efficacy of the approved SSAs; this threshold is also accepted by the scientific societies as demonstration of the disease control. Lastly, the Sponsor indicated that the GH threshold of < 2.5 ng/mL versus < 1 ng/mL for the responder definition was chosen because it is associated with reduction in mortality rate to background levels.

- Time of IGF-1 and GH collections during the visits on the trial

The GH levels were collected starting 2 hours after Mycapssa administration (which corresponds to C_{max} and GH is expected to be maximally suppressed); the collection of GH levels at the time of maximum suppression may overestimate the control of the disease. The Sponsor did not specify at what time IGF-1 levels were measured relatively to the time of the drug administration. Overall, IGF-1 has longer t1/2 and concentrations are usually stable during the steady-state, thus IGF-1 values are less likely affected by the time collection late in the study. However, the suppression might still be overestimated early in the study during the dose titration period. In general, without the established PK/PD characteristics of Mycapssa in earlier trials (refer to Clin.Pharm section) it is complicated to evaluate the observed GH and IGF-1 response.

It should be also noted that in the pivotal studies evaluating Sandostatin LAR, lanreotide and pasireotide for the treatment of acromegaly the GH and IGF-1 levels were collected prior to the morning dose. The Sandostatin IR label also recommends to start collection of GH at time 0 and to continue collection for 8 hours. Lastly, Endocrine Society Guideline also recommend evaluating control of the disease by the collecting of GH levels prior to the next dose administration: "effectiveness of treatment is based on measurement of serum IGF-1 and GH which should be measured…just prior to the next dose"[12].

- (b) (4)

The prespecified primary analysis was conducted as (b) (4) The Agency disagreed with this analysis and specified that the population for the primary analysis

[11] Cook DM, Ezzat S, Katznelson L, Kleinberg DL, Laws ER Jr, Nippoldt TB, Swearingen B, Vance ML. AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract. 2004 May-Jun;10(3):213-25.

[12] Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA. Acromegaly: an endocrine society clinical practice guideline. Endocrine Society. JCEM. 2014 Nov;99(11):3933-51.

should be all subjects enrolled and treated patients at baseline, i.e. Intent-To-Treat population (ITT population), and that missing values should be imputed as non-responders instead of LOCF. This analysis was conducted as a post-hoc analysis (refer to the brief discussion of both analyses in Efficacy Results section below).

- Prespecified primary endpoint

As noted in Regulatory Background section above, the originally prespecified primary efficacy endpoint was IGF-1 levels only at the end of the treatment period. However, the primary endpoint was changed to the proportion of the responders at the end of the treatment period (defined as IGF-1<1.3xULN and GH< 2.5 ng/ml) later during the study. Overall, altering the endpoints mid-study introduces bias and it is not clear whether the change in the prespecified endpoint was independent of the trial data.

Secondary efficacy outcomes

- Proportion of patients with various measures of control by IGF-1 and GH values at baseline and at the end of the Core Treatment Period (refer to the clinical review for the detailed description of various subgroups to be analyzed)
- Maintenance of IGF-1 response during the Fixed Dose Phase (Core) defined as proportion of patients with IGF-1 levels < 1.3 X UNL at the end of the Core Treatment Period who also had IGF-1 levels < 1.3 X UNL at the first assessment in the Fixed Dose Phase.
- Maintenance of IGF-1 and GH response during the Fixed Dose Phase (Core) defined as proportion of responders (IGF-1 levels < 1.3 X UNL and integrated GH < 2.5 ng/mL) at the end of the Core Treatment Period who also had IGF-1 levels < 1.3 X UNL and GH < 2.5 ng/mL at the first assessment in the Fixed Dose Phase.

It should be noted that secondary endpoints were analyzed using LOCF method in mITT population (#1 and #2) or in fixed dose population (#3, subgroup of patients defined as those who entered Fixed Dose Period).

Baseline demographic and disease characteristics

A total of 155 patients with acromegaly were enrolled in study CH-ACM-01.

- Demographic characteristics

The patients' characteristics at enrollment in study CH-ACM-01 were generally consistent with those patients with acromegaly seen routinely in clinical practice. The mean age at baseline was 54 years; 88/155 (56.8%) of all patients were females, and 137/155 (88.4%) of patients were white.

- Disease characterestics

With respect to the underlying diagnosis of acromegaly, majority of patients had pituitary micro- or macroadenoma without extrasellar extension (51 (32.9%) and 53 (34.2%) patients, respectively). Of 155 patients enrolled in the study, majority of patients (121 (78%)) were treated with surgery in past and 13 (8.4%) patients were treated with radiation.

As stated above, none of the patients had diagnosis reconfirmation prior to the study enrollment. All information regarding the diagnosis was obtained from patient's medical records. Moreover, such information was missing in 8 patients who did not have any records regarding confirmation of the disease status by OGTT or IGF-1 levels. The potential impact of such missing data is that these patients might have had inactive disease and the observed

responses at the end of the trial might be due to the inactivity of the disease and not to the drug itself (refer to the discussion of the efficacy results below).

- Use of concomitant medications

The use of estrogen was allowed during the study and five patients continued treatment with estrogens during the study. However, it should be noted that estrogens/glucocorticoids may suppress IGF-1 levels (refer to the discussion of efficacy results below).

- Responders to SSAs at baseline (intended population)

- The indication for Mycapssa is "treatment in acromegaly patients (b) (4) (b) (4) and the inclusion criteria indicated that patients who were stable on SSAs for 3 months were eligible to participate in the study. However, 15 patients were treated concomitantly with other medications such as dopamine agonists (14 patients) or pegvisomant (1 patient) during the screening period and were most likely, only the partial responders to SSAs. Thus, the enrolled population does not reflect exactly the population for whom the drug is indicated.
- At screening, all patients met the criteria for responders (IGF-1 < 1.3XULN and GH < 2.5 ng/ml). Of these, 18 patients (12 %) lost disease control over 3 months and only 88% of patients were responders at baseline. Mean IGF-1 level was 0.94 XULN and mean GH levels were 0.93 ng/ml at baseline.
  However, the exact number of responders at the beginning of the screening period and at baseline cannot be established with confidence. The time of IGF-1 and GH collections for the evaluation of the response to SSAs during screening visit and at baseline visit was not specified in the study; for example, blood samples for the determination of IGF-1 and GH baseline values were collected between 0 and 82 days after the last dose of SSAs administration (average 17.5 days). Thus, the number of the responders could have been overestimated (due to the oversuppression of markers when they are collected soon after the last dose) or underestimated (due to the blood collections close to trough when the levels begin to increase).

Efficacy results

Primary analysis

The Sponsor initially conducted prespecified primary analysis in mITT population that included 151/155 patients using LOCF approach (4 patients dropped out prior to the first dose administration and did not have post baseline IGF-1 and GH assessments). The results of this analysis demonstrated that 64.9% of patients were responders (95% CI 58.4%-74.2%) at the end of 7 month treatment period.

As stated above, the Agency considered mITT population as a secondary population and analysis based on mITT population as supportive. Thus, following the Agency advice (from 2/20/2014), the Sponsor also conducted post-hoc primary analysis in ITT population (155 patients, including those 4 patients who did not receive any dose of Mycapssa) using worst case scenario (imputing missing values as non-responders) instead of LOCF. The results of this post-hoc analysis in ITT population demonstrated that 52.9% of patients were responders at the end of treatment (95% CI 44.7-61%).

Dr. Anna Kettermann repeated both primary analyses: primary analyses using LOCF approach in mITT population and worst case scenario approach in mITT and ITT populations.

The results of the biostatistician's analyses are (Table 3):

- Repeated primary analysis using LOCF approach in mITT population generated the same percent of responders as by Sponsor's analysis (64.9%), but the different 95% CI. Dr. Kettermann noted that the original 95% CI reported by the Sponsor was generated using a subset of mITT population - 147 patients (additional 4 patients who did not have post-baseline GH assessment were excluded from mITT population). She also indicated that the analyses using mITT dataset artificially increased the proportion of subjects that succeeded in the trial, because the subjects who did not have post-baseline observations were not included in the denominator of the proportion. As per her review, the dropout subjects prior to the first dose administration should have been considered as nonresponders; since "these "subjects had an adverse event, removing these subjects from the efficacy analysis can be misleading" and "examination of the endpoint based on the ITT principle, i.e. including all participants, will be more appropriate to reflect those dropouts". Overall, I agree with the clinical reviewer and biostatistician that LOCF approach should not be used for primary analysis. Using the LOCF method for missing data can lead to misinterpretation of study results and misleadingly counts any patient that dropped out earlier as "responders" at the end of the study (particularly when the study does not have control group and dropout rate is high and is due to adverse events/ treatment failure). Thus, the results of primary analysis using LOCF methods should not be used to demonstrate the efficacy of the drug. However, in my opinion, the 4 patients who were excluded from ITT population did not receive any doses of Mycapssa, thus, the evaluation of the drug efficacy in mITT population who received at least one dose of the drug is appropriate.
- Both primary efficacy analyses using worst case scenario approach in mITT and ITT populations also met the criteria for demonstration of efficacy; however, the response rate was lower compared to the response rate assessed by the prespecified analysis using LOCF approach. As per these analyses, only half of patients succeeded in the trial. The lower bound 95%CI generated by this analysis also dropped below the expected "clinically meaningful rate" (50%) indicating that the response rate might be as low as 45%. Of note, the lower bound 95% CI generated by the prespecified LOCF primary analysis (58.43%) remained above the response rate considered "clinically meaningful" by the experts in acromegaly field (50%).

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Table3. Results of primary analyses (the Sponsor's analyses and FDA analyses)

Author	Responder (yes/no)	Frequency (n)	Percent	95%CI
Sponsor	**LOCF approach, all patients who received at least one dose of Mycapssa (mITT, n=151)**			

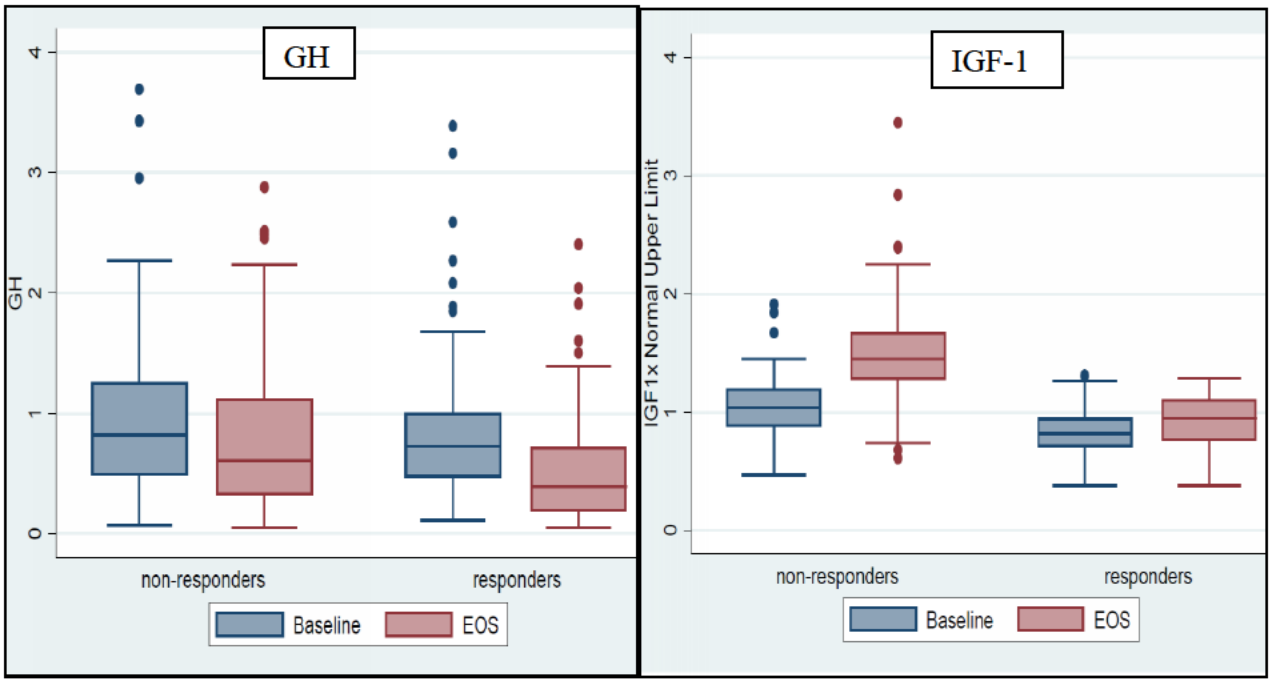
	Yes	**98**	**64.9**	**58.43**	**74.22**
	No	53	35.1		
FDA	**LOCF approach, all evaluable patients (mITT subset, n=147)**				
	Yes	98	66.67	58.43	74.22
	No	49	33.33		
FDA	**LOCF approach, all patients who received at least one dose of Mycapssa (mITT, n=151)**				
	Yes	98	64.9	56.72	72.48
	No	53	35.1		
FDA	**Worst case scenario approach all patients who received at least one dose of Mycapssa (mITT, n=151)**				
	Yes	**82**	**54.30**	**46.01**	**62.43**
	No	69	45.70		
Sponsor, FDA	**Worst case scenario approach all patients who were enrolled in the study (ITT, n=155)**				
	Yes	**82**	**52.90**	**44.73**	**60.96**
	No	**73**	**47.10**		

ITT population (155 patients)= all patients enrolled in the study (155 patients)
mITT population (151 patients)= all patients enrolled in the study who received at least one dose of Mycapssa and had one post baseline evaluation of IGF1 and/or GH (4 patients who developed adverse events prior to the first dose administration were excluded)
"all evaluable patients" (147 patients) = mITT subset of patients (additional 4 patients who did not have post-baseline GH assessment were excluded from mITT population)
Source: Statistical review, Table 7, modified.

The other biostatistician's concerns with the study design and results were: the absence of comparator arm in the study, the absence of second confirmatory study and high drop-out rate. She noted that only 65.8% (n=102) of all subjects completed 7 months of the trial; more than 1/3 of enrolled subjects (n=53; 44.2%) discontinued the trial preliminary because of adverse events (24/ 102 subjects; 45.8%) or treatment failure (24/102 patients; 39.6%).

In order to understand the results of the study in the absence of comparator arm, Dr.Kettermann conducted multiple post-hoc analyses comparing responders to non-responders. One of such analysis demonstrated that there was a trend in decreasing GH levels over time in both groups, responders and nonresponders. However, the same analysis of IGF-1 levels demonstrated that IGF-1 levels had tendency to increase over time in both groups, responders and nonresponders (Figure 3). This lack of consistency does not provide reassurance of the robustness of the efficacy results. Additionally, as pointed out in Dr. Abraham's review, the suppression of GH levels might be artificially overestimated due to the fact that the GH levels were collected 2-4 hours after Mycapssa administration (at Cmax; i.e. at time of maximum suppression).

Figure 3. Boxplots for GH and IGF-1



Source: Statistical Review, Figures 7 and 11.

Lastly, the short duration of the trial also puts into the question the durability and sustainability of the response. As pointed out in Dr's. Kettermann review, the fact that IGF-1 levels did not stabilize during the trial and continue to rise from baseline could be a potential issue with maintenance of the disease control (the proposed indication) over the longer period of time (>7 months) if the levels continue to rise. However, the short duration of the study did not allow to evaluate this issue of potential concern further.

Reliability of the results

It should also be noted that the most uncertainties with the observed results seem to be related to the lack of convincing evidence that all patients in the trial had an active disease and the lack of well-understood PK and PD characteristics of Mycapssa.

- As Dr. Abraham and Dr. Sista pointed out in their reviews, the PK bridge between Mycapssa and Sandostatin IR has not been established and PK characteristics of Mycapssa and Sandostatin IR are different. Thus, without such bridge, one cannot conclude that PD characteristics of Mycapssa are expected to be similar to PD effect of Sandostatin IR (e.g. the sustainability of GH/IGF-1 levels during the at least 12 hours after the drug administration). As stated above, the other factors affecting the drug PK (e.g. juice, water intake, posture) also confound the accuracy of the observed results. These factors are discussed in details in Clin.Pharm section of this memo above.
- The interpretation of the observed results are further complicated by the lack of the evidence of the disease activity and fact that some patients were able to maintain low IGF-1 and GH levels on the lowest dose of Mycapssa and/or after the drug was discontinued. The potential impact of this uncertainty is that these patients might have had inactive disease and the observed response to the drug at the end of the trial is due to the inactivity of the disease and not to the drug itself.

Examples of the individual patient data raising the question whether some patients had disease in remission during the trial:

- Of eight patients who did not have confirmation of the disease by OGTT or IGF-1 levels from the retrospective medical records, one patient was a responder at the end of the trial and was treated with the lowest dose of Mycapssa. This patient also did not have any symptoms of acromegaly and had normal IGF-1 and GH levels at baseline.
- Detailed analysis conducted by Dr. Abraham in her clinical review identified multiple patients who were responders at the end of Core phase, however, were also able to maintain the disease control without any treatment (after Mycapssa was discontinued or prior to the first dose of Mycapssa when SSAs were discontinued). These patients also required the lowest dose of Mycapssa to maintain control of the disease during the trial. For example, 2 patients who were treated with lanreotide 60 mg every 4 weeks and 120 mg every 4 weeks, respectively, during the screening period were able to maintain control of the disease for > 30 days (82 and 58 days, respectively) after SSAs were discontinued and prior to the first dose administration of Mycapssa (protocol violation). Both patients had normal IGF- and GH levels at baseline and at the end of the treatment and required only 40 mg of Mycapssa. Another example is that 3 patients, who were on the Mycapssa 40 mg during the trial, did not resume the treatment with SSAs at the end of the trial after Mycapssa was discontinued. Of these patients, two patients also required very low doses of SSAs (20 mg every 4 weeks and 10 mg every 4 weeks, respectively) for the disease control during the screening period.
- Lastly, she also identified 3 patients who received radiation therapy within 10 years prior to the study enrollment (protocol violators). Of these patients, 2 patients (treated with gamma knife 7.9 and 7.4 years prior to screening, respectively) were responders and required Mycapssa 40 mg. Occasionally, the radiotherapy to the pituitary has delayed effect and may confound the efficacy results, particularly in an uncontrolled study.

Results of the Sponsor's analyses raising the question whether some patients had inactive disease during the trial:

The Sponsor conducted multiple post-hoc analyses in subgroups including analyses by the Mycapssa dose and by the SSAs dose prior to the study. The Sponsor concluded that these analyses "provide evidence for a dose response on Mycapssa similar to the prior injection SSAs therapy" and "confirms that Mycapssa is efficacious". However, these analyses are conducted in the subgroups only and are not prespecified analyses; thus, they do not provide convincing evidence of the drug efficacy in the intended population. On the other hand, I think that the results of these analyses rather raise the same concerns regarding the unknown status of the disease and whether the observed responses are due to the drug itself or the disease being in a remission. The results of these analyses are briefly discussed below:

- Responders by dose (Table 4)
  As demonstrated, the highest response rate was observed among the patients who were started on the lowest dose of Mycapssa (40 mg) and did not require any dose adjustments during 7 months of the study: of 65 patients in 40 mg group, 48 patients (73.8%) were responders compared to 15/57 responders in 80 mg group (26.3%).

Table 4. Summary of Responders at the end of Treatment by Dose

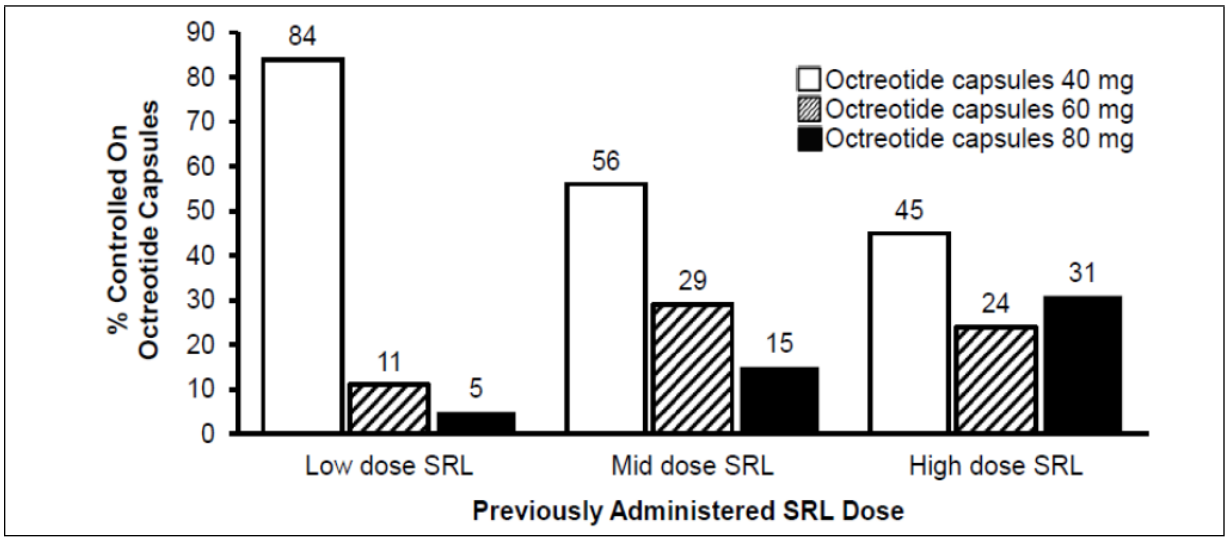
Category Statistic	Dose at the End of Treatment	Total

	OCT 20 + 20		OCT 40 + 20		OCT 40 + 40			
mITT, LOCF	**N=61**		**N=33**		**N=57**		**N=151**	
Responders	N	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
	53	**89** (83.0 – 98.1)	22	66.7 (48.2-82.0)	23	40.4 (27.6-54.2)	98	64.9 (58.4-74.2)
ITT, Worst Case Scenario	**N=65**		**N=33**		**N=57**		**N=155**	
Responders	N	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
	48	**73.8** (61.5-84.0)	19	57.6 (39.2-74.5)	15	26.3 (15.5-39.7)	82	52.9 (44.7-61.0)

Source: Sponsor's Tables 20 and 21, CSR, p.11-112, modified

- Responders by the previous SSAs dosing regimen required for the disease control during the screening period (Figure 4)
  Of those patients who required only low dose of injectable SSAs (Sandostatin LAR < 60 mg/month or Somatuline Depot < 10 mg/month) for the disease control at baseline, 84% of patients were able to maintain the disease control during the study on the lowest dose of Mycapssa without any further dose adjustment.

Figure 4. Relationship between Injectable Somatostatin Receptor Ligands (SRL) Dose and Subsequent Octreotide capsule (Mycapssa) Dose in responders in Core Treatment Period (mITT population, 82 responders by LOCF)



High SRL dose = Sandostatin LAR ≥ 120 mg/month or Somatuline depot ≥ 30 mg/month; mid SRL dose = Sandostatin LAR 90 mg/month or Somatuline depot 20 mg/month; and low SRL dose = Sandostatin LAR ≤ 60 mg/month or Somatuline depot ≤ 10 mg/month.
Source: the Sponsor's Figure 3, 2.7.3 Summary of Clinical Efficacy.

In conclusion, the results of the above analyses evoke the same question again whether these patients did not require higher doses of SSAs and subsequent adjustments of Mycapssa doses because the disease was in the remission or because they were extremely sensitive to the lowest doses of octreotide. In general, experts in acromegaly fields recommend the "drug withdrawal" and monitoring of IGF-1 levels in these type of patients who require the lowest doses of SSAs or with extended dosing intervals for the disease control[13]. However, this was

not done during the trial. Thus, with no knowledge of Mycapssa dose-response relationships and in the absence of the evidence of the disease activity prior to the study enrollment, these questions remain unanswered and add more complexity to the interpretation of the results.

- Lastly, the use of medications that may also affect IGF-1/GH levels (estrogen, glucocorticoids, PPI), underestimated washout period required to eliminate residual effect of SSAs also confound further the efficacy results. For example, Dr. Abraham identified 5 patients who were treated with estrogens during the study; IGF-1 levels increased in 3/5 patients and remained low in 2/5 patients.

Integrity of data

There were other concerns with the trial conduct and integrity of the data that are summarized in Dr. Abraham's review. For example, some patients who had protocol violations were not reported as the protocol violators and continued participation in the study (e.g., 7 patients were treated with SSAs for < 3 weeks (exclusion criteria), 8 patients did not have confirmation of the disease by OGTT and/or IGF-1 levels). The fact that the time of some important blood collections used for the assessment of efficacy was not fixed relative to the drug administrations (as discussed in the study design and baseline disease characteristics sections above) also complicates the evaluation of the disease control and may overestimate (if levels collected close to Cmax of Mycapssa or SSAs) or underestimate IGF-1 and GH suppression (if levels collected close to trough of the drugs). Thus, all these uncertainties and discrepancies highlighted in Dr. Abraham's review impacts the overall confidence in the integrity of the data for this application and in the validity of the observed results.

Secondary endpoints

The analyses of the secondary endpoints do not provide convincing evidence of Mycapssa efficacy either. Moreover, the Sponsor conducted assessment of the secondary endpoints using LOCF approach (the issues with using LOCF method are described above). Thus, these endpoints will be discussed briefly for the completeness of the review only.

- Proportion of patients with various different measures of control by IGF-1 and GH values at baseline and at the end of the Core Treatment Period (Table 5)

Table 5. IGF-1 and growth hormone suppression at End of Treatment compared to Baseline, mITT (n=151), CORE, LOCF

Response Category	Baseline, n (%)	End of Treatment, n (%)
IGF-1<1.3XULN and GH<5.0 ng/ml	138(91.4)	99 (65.6)
IGF-1<1.3XULN and GH<1.0 ng/ml	95 (62.9)	80 (53.0)
IGF-1≤1.0XULN and GH<5.0 ng/ml	96 (63.6)	54 (35.8)
IGF-1≤1.0XULN and GH<2.5 ng/ml	**93 (61.6)**	**54 (35.8)**

[13] Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, van der Lely AJ, Strasburger CJ, Lamberts SW, Ho KK, Casanueva FF[0], Melmed S. Expert consensus document: A consensus on the medical treatment of acromegaly. Nat Rev Endocrinol. 2014 Apr;10(4):243-8.

IGF-1≤1.0XULN and GH<1.0 ng/ml	65 (43.0)	48 (31.8)
IGF-1<1.3XULN	138 (91.4)	101 (66.9)
IGF-1≤1.0XULN	96 (63.6)	56 (37.1)
GH<5.0 ng/ml	151 (100)	147 (97.4)
GH<2.50 ng/ml	145 (96.0)	143 (94.7)
GH<1.0 ng/ml	100 (66.2)	117 (77.5)
IGF-1≥1.3XULN and GH<2.5 ng/ml	11 (7.3)	45 (29.8)
IGF-1<1.3XULN and GH≥2.5 ng/ml	4 (2.6)	1 (0.7)
IGF-1≥1.3XULN and GH≥2.5 ng/ml	2 (1.3)	3 (2.0)

Source: Dr. Abraham's review, Table 13, modified

The response rate among "complete responders" (defined as IGF-1 <1XULN and GH<2.5 ng/ml; highlighted in green) deserved further discussion. These criteria are the criteria of the disease control accepted by scientific societies[14] and by the Agency for the approval of other SSAs. The Sponsor demonstrated that of 93 patients who were complete responders at baseline, 54 maintained the response at the end of Core period (58%). Dr. Abraham reanalyzed this data considering all dropouts as nonresponders and demonstrated that actually only 43/93 patients (46 %/) were able to maintain the complete response at the end of treatment (Clinical Review, Figure 5, page 58). This low response rate raises question regarding overall efficacy of Mycapssa for the disease control further.

Additionally, the data in the table above show that GH was well controlled in the majority of patients. However, I am not confident in the accuracy of the observed values due to the multiple deficiencies discussed above (potential overestimation of the effect due to the collection of samples at Cmax, unknown disease status, residual effect of SSAs, etc.). The Sponsor argued that IGF-1 is more reliable marker and is most commonly used to biochemically assess the long-term effectiveness of acromegaly therapy (refer to the Sponsor's response to information request from 4/1/2016). However, as demonstrated in the table, approximately 1/3 of patients lost control of IGF-1 at the end of the study compared to baseline (only 66.9% of patients had IGF-1 X1.3UNL vs. 91.4% of patients at baseline; highlighted in yellow). Thus, the same concern is raised again regarding the durability of the effect.

- Maintenance of IGF-1 response during the Fixed Dose Phase defined as proportion of patients with IGF-1 levels < 1.3 X ULN at the end of the Core Treatment Period who also had IGF-1 levels < 1.3 X ULN at the first assessment in the Fixed Dose Phase.

- Maintenance of IGF-1 and GH response during the Fixed Dose Phase (Core) defined as proportion of responders (IGF-1 levels < 1.3 X ULN and integrated GH < 2.5 ng/mL) at the end of the Core Treatment Period who also had IGF-1 levels < 1.3 X ULN and GH < 2.5 ng/mL at the first assessment in the Fixed Dose Phase.

As stated in Dr. Abraham's review, both endpoints were analyzed in a Fixed Dose population defined as all patients who were able to enter the Fixed Dose phase. The Sponsor considerd Fixed Dose population to be the "intended target population" for the treatment with Mycapssa.

[14] Scientific Society Guidleines

However, the study was not designed to demonstrate the efficacy and safety of the drug in this "intended popualtion". Thus, this analysis should be considered as a subgroup analysis and does not replace the analysis of responders vs. non-responders. Moreover, this analysis does not provide convincing evidence that the response to the drug is sustained over the long period of time in patients with acromegaly who are responders to SSAs (proposed indication). The data demonstrate only that small subgroup of patients who tolerated the drug reasonably well during the titration period of the study (for 2-5 months) and did not discontinued the study due to the AEs or treatment failure were able to maintain the GH and IGF-1 levels during the variable fixed dose period (2-5 months). Moreover, the concerning trend in increasing IGF-1 levels was noted among the responders and non-responders (refer to the discussion above). Lastly, it should be also noted that the duration of Fixed Dose period was variable in the study and could be as short as 2 months or as long as 5 months. Thus, the variability in the duration of "maintenance of the IGF-1 control" and maintenance of such control during 2 months only does not provide convincing evidence that this control may translate into the long-term control of the disease and does not support the proposed indication for Mycapssa as for long-term maintenance therapy.

Other analyses (exploratory and subgroup)

- Exploratory analysis evaluating patients' satisfaction with Mycapssa treatment using questioners (although not validated) was generally consistent with low biochemical control of the disease. As outlined in Dr. Abraham's review, more patients were not satisfied with the treatment and reported deterioration of the disease control (42.4%) during the treatment with Mycapssa compared to those patients who reported that the disease improved (31.7%).
- The Sponsor carried out also multiple post-hoc subgroup analyses demonstrating that the drug might be more effective in patients with better control of the disease at baseline (lower IGF-1 and GH), in patients who required lower doses of SSAs during screening period, patients who required lower doses of Mycapssa to maintain the response, etc. While the applicant argues that the analysis of Mycapssa in these various subgroups of patients demonstrated reasonable efficacy of Mycapssa, the argument that the different post-hoc analyses is more appropriate when it fits the data better is not the most convincing proof of efficacy and does not substitute the standard of substantial evidence of effectiveness. Moreover, as discussed above, results of some of these analyses (e.g. the ability to maintain the disease control on the lowest dose of Mycapssa) raise the question again about the disease activity and whether or not these patients require treatment at all.
  However, the clinical benefits suggested by these analyses may be used to justify initiation of the prospective controlled trial to verify these exploratory findings.

The Sponsor claimed that the response was maintained by the majority of patients who were enrolled in the extension study (69 patients at the end of extension period). However, this analysis is biased by the using LOCF method and not counting patients who dropped out earlier as nonresponders (as discussed above). Additionally, the quantitative efficacy data obtained from such an open-label, extension trial without the control group cannot be used as supportive evidence of the drug efficacy because, by the very nature of its design, the extension period selected a patient subpopulation (88 patients) who already tolerated the drug well and majority of these patients were responders to the drug (74/88 patients) at the end of 7-month period and thus is expected to have further benefit from the drug. Lastly, even though,

69/88 (78%) patients in this subgroup were the responders at the end of the 13-month period (by the Sponsor's analysis), 9/74 patients who were responders in Core phase and entered the extension study lost the disease control and 6 patients discontinued study earlier (2/6 patients- due to the AEs and 2/6-due to the treatment failure). Moreover, the overall response rate significantly decreased in the intended population compared to the beginning of the study: 100% (151 patients) of patients were responders at baseline, 65 % (98/151 patients by LOCF method) were responders at the end of 7 month period and only 69/151 patients remained responders at the end of extension period (45%)). Thus, the extension study not only did not demonstrate efficacy of the drug, but rather raised the same concerns discussed in this memo regarding long-term maintenance of the disease control in patients who are responders to SSAs.

To conclude, I am in agreement with both the statistical and clinical recommendations for Complete Response. The results of the trial did not provide substantial evidence of efficacy of Mycapssa in intended population (i.e. in patients who are well-controlled on SSAs) and that the results of the trial are unreliable due to the multiple uncertainties described above. I agree that without apparent hypothesis testing, this study appeared to be more descriptive than confirmatory study. Demonstration of effectiveness of Mycapssa for the treatment of acromegaly will require a confirmatory, prospective, well controlled, randomized study in intended patient population (e.g., patients who respond to the lower doses of SSAs, patients with mild disease). Such trial should also incorporate the appropriate washout period in order to confirm the status of the disease and to eliminate such confounding factors as residual effect of SSA, inactive disease, etc. The available data obtained with Mycapssa could help formulate a protocol for a confirmatory study.

8. Safety

All the safety information in this memorandum is derived from Dr. Abraham's clinical review which summarizes in detail the results of Study CH-ACM-01 and its extension, as well as safety data from 11 Phase 1 studies conducted by Chiasma with Mycapssa in healthy volunteers and patients with renal and hepatic impairments. However, as noted in Dr. Abraham's review, the results from the non-pivotal studies do not add substantive safety information due to limited dosing over a short period of time (mostly single dosing). Thus, this memorandum will focus on safety observations made in the pivotal trial.

The Mycapssa Phase 3 clinical program for the acromegaly indication provides safety data obtained from 155 patients who received at least one dose of Mycapssa in the pivotal trial. Of these patients, 116 patients were treated with Mycapssa for at least 6 months in the pivotal trial, and 82 patients were treated for at least 12 months in the extension trial. Daily Mycapssa doses ranged between 40 mg and 80 mg. There was a high dropout rate in the study: a total of 53 patients (34%) discontinued trial preliminary; of these, 24 patients discontinued trail due treatment failure and 24 patients- due to AEs.

Death

There were two deaths in pivotal study. One of two patients died of sepsis and bile duct obstruction; Dr. Abraham considered this death as drug-related since the bile duct obstruction

is known AE associated with octreotide use. The second patient died because of pancreatic adenocarcinoma; Dr. Abraham concluded that the death was most likely not drug-related and the patient had insidious tumor prior to the start of therapy with Mycapssa. I agree that the basis for a relation between pancreatic tumor, acromegaly and Mycapssa cannot be established at this time.

AEs that led to the study discontinuation

The Sponsor reported a total of 21 subjects who discontinued Core study prematurely due to the adverse events; however, Dr. Abraham identified 2 additional subjects who discontinued Core study due to the AEs (reported initially as subjects who discontinued the study due to the subject's request). Thus, a total of 23 subjects (14.8%) discontinued Core study prematurely due to the AEs: the majority of these subjects discontinued the study during the dose titration (16/23 subjects). Of these 23 subjects, 6 subjects discontinued study prematurely due to the serious adverse events (death (2), meningioma (1), malignant neoplasm (1), jaundice (1), and colon cancer (1)). The most frequent AEs that led to the study discontinuation were GI-related AEs (9 patients: nausea, abdominal pain, diarrhea, etc.) and malignancy (4 patients).

Serious Adverse Events (SAE)

A total of 22 (14%) subjects developed 40 SAEs in pivotal Phase 3 study (including two cases of death). Of 20 patients with non-fatal SAEs, 14 subjects experienced 18 SAEs during Core treatment, 2 subjects experienced SAEs in Core and extension periods (2 SAEs in Core period and 2 in extension period), and 4 patients experienced 7 SAEs in extension period only.
The only SAE that occurred in more than one patient were malignancies (5) and hepatobiliary-related AEs (6). Outcome of case narrative review for both of these events is discussed in the dedicated sections below. All other AEs occurred in one patient each (hyponatremia, transient ischemic attack, intervertebral disk protrusion, urinary tract infection, pulmonary embolism, corneal abscess, herpes simplex, hypoglycemia, sciatica, seizures, delayed wound healing, melena, headache, tinnitus, vertigo, polymyalgia rheumatic, osteoarthritis, sinusitis) and were considered by Dr. Abraham as unrelated to the study drug.

Hepatobiliary adverse events

Hepatobiliary AEs are not unusual and are labeled AEs for all SSAs; octreotide is known to inhibit gallbladder contractility and to induce bile stasis.
Dr. Abraham identified a total of 18 patients (11.6%) who had 22 hepatobiliary-related AEs. There were a total 6 hepatobiliary-related SAEs that occurred in 5 patients (including one case with fatal outcome) during the treatment with Mycapssa: 5 SAEs occurred in 5 patients in Core period (cholelithiasis, jaundice, acute biliary pancreatitis, bile duct stone and bile duct obstruction (fatal case)) and 1 during the extension period (acute cholecystitis) and 1 SAE of acute cholecystitis occurred in 1 patient in extension period (the same patient had SAE of bile duct stone in Core period). Dr. Abraham reviewed all narratives of cases with hepatobiliary-related SAEs, non-serious AEs and results of the gallbladder ultrasound performed as part of safety monitoring (at baseline and at follow-up visit) and concluded that there were no increased in severity or frequency of hepatobiliary AEs associated with use of Mycapssa compared to the frequency or severity of these AEs reported in the injectable SSA labels.
In conclusion, I agree with Dr. Abraham no new safety signals have been identified; the assessment of the gallbladder and pancreas in pivotal study of Mycapssa showed evidence

consistent with the known propensity of somatostatin analogs to reduce gallbladder motility. However, it should be also acknowledged that the comparison of adverse event rates across trials is complicated given different times of exposure to the drug, different route of administration and formulations (oral vs. injectable), inherent patient variability, etc.

Malignancies
Dr. Abraham identified a total of 10 patients who experienced 11 events of neoplasms during the study (4 malignant tumors and 7 benign tumors). Of these 10 patients, 5 patients experienced SAEs of neoplasms: 4 malignant tumors (breast, pancreatic, bone, colon) and one meningioma. All other reported AEs of neoplasms were non-serious events of benign neoplasms: hemangioma of the liver (2), lipoma, renal hemangioma, skin papilloma, and thyroid neoplasm. The review of case narratives did not identify causal relationships between the events and the drug; each type of tumor was reported in one patient each. The further assessment is also complicated by the multiple confounding factors (presence of neoplasm at baseline prior to the onset of treatment with Mycapssa, increased risk of neoplasm associated with uncontrolled disease itself, prior history of radiation, etc.). Lastly, no safety signals associated with malignancy were identified in non-clinical studies (although no dedicated carcinogenicity studies were conducted by the Sponsor) and there is no known malignancy potential associated with octreotide formulations. Thus, I agree with Dr. Abraham's conclusion that no safety signals for neoplasms has been identified in Mycapssa development program, however, no firm conclusion can be drawn at this time due to the absence of the control group and short duration of the trial.

Common Adverse Reactions (Table 6)
A total of 86.5% of Mycapssa-treated subjects reported 1096 AEs. The frequency of treatment-emergent adverse events appeared to be not dose-dependent (74.8% of patients in 40 mg group, 67.8% of patients in 60 mg group and 66.7% in 80 mg group), however, no firm conclusion can be made at this time due to the high drop-out rate early in the Core period.

Adverse events with a frequency >5% were gastrointestinal (56.8%: diarrhea, abdominal pain and distention, nausea, vomiting, dyspepsia, flatulence), headache (33.5%), arthralgia (27.1%), asthenia (22.6%), peripheral edema (16%), hyperhidrosis (21.9%), dizziness (5.2%), fatigue (5.2%), nasopharyngitis (7.7%), influenza (6.5%), upper respiratory tract infection (5.2%).

Table 6. Incidence of most common (≥ 5% of total patients) adverse events in Core, safety population

System organ class Preferred term	Dose at Onset of Adverse Event						Total (N=155)	
	OCT 20 + 20 (N=155)		OCT 40 + 20 (N=90)		OCT 40 + 40 (N=57)			
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAE	**116 (74.8)**	**586**	**61 (67.8)**	**257**	**38 (66.7)**	**245**	**134 (86.5)**	**1096**
Gastrointestinal disorders	71 (45.8)	131	30 (33.3)	60	15 (26.3)	32	88 (56.8)	223
Nausea	30 (19.4)	35	14 (15.6)	16	6 (10.5)	10	46 (29.7)	61
Diarrhoea	18 (11.6)	22	8 (8.9)	11	3 (5.3)	4	27 (17.4)	37
Dyspepsia	11 (7.1)	14	1 (1.1)	1	1 (1.8)	1	13 (8.4)	16
Flatulence	9 (5.8)	9	1 (1.1)	2	2 (3.5)	3	9 (5.8)	14
Abdominal pain upper	9 (5.8)	9	2 (2.2)	3	1 (1.8)	1	12 (7.7)	13
Abdominal distension	7 (4.5)	8	4 (4.4)	4	1 (1.8)	1	10 (6.5)	13
Vomiting	4 (2.6)	4	3 (3.3)	3	3 (5.3)	3	9 (5.8)	10
Nervous system disorders	53 (34.2)	96	23 (25.6)	44	21 (36.8)	62	62 (40.0)	202
Headache	41 (26.5)	70	18 (20.0)	37	19 (33.3)	52	52 (33.5)	159
Dizziness	7 (4.5)	8	1 (1.1)	1	2 (3.5)	4	8 (5.2)	13
Musculoskeletal and connective tissue disorder	32 (20.6)	61	26 (28.9)	37	19 (33.3)	44	58 (37.4)	144
Arthralgia	22 (14.2)	43	20 (22.2)	25	10 (17.5)	20	42 (27.1)	88
General disorders and administration site conditions	42 (27.1)	78	14 (15.6)	29	12 (21.1)	17	53 (34.2)	127
Asthenia	24 (15.5)	33	11 (12.2)	13	7 (12.3)	9	35 (22.6)	56
Oedema peripheral	18 (11.6)	27	8 (8.9)	10	5 (8.8)	5	25 (16.1)	42
Fatigue	5 (3.2)	6	1 (1.1)	1	1 (1.8)	1	8 (5.2)	9
Infections and infestations	31 (20.0)	47	17 (18.9)	19	16 (28.1)	22	53 (34.2)	89
Nasopharyngitis	5 (3.2)	8	4 (4.4)	4	5 (8.8)	5	12 (7.7)	17
Influenza	6 (3.9)	6	3 (3.3)	3	2 (3.5)	2	10 (6.5)	11
Upper respiratory tract infection	4 (2.6)	4	1 (1.1)	1	3 (5.3)	4	8 (5.2)	9
Skin and subcutaneous tissue disorders	28 (18.1)	51	11 (12.2)	17	8 (14.0)	10	42 (27.1)	80
Hyperhidrosis	20 (12.9)	36	9 (10.0)	14	6 (10.5)	6	34 (21.9)	57

Source: Clinical Review, table 38.

Interestingly, that such AEs as hyperhidrosis and peripheral edema are not typically observed during the treatment with injectable SSAs and are not listed in the labels for other SSAs (Sandostatin, lanreotide), however, they were reported in patients treated with Mycapssa. Other AEs including arthralgia and headache had a higher incidence in patients taking Mycapssa when compared to the frequency of these adverse events reported in the other SSAs labels. On the other hand, edema, excessive sweating, arthralgia and headache are typical symptoms observed in patients with uncontrolled acromegaly. Thus, the presence of these AEs

in substantial number of patients during the study (hyperhidrosis in 21% of patients, edema in 16%, arthralgia in 27%, headache in 33.5%) might indicate a poor control of the disease by Mycapssa in these patients. However, absence of the control group does not allow to differentiate adverse events that may be due to the underlying condition from those due to the drug itself.

Finally, analyses of laboratory values and vital signs summarized in the clinical review do not identify any safety signals.

In conclusion, I agree with Dr. Abraham's assessment that no new safety signals were identified during the 7-month trial and overall safety profile of Mycapssa was similar to the reported in the previous trials with injectable Sandostatin analogs. However, even though the safety profile of injectable octreotide formulations is well characterized, the rate of known AEs as well as long-term safety profile of orally administered octreotide might be different (due to addition of TPE, first pass metabolism, etc.). It should be also noted that the frequency of the adverse events associated with Mycapssa might be also underestimated due to the high drop-out rate early during the study. Lastly, it is also extremely difficult to distinguish adverse events that may be due to the drug itself from those due to the underlying condition or to background events in the absence of the controll group. Thus, comparative safety data obtained from the study of longer duration will be more scientifically useful in order to better characterize safety profile of oral formulation of octreotide in the intended population.

9. Advisory Committee Meeting

No AC meeting was held.

10. Pediatrics

Mycapssa has received orphan-drug designation on May 11, 2010 for "the oral treatment of acromegaly". Therefore, the requirements of the Pediatric research Equity Act do not apply to this application.

11. Other Relevant Regulatory Issues

OSI inspection

A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on January 29, 2016. Three principal investigators were investigated. The audit resulted in one Voluntary Action Indicated letter and two No Action Indicated decisions. The inspection of the Sponsor also resulted in Voluntary Action Indicated letter due to the regulatory violations, however, the review concluded that these violations "are unlikely to significantly impact primary safety and efficacy analyses and data from the Sponsor appears to be acceptable". Overall, the review concluded that "the inspectional findings support validity of the data as reported by the Sponsor under this NDA".

Financial Disclosure
Financial disclosure documentation was reviewed by Dr. Abraham. She identified two Investigators who received compensations. One Investigator received moderate compensation, however, there was no clear evidence that the data contributed by his site could have affected the study results. This site enrolled (b) (6) patients only and was ranked (b) (6) of (b) (6) sites evaluated for the risk ((b) (6) is the site with the highest risk according to the FDA site selection tool). The second Investigator received significant amount of compensation as a consultant, however, (b) (6) (b) (6); thus, it is unlikely that he influenced the results of the study.

12. Labeling

Proprietary name
The proposed proprietary name, Mycapssa, was found to be acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on July 30, 2015.

Labeling
No labeling negotiations were conducted with Chiasma because the recommendations are for a Complete Response.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend Complete response because applicant did not provide substantial evidence supporting the efficacy claims proposed in this NDA, i.e. that the drug is effective as long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)

The major deficiencies and concerns are:
1. The trial did not provide robust evidence that the drug can maintain the control of the disease achieved by SSAs: approximately half of patients who were responders to SSAs at the beginning of the study (defined as IGF-1< 1.3XULN and GH<2.5 ng/ml) lost control of the disease over 7 months of the treatment with Mycapssa (54%; 82/151 patients), and the response rate decreased further at the end of 13 month treatment period (69/151 patients maintained the control of the disease at the end of the extension phase).
2. The response rate among the "true" responders, i.e. with IGF-1<1XULN and GH<2.5 ng/mL (the recommended and previously accepted criteria for the disease control by scientific societies and by Agency) at baseline (98 patients) who was able to maintain the control of the disease at the end of the 7-month period was even lower, 46%, raising the same question regarding the overall efficacy of Mycapssa for the treatment of acromegaly.
3. The drug is indicated for the long-term maintenance therapy. However, the short duration of the trial puts into question the durability and sustainability of the response. Moreover, the observed trends in losing the overall disease control at the end of 13-month treatment period

(as discussed above) and in increasing IGF-1 levels during the first seven month of treatment with Mycapssa raise this concern further.
4. The observed efficacy results are unreliable due to the multiple uncertainties and confounding factors including but not limited to: high dropout rate due to the drug intolerance and/or treatment failure, unknown status of the disease at baseline (active vs. in remission), possible residual effect of long-acting SSAs (due to the long t1/2 and relatively short wash-out period), effect of the concomitant medications on the disease control (estrogens, glucocorticoids, etc.), possible overestimation of the GH suppression due to the collection of the samples at time of expected maximum suppression.
5. The studied population did not accurately reflect the population in whom the drug is intended to be used, i.e. patients in whom prior treatment with SSAs has been shown to be effective:
- First, the study included some patients in whom SSAs were only partially effective and thus these patients required two-drug therapy at baseline (cabergoline or pegvisomant) for the disease control prior to the onset of therapy with Mycapssa.
-Second, the actual percent of the responders to SSAs at screening and at baseline also cannot be verified with confidence due to the variability in the time of biomarkers collection that elapsed from the last dose of SSAs administration (from 0 to 82 days). Thus, the percent of responders at screening (100%) and at baseline (89%) might be overestimated (due to the oversuppression of markers when they are collected soon after the last dose) or underestimated (when the levels are collected at trough).
6. The absence of the control group in this study does not allow to discriminate between the responses caused by the drug itself and the response due to the other factors. The Sponsor's selection of the open label single arm trial was based on the assumption that all patients enrolled in the trial had an active disease, thus adding of a comparator arm was not necessary and would not add scientific value to the study. However (as discussed above), the disease status was unknown in the enrolled patients. Overall, a single-arm study is not as informative as a controlled study and there is always concern in interpreting data from a single arm trial wherein some patients may improve spontaneously.
7. Lastly, Mycapssa clinical program lacks such essential elements of the drug development as characterization of PK/PD profile of the drug. Sandostatin IR and Mycapssa are not bioequivalent and PK/PD bridge between these drugs was not established. The lack of PK/PD comparability between Mycapssa and Sandostatin complicates further the interpretability of the Phase 3 results.
8. There were also deficiencies associated with the integrity of data identified during the review of application decreasing my confidence in the reliability of the observed results further.

In conclusion, I am in the agreement with the recommendations made by statistical, clinical and Clin.Pharm teams that there is a need for:

1) A controlled confirmatory study that will evaluate prospectively the efficacy and safety of Mycapssa in patients with acromegaly.
   This new study should be a randomized, controlled study. The study should select the population in whom the drug is intended to be used (e.g. treatment-naïve patients, patients with proven efficacy to SSAs, patients who required only certain doses of SSAs). This study should be conducted in patients with confirmed and documented active disease rather

than in patients in whom the status of the disease is unknown or cannot be reliably confirmed. Thus, the study should include appropriate washout period in order to remove such confounding factors as inactivity of the disease secondary to radiation, surgery or prolong suppression of biochemical markers, or residual effect of previous treatment with SSA. Lastly, the study should be of longer duration in order to demonstrate the sustainability of the disease control with the drug intended for chronic maintenance therapy.

2) A dedicated steady-state PK/PD study in acromegaly patients demonstrating that PD (GH and IGF-1) is comparable between bid Mycapssa and tid Sandostatin
3) The PD effect of Mycapssa should be characterized in the future study(s). It should be also demonstrated that PD effect is maintained for the duration of the proposed dosing interval.
4) The Sponsor has to characterize the PK/PD (GH) relationship of Mycapssa; a minimum of 12 hour GH profile and 12 hour octreotide profile should be evaluated following a 20 mg dose of Mycapssa

Lastly, there are also manufacturing facility deficiencies identified during the OPQ inspection that are required the satisfactory resolution before this application may be approved.

- Risk Benefit Assessment

One cannot fully assess the risk/benefit of Mycapssa in absence of well-established PK/PD characteristics of the drug and without reliable demonstration of the efficacy in randomized controlled study(s) (refer to the discussion in the section above).
Even though, the overall safety profile of Mycapssa was similar to the reported in the previous trials with injectable Sandostatin analogs in this open label single arm trial of short duration, one cannot predict the long-term safety profile of orally administered Mycapssa (due to the addition of TPE, first pass metabolism, etc.). The rate of the observed AEs as well as occurrence of new safety signals might be also over or underestimated in this trial due to the lack of control group and high dropout rate due to the adverse events. Lastly, it is also extremely difficult to distinguish adverse events that may be due to the drug itself from those due to the underlying condition or to background events in the absence of the controlled group. Thus, comparative safety data obtained from the study of longer duration will be more scientifically useful in order to better characterize safety profile of oral formulation of octreotide in the intended population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  Not applicable

- Recommendation for other Postmarketing Requirements and Commitments

  Not applicable

- Recommended Comments to Applicant

The action letter will communicate the deficiencies identified in the clinical, statistical, clinical pharmacology and OPQ reviews.

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/s/

MARINA ZEMSKOVA
04/15/2016

JEAN-MARC P GUETTIER
04/16/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208232
Applicant Name	Chiasma Inc.,
Date of Submission	June 12, 2015
PDUFA Goal Date	
Proprietary Name / **Established (USAN) Name**	Mycapssa/Octreotide acetate
Dosage Forms / Strengths	Capsule/20 mg
Proposed Indication(s)	*Long term maintenance treatment in acromegaly patients* (b) (4) (b) (4)
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Smita Abraham, MD
Statistical Review	Anna Ketterman, PhD
Pharmacology Toxicology Review	Jessica Hawes, PhD
CMC Review/OBP Review	Team Lead review by Suong Tran, PhD
Clinical Pharmacology Review	Sury PhD and Lian Ma PhD
DSI	Cynthia Kleppinger, MD
CDTL Review	Marina Zemskova, MD

OND=Office of New Drugs
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

On June 12, 2015 Chiasma Inc., submitted a New Drug Application (NDA) for Mycapssa pursuant to section 505(b)(2) of the Food, Drug and Cosmetic Act. Mycapssa is a capsule containing 20 mg of the somatostatin receptor agonist octreotide acetate. Mycapssa is to be administered orally twice daily. The applicant seeks to rely in part on FDA's previous finding of safety and effectiveness for the listed drug, Sandostatin (octreotide acetate for injectable suspension; NDA# 19667) to support approval of Mycapssa. The applicant proposes to indicate Mycapssa for *long term maintenance treatment in acromegaly patients* (b) (4) (b) (4)

2. Background

Disease

Acromegaly is a clinical syndrome caused in most cases by a growth hormone (GH) secreting pituitary adenoma. The syndrome is characterized by disordered somatic growth and metabolic abnormalities and arises due to chronic hyper-secretion of growth hormone (GH) which will act to stimulate production of insulin-like growth factor-1 (IGF-1) from effector organs. Acromegaly has historically been considered a rare disease, with a reported estimated prevalence ranging from 38 to 69 cases per million and an annual incidence rate of 3 to 4 cases per million though recent cross-sectional studies, using screening techniques relying on IGF-1, have reported a much higher disease prevalence (i.e., 480-1000 per million individuals)[1,2].

The clinical manifestations of acromegaly include signs and symptoms attributed to tumor mass effects (i.e., headaches, vision loss, pituitary dysfunction), disordered somatic growth (i.e., enlargement/overgrowth of soft tissue, skin, bone, joints and other visceral organs) and disordered metabolism (e.g., insulin resistance/diabetes). The effects on somatic growth and on metabolism are the direct results of excess GH/IGF-1 levels and are believed to be major contributors to the increased mortality[3] in patients with acromegaly.

Therapeutic Goals

Treatments aim to correct tumor-related mass effects and to normalize both excess GH secretion and elevated IGF-1 levels (i.e., biochemical normalization[4]). Biochemical normalization has been reported to improve soft tissue swelling (e.g., carpal tunnel syndrome), hyperglycemia, sleep apnea visceral enlargement (e.g., left ventricular mass) and cartilaginous overgrowth in case series.

Treatments

Surgery

Trans-sphenoidal surgery (TSS) to remove the pituitary tumor is the primary therapeutic modality for acromegaly. Disease remission following trans-sphenoidal surgery depends on the technical expertise

[1] Clinical Endocrinology (Oxf). 2008 Sep;69(3):432-5.
[2] Pituitary. 2011 Sep;14(3):217-21.
[3] Patients with acromegaly die predominantly from cardiovascular complications which has been attributed hypertension, left ventricular hypertrophy, cardiomyopathy, and sleep apnea that arises due to excess GH/IGF-1
[4] Defined by professional guidelines as IGF-1 levels within the normal range for age and GH levels less than 1 ng/mL. Refer to Acromegaly: an endocrine society clinical practice guideline in J Clin Endocrinol Metab. 2014 Nov;99(11):3933-51.

of the neurosurgeon and the size of the tumor. Biochemical normalization rates after trans-phenoidal surgery have been reported to range from 75 to 95% and 40 to 70% at one year for microadenoma (tumors less than 1 cm in diameter) and macroadenoma respectively.

Drugs

Drug therapy is reserved for patients who; have persistent or recurrent disease after surgery, refuse surgery, have tumors that cannot be resected[5] or have unacceptable surgical risks (e.g., severe cardiomyopathy or cardiopulmonary disease). Approved therapies with an indication for the treatment of acromegaly include somatostatin analogs[6], a GH receptor antagonist[7] and a dopamine agonist (bromocriptine). Most products were approved in part on the basis of demonstrating large reduction in GH or IGF-1-levels in two or more randomized controlled studies in patients with active disease at baseline. Most products are injectable and three of these products are administered at once monthly intervals. The dopamine agonists cabergoline (off-label use) and bromocriptine (labeled use) are also used for the treatment of acromegaly typically in patients with mild disease because dopamine agonists have been reported to be less effective than alternatives. Dopamine agonists are administered orally once or twice weekly (cabergoline) or daily (bromocriptine).

Radiation

Radiation therapy is another treatment modality that is used in patients with residual tumor following surgery, or if medical therapy is unavailable, unsuccessful, or not tolerated. The therapeutic effect of this therapy may take years to manifest and guidelines recommend monitoring effectiveness of this therapy by assessing for biochemical normalization on an annual basis after medications used to treat acromegaly have been withdrawn and adequately washed out.

Considerations Related to the Efficacy Assessment in the Mycapssa Program

There are a two important points to highlight related to acromegaly treatments that impact interpretation of the efficacy assessment submitted in this application.

The first is that biochemical disease **may not** have been present in all patients enrolled[8] in the applicant's prospective single arm, observational, cohort study submitted to support that Mycapssa is effective. There are many potential reasons for this including but not limited to the fact that: the residual tumor could have infarcted[9], the need for drug therapy was never reassessed in the course of the disease, past radiation treatment may have had its intended cytotoxic effects, the drugs themselves over time could have exerted a cytostatic/toxic effect and induced apoptosis[10] etc. Recent reports suggest that ~20% of patients with acromegaly who have disease histories similar to the population under study in this application[11] and who have been chronically treated with somatostatin analogs do not have biochemical disease when they undergo a prolonged (12-18 months) somatostatin analog de-challenge[12].

A drug washout period after screening potential participants to confirm that all patients had active disease at baseline would have ensured that all patients indeed had disease. Confirmation of

[5] Such as large tumors invading the cavernous sinus in close proximity to the internal carotid
[6] octreotide (sandostatin and sandostatin LAR), lanreotide (somatuline depot), pasireotide LAR (Signifor LAR)
[7] Pegvisomant
[8] Patients with a history of acromegaly who were treated with surgery (plus or minus radiation) and drugs and had normal GH and IGF-1 biochemistry at baseline were eligible to participate.
[9] Ann Intern Med. 1961; 55(3):478-481 and Acta Neurochir. 1997; 139: 992-994 and Endocr Pract. 2009; 15(7):725-31,
[10] Mol. Endocrinol. 1996. 10; 1688-1696 and J. Clin. Endocrinol. Metab. 2005. 90; 6156-6161.
[11] i.e., those with previous remote history of microadenomas controlled on a low dose of a somatostatin analogs
[12] Clin Endocrinol. 1999; 50:295-299 and Pituitary. 2000; 3:193-197 and Eur. J. Endocrinol. 2008; 158: 19-25 and Eur. J. Endocrinol. 2012; 166: 21-26 and Endocrine. 2014; 46: 577-584.

biochemical disease at baseline was carried out in other drug development programs[13]. Alternatively, randomization and use of a placebo control arm could have estimated the bias (proportion of patients in the cohort with non-active disease at month seven would have been captured in the placebo arm).

Since the applicant chose not to assess for the presence of active disease at baseline, it is highly likely that the response rate the applicant is reporting for Mycapssa considerably overestimates the drug's effect (i.e., by as much as 20%) as patients who may not have had active disease at month seven were counted as responders in all analyses (i.e., in the main sponsor's analysis and in the most conservative of sensitivity analyses performed by FDA).

The second and somewhat related point is that long acting somatostatin analogues used by all participants and other active therapies (dopamine agonists/pegvisomant) used by some patients prior to participating in the applicant's prospective, observational, single arm cohort study were still exerting therapeutic effects in the "efficacy-assessment" phase of the study. The long acting somatostatin analogs, once injected into muscular tissue, keep releasing effective drug from the intramuscular depot into the circulation for weeks to months after injection. The full prescribing information for sandostatin LAR notes, for example, that octreotide in plasma was detected for up to 3 months after a single injection of sandostatin LAR in healthy volunteers[14].

In the applicant's study the mean time between the last injection of long-acting SSA and first dose of Mycapssa was 1 month (refer to Table 5 in Dr. Abraham's review). Residual effects of pre-trial long acting SSA on disease activity in the efficacy assessment phase confound interpretability of the efficacy (and safety) results. This is important to note in light of the fact that approximately 44% of subjects prematurely discontinued from the study before month seven and efficacy for those subjects was handled by carrying forward the last on study assessment. The confounding effect of pre-trial drug activity and method to handle missing data in these patients biases the estimate of efficacy in favor of Mycapssa and could have potentially been handled through use of randomization and a placebo-control (i.e., residual effect of pre-trial drug would have been captured in the placebo arm and adjusted for in the efficacy assessment).

The issue of the need for a drug washout was raised by the Agency at the end of phase 2 meeting. The applicant did not change the study design after receiving this Agency comment as they did not perceive this to be a problem, arguing instead that in their opinion all antecedent drug therapies effective to treat acromegaly should be washed out by month seven (the intended end of study time point to assess for presence of active disease). The validity of this assumption was in part contingent on all participants completing the study (which turned out not to be the case). While the threshold for seven month was not completely unreasonable, there are no robust data to corroborate the assertion that after a seven month washout period active drug is indeed guaranteed to no longer be detectable in the circulation of all patients who have been treated chronically with long acting SSA agonists. In addition and as stated above, the effectiveness of these products has been postulated to be attributable to their potential cytostatic/toxic effects so residual inhibitory effect on pituitary GH secretion could outlast the presence of these products in circulation.

Dr. Abraham looked into these issues in the review of this application. The applicant could not confirm that all patients had active disease at baseline as this was not a required part of the protocol.

[13] Refer to full prescribing information for lanreotide.
[14] Refer to Section 12.3 of the full prescribing information for Sandostatin LAR.

The applicant also could not confirm that all "responders" had active disease two weeks after being washed out from Mycapssa because these data were not captured in the schedule of assessments. In examining protocol violations, Dr. Abraham identified at least two patients who were "responders" at baseline despite not having received an injection of somatostatin for ~3 months in one (patient # (b) (6)) and ~ 2 months in another (patient # (b) (6)). This is unusual since long acting somatostatin analogs used in the study are recommended as a once monthly injection and suggests these individuals did not have active disease. These two patients were categorized as responders at end of treatment. In addition Dr. Abraham identified three patients classified as "responders" at end of treatment who never resumed therapy and were controlled on no therapies after study completion (Patient (b) (6) These few cases call into question whether all patients truly had disease when the efficacy assessment was carried out and suggest this bias was present in the trial. The review could not ascertain the extent to which this specific bias affected the efficacy estimate.

In light of these two issues, the estimate of efficacy derived from the single arm, observational, cohort study and attributed to Mycapssa is likely to lead to important biases in favor of the drug product and to overstate the product's true efficacy.

Regulatory History and Changes to Protocol during Development

Drs. Zemskova and Abraham have summarized key aspects of the regulatory history in Sections 2 and 2.5 of their respective reviews. A pre-IND (2 March 2010), End of Phase 2 (9 August 2011), Pre-NDA (1 May 2014) and second Pre-NDA meetings (referred to a Type C guidance meeting on 8 December 2014) were held. The applicant did not pro-actively seek Agency guidance or agreement on changes made to the protocol following the End of Phase 2 meeting.

While the Agency did not reject the applicant's phase 3 study synopsis at End of Phase 2, Agency guidance was predicated on a partial understanding of summary data available at the time and submitted to support discussions of questions raised by the applicant. It was clear that the applicant sought to establish a "bridge" between the listed drug and Mycapssa through a comparative bioavailability study but exactly how the applicant was going to utilize these comparative data in support of the application was unclear at the time. The summary data in the briefing package implied that exposure to octreotide was "similar" between a 20 mg single dose of Mycapssa and a 0.1 mg single dose of the listed drug in healthy volunteers. If exposure was indeed sufficiently similar between the two products then one would not necessarily need to confirm efficacy of the novel formulation or route of administration. Allowing a single one arm trial to obtain data on safety when efficacy is established through a PK bridge could be an appropriate regulatory path. It was clear from the Agency comments made at the EOP-2 meeting that the full assessment of exposure similarity between Mycapssa and the listed drug would be assessed at the time of NDA review with data on hand. The applicant stated however that they would also "establish" the efficacy of Mycapssa through their own phase 3 study. The proposed phase 3 program was unusual in the following respects;

- It was based on a single study (programs for a new molecular entity in acromegaly have traditionally relied on two trials).
- It was based on a study that was not randomized, blinded or concurrently controlled (programs for a new molecular entity in acromegaly have traditionally relied on randomized and concurrently controlled trials).

- It was studying only a subpopulation of patients with Acromegaly by enriching the population with patients who had declared themselves "responders" and who "tolerated" somatostatin analog treatments [programs for a new molecular entity in acromegaly have traditionally enrolled patients who would be candidate for drugs (drug treated and drug naïve) and have not limited enrollment to patients who respond and tolerate the class of drug being evaluated].
- It did not require confirmation of active disease after a somatostatin analog washout at baseline.
- Although IGF-1 levels was designated as the primary endpoint variable at the end of phase 2 (See June 2011 version of the protocol); The primary responder criterion was selected after the study was completed (Protocol Amendment #4; December 2013) to a liberal definition of "response" (i.e., IGF-1 < 1.3 times the upper limit of the age adjusted normal range and GH < 2.5 ng/mL). Patients with IGF-1 levels between 1 and 1.3 actually have 'active disease' and are not actual responders.
- It was defining "long-term maintenance" as response status at 7 months

The study that the applicant relies upon to demonstrate the efficacy of Mycapssa is essentially an observational cohort study and is subject to all the limitations and biases of such studies.

It is important to note that there was no a-priori hypothesis to be tested, and that there were no questions to the Agency, discussions or agreement on what would constitute an "appropriate" response for this population. In 2012[15], and apparently without Agency input, US and EU clinical advisors to the applicant decided that a 50% responder rate at 7 months in this population pre-selected to be responders to SSA at baseline would be clinically acceptable. The trial was 33% enrolled at that time (see DMC discussion below) and the study chair (Dr. Melmed) and several key investigators who had enrolled and were following patients (e.g., Drs. Strassburger and Popovic) participated in this symposium. The decision appeared to have been based solely on consensus opinion and not informed by any robust empiric considerations (e.g., considerations usually undertaken for non-inferiority margin derivation for example). It is not clear from the applicant's record submitted to the NDA what endpoint variable defined response in their deliberations at that time. In the protocol reviewed by FDA in 2011 and in 2012 however, IGF-1 concentration was the primary endpoint variable listed in the protocol and the proportion of subjects with normalized IGF-1 levels (adjusted for age) was the only categorical variable listed as a 'responder criterion' in a list of secondary endpoints. As stated above, professional guidelines and other drug programs have defined response as normalization of age appropriate IGF-1 levels and GH of < 1 ng/mL (after serial measurements or after an oral glucose stimulation test).

As Dr. Zemskova points out in her review, one could have just as well predicted that more than 50% of patients would have been "responders" on the basis of the fact that the participants selected for the study had already declared themselves to be "responders" who "tolerated" the class of drug to which Mycapssa belongs (somatostatin analogs). This type of enrichment strategy, which consists of selecting patients most likely to respond to a therapy, is commonly referred to as predictive enrichment.

[15] The complete study report states the following to justify what magnitude of response would constitute a clinically meaningful response: *"A clinically relevant response rate was confirmed by a community of US and EU acromegaly experts, joined by the Sponsor on December 2012. The feedback was that 50% response rate would be meaningful."* The sponsor responded to an information request on 11 April 2016 and 12 April 2016 with the list of attendees and a record of the minutes from this meeting (some of the content redacted). This will be discussed further in the review.

It is also important to note that investigators and the applicant had access to efficacy and safety information during study progress and could make decisions and changes to study protocol, study conduct, endpoints and analysis plan based on accumulating data. Although the Agency had seen a protocol of the intended study at the end of phase 2, the FDA received a final protocol and statistical analysis plan close to the date of study completion (November 2013).

The trial was open label and patients, investigators and the applicant had access to accruing efficacy information as the trial was ongoing. The protocol in fact stipulated that a data monitoring committee (DMC) would be established to monitor both safety **and efficacy** at regular intervals during trial progress so as to serve in an advisory capacity to the applicant. No rationale for examining efficacy (i.e., for cause, for futility) is laid out in the IDMC charter. The IDMC members along with members of (b) (4) and Chiasma, met on 12 November 2012 (at 33% accrual), 21 May 2013 (at 66% accrual) and 28 August 2013 (at 100% accrual) to discuss study progress[16]. The protocol justifies the unusual practice of monitoring aggregate efficacy for a DMC in the following summary statement from the protocol**; *"For ethical reasons and to ensure trial integrity, interim examination of key efficacy and safety data will be performed at regular intervals during the course of the trial."*** Relaying aggregate ongoing efficacy results to the applicant would have an effect opposite than the intended effect on study integrity.

The statistical analysis plan was prepared (Version 1.0 dated October 2013) after almost all efficacy data had accrued likely after the applicant had had a chance to review the study. In protocol amendment 4, dated 6 December 2013 after study completion (26 November 2013), the applicant changed what had always been the primary endpoint specified in the protocol (i.e., IGF-1 concentration at the end of the Core Treatment Period) to "*the proportion of individuals with an IGF-1 value less than 1.3 times the upper limit of normal and a GH value less than 2.5 ng/mL"*. This change was made right around the time of database lock ***"to allow more educated and informative data interpretation"***. It also happens that this response criterion was different than the response criterion pre-specified as a secondary endpoint in earlier protocol versions [i.e., Proportion of subjects with normalized IGF-1 levels (adjusted for age)]. This choice ended up serving them well since they would not have otherwise demonstrated that 50% of patients were still "responders" at the last on-treatment biochemical assessment had they used the response criterion that had been pre-specified in the protocol since 2011. The major problem with this approach given the timing of this change is that selection of this endpoint was likely informed by knowledge of nearly full study results. Even for an open-label cohort study this is poor form as it appears the "primary" endpoint was retrospectively selected to fit an priori hypothesis.

I disagree with the response criterion that they ultimately selected for the primary efficacy analysis because the criterion is insensitive to detecting small but clinically meaningful changes in disease control. A full responder at baseline who goes from an IGF-1 level of 0.8 times the upper limit of normal to 1.2 times the upper limit of normal within a 7 month time frame would be considered a "responder" with the criterion selected by the applicant. However, this same patient, with the same IGF-1 trajectory, would be considered a "non-responder" with the criterion used by current professional society guidelines to define disease control (i.e., a criterion that uses an IGF-1 level less

[16] The applicant was asked to provide all records from these meetings on 4/10/2016 but only submitted the one page letter issued by the IDMC Chair. Per the DMC charter the applicant (sponsor) was responsible for "overseeing" the preparation of the DMC reports by the data management group. The applicant was asked to provide the DMC reports used at the three key milestone meetings on 4/12/2016 and to clarify the affiliation of the study statistician preparing these reports.

than 1 times the upper limit of normal normalized for age). From a clinical standpoint, it is likely that a sustained 50% increase in IGF-1 levels within a 7 months' timeframe, in the example patient described above who had stable disease at baseline, would represent a clinically meaningful change in disease activity. Furthermore in a study designed to evaluate "loss of control" choice and use of a more conservative failure criterion to estimate drug effect is more likely to represent substantial evidence.

3. CMC/Device

The CMC/Device aspects of this application were summarized by Drs. Tran and Zemskova. CMC recommends a complete response on the basis of GMP deficiencies identified during inspection.

The CMC deficiency to be conveyed is:

> *"During a recent inspection of* (b) (4) *located at* (b) (4) (b) (4) *our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application can be approved"*

The drug substance, octreotide acetate, is manufactured by (b) (4) and is controlled under drug master files (b) (4) and (b) (4) The CMC reviewer concludes that the regulatory specifications for the drug substance are adequate to support use in Mycapssa manufacturing.

The drug product is manufactured for Chiasma Inc., by the Lyophilization Services of New England (LSNE) Inc., and by Encap Inc. The drug product is an enteric coated capsule (b) (4) (b) (4) (b) (4) a proprietary formulation (referred to as "Transient Permeability Enhancer"), which was developed by the applicant to enhance peptide absorption at the (b) (4) A single strength of 20 mg is proposed. The CMC reviewer concludes that the regulatory specifications for the drug product are adequate to support Mycapssa manufacturing.

An expiry of 36 months for storage between 36 and 46 degrees Fahrenheit and 1 month for storage at room temperature is supported by data submitted in the application and is granted.

4. Nonclinical Pharmacology/Toxicology

Dr. Jessica Hawes, the nonclinical pharmacology/ toxicology reviewer, notes no outstanding nonclinical pharmacology/toxicology issues in this application. The toxicology studies allowed for an abbreviated non-clinical development program and provides scientific justification for reliance on FDA's previous finding of safety for Sandostatin (as reflected in product labeling that describes, among other things, reproduction and early development, and carcinogenicity). Additionally, the toxicology studies performed by the applicant qualify, from a toxicological perspective, the novel excipients (referred to by the applicant as the "Transient Permeability Enhancer"), degradation products and impurities that are not found in the listed drug product. Refer to Dr. Hawes executive summary and Zemskova's review for a summary of the pharmacology/toxicology findings.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Suryanarayana Sista, the clinical pharmacology reviewer, recommends a complete response. The pharmacokinetic properties of Mycapssa are not bioequivalent to those of the listed drug Sandostatin and the applicant has provided no exposure response data to characterize what the impact of these differences would have on the efficacy. The pharmacokinetic properties of Mycapssa and the listed drug are not sufficiently similar to justify reliance, in part, on FDA's previous finding of effectiveness for Sandostatin to establish the effectiveness Mycapssa.

Key Clinical Pharmacology Findings for Mycapssa

Mycapssa exhibits linear pharmacokinetics in the dosing range studied (3 to 80 mg). The maximum serum concentration is achieved ~ 2 hours after a dose (this was the time used to measure GH levels in the pivotal trial). The ½ life at steady state in patients with acromegaly is ~ 3.5 hours.

Mycapssa is poorly bioavailable (relative bioavailability of oral versus subcutaneous = 0.5%). Circulating octreotide (i.e., drug) concentrations achieved after an oral dose are highly variable. Food, water and proton pump inhibitors were shown to reduce absorption significantly by 90%, 25% and 50% respectively. The impact of the intestinal permeability enhancer on absorption of other drugs was evaluated in drug-drug interaction studies and is summarized in Dr. Sista's review. The applicant's data has not established a dose response or exposure response relationship between Mycapssa and GH or Mycapssa and IGF-1.

Dose Selection

The applicant's method used to select the phase 3 dose was somewhat unusual. The dose of 20 mg was selected based on an assumption that circulating octreotide concentration above 1 ng/mL would be required to effectively suppress growth hormone in patients with acromegaly. This drug concentration threshold was reported in a reference from a review article on octreotide pharmacokinetic published by Chanson et al. in 1993[17]. The applicant used comparative PK data obtained after a single 0.1 mg subcutaneous dose of immediate release sandostatin (NDA# 19667) and a single oral doses (3, 10, 20 mg) of Mycapssa in healthy volunteers to calculate the time duration (in hours) when the concentration of octreotide would be above 1 ng/mL to select a phase 3 dose. The point estimate of median time (in hours) above 1 ng/mL was interpreted by the applicant to be similar between 0.1 mg of Sandostatin and 20 mg of Mycapssa [refer to Table 6 in Dr. Sista's review adapted below for reference; note the large difference in variability between the two products].

	Sandostatin 0.1 mg SC Median [Range]	**Mycapssa 20 mg PO** Median [Range]
Time (in hours) where octreotide concentration is ≥ 1 ng/mL	3.9 [2.9-4.9]	4.1 [0.3-11]

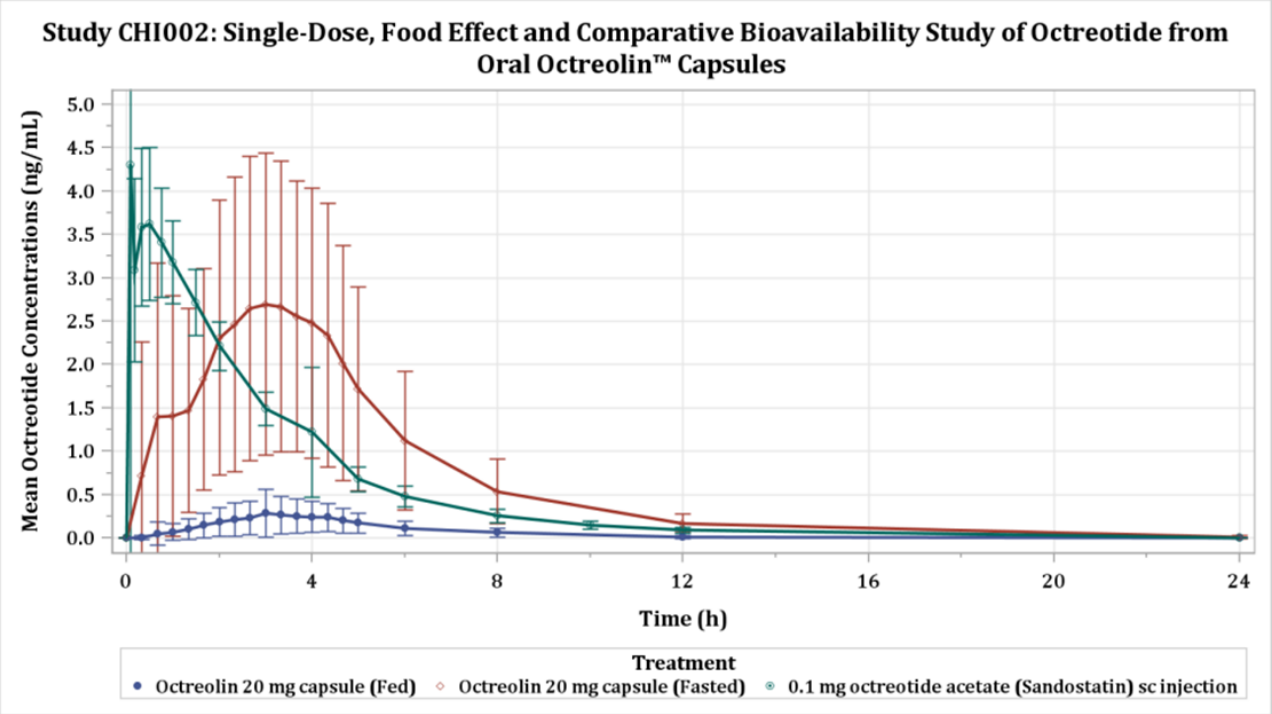
Comparative PK Data Between Mycapssa and Sandostatin

The comparative pharmacokinetic data between Sandostatin and Mycapssa demonstrate that both the rate and extent of octreotide absorption differs significantly between Mycapssa and the listed drug [octreotide acetate injection (Sandostatin NDA 19677)]. Pharmacokinetic properties of

[17] Clin. Pharmacokinetic. 1993: 25(5); 375-39.

Mycapssa and the listed drug are not sufficiently similar to justify reliance, in part, on FDA's finding of safety and effectiveness for Sandostatin to establish the effectiveness Mycapssa.

A graphical representation of the plasma octreotide concentration over time after a single dose of 20 mg of Mycapssa [maroon and blue lines (fasted and fed state respectively)] and a single dose of 0.1 mg of octreotide acetate (green line) in healthy volunteers is shown in Figure 6 of Dr. Sista's review and reproduced below.

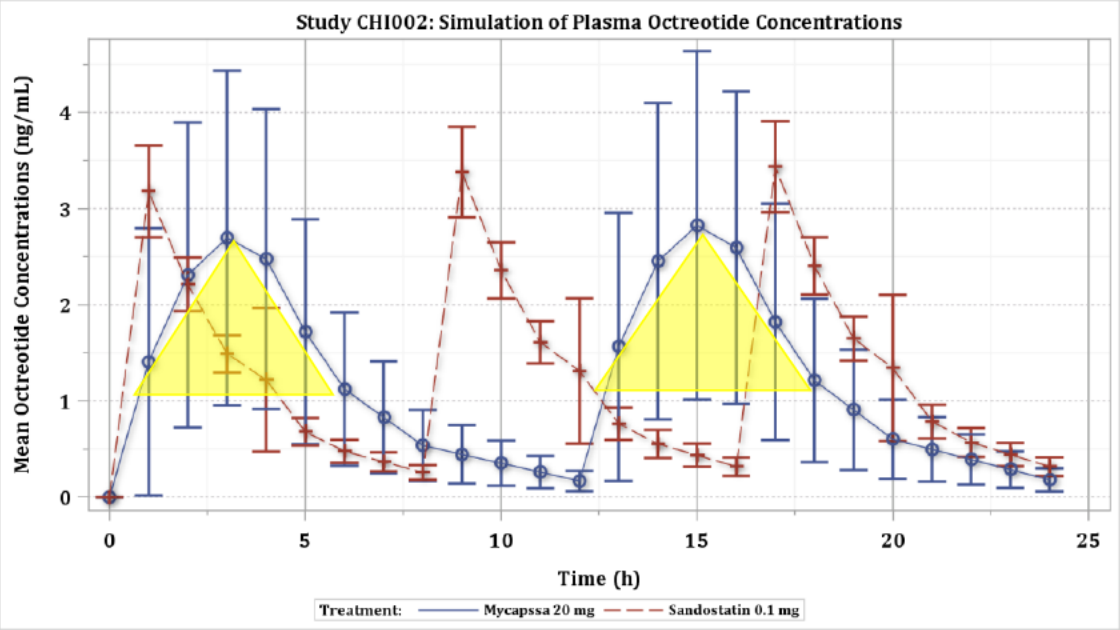


Both the time to reach maximum drug concentration and the extent of absorption [maximum (C_{max}) and overall (AUC_{0-t}) exposure] after a single dose differ between the two products. The figure shows Mycapssa is absorbed more slowly and exposure to octreotide with MyCapssa is highly variable compared to the listed drug. The two drugs are not bioequivalent[18] as shown in Table 8 of Dr. Sista's review (adapted and reproduced below).

	Ratio (90% C.I.) of Least Square Mean
AUC_{0-t} Mycapssa Fasted/ AUC_{0-t} Listed Drug	0.97 (0.73-1.28)
C_{max} Mycapssa Fasted/ C_{max} Listed Drug	0.64 (0.45-0.90)

Based on results from this single dose study in healthy volunteers, Dr. Sista simulated plasma octreotide concentration for the proposed Mycapssa dosing regimen (twice daily fasted state in blue) and compared it to simulated plasma octreotide concentration for the approved listed drug dosing regimen (three times daily in red) over a twenty four hour period (shown in figure 12 of his review reproduced below for convenience).

[18] i.e., 90% confidence interval for the ratio of Mycapssa/Listed Drug is outside 0.80 and 1.25 for both AUC and C_{max}



In this simulated scenario the overall and maximum exposure to octreotide over a twenty four hour period would be predicted to be much lower with Mycapssa than with the listed drug as shown in Table 10 of his review (adapted and reproduced below).

	Ratio (90% C.I.) of Least Square Mean
AUC_{0-t} Mycapssa Fasted/ AUC_{0-t} Listed Drug	0.77 (0.58-1.02)
C_{max} Mycapssa Fasted/ C_{max} Listed Drug	0.80 (0.63-1.05)

It is important to note that this simulated scenario represents a "best case" scenario since it ignores many factors that were found to affect absorption of octreotide from Mycapssa and are expected to be present in a "real world" clinical setting (i.e., food, drinks, posture, and other drugs). It is also clear from this scenario that time above 1 ng/mL (i.e., the concentration that is purported to suppress GH) are very different between the two products when one considers the 24 hour dosing interval and begs the question as to why Mycapssa was not developed as a three times daily drug. The yellow shading in the figure graphically represents the time when the concentration of octreotide is above 1 ng/mL (effective concentration of octreotide per the applicant) after a single dose of 20 mg of Mycapssa.

6. Clinical Microbiology

There are no outstanding clinical microbiology or sterility issues.

7. Clinical/Statistical-Efficacy

Drs. Abraham and Ketterman have reviewed the efficacy findings in details and Dr. Zemskova has summarized key review issues in her CDTL memorandum. Refer to these reviews for full details. All reviewers recommend a complete response on the basis that the study has not provided substantial

evidence that the drug is effective because the efficacy of sandostatin (the listed drug) cannot be extrapolated to Mycapssa (Refer to Section 5 above) and because the clinical study that was intended to demonstrate the efficacy of Mycapssa cannot distinguish the effect of the drug from other effects such as an absence of active disease, residual effects of pre-trial therapy (ies), and early trial discontinuation. These issues are sources of bias in the estimate of the drug's effect. The impact of bias on the estimate cannot be resolved with retrospective data analyses. Because the efficacy results derived from the study are severely confounded they cannot be purported to accurately represent the drug's true therapeutic effect and the true drug effect is unknown.

Issues with the study conduct identified in the review include but are not limited to:

- The applicant, investigators and patients had access to efficacy information as the trial was ongoing and access to this information could have influenced study conduct, and choice of analyses (e.g., someone not tolerating drug could be thrown out before declaring themselves a non-responder; selection/specification of the response criterion appeared to have been specified after the bulk of study data were collected).
- The original protocol submitted to FDA at end of phase 2 had no pre-specified hypothesis, did not pre-specify the response criterion that would be used in the primary analysis, and did not pre-specify a statistical analysis plan until after almost all efficacy data were collected.
- The biochemical cutoff criterion selected to define participants as "responder" at seven months was liberal and in fact includes patients with active disease (i.e., those with IFG-1 levels between 1 and 1.3 times the upper limit of normal) and overstates the efficacy of the product.
- The disease activity was not stable by end of treatment as mean IGF-1 levels were observed to be on an upward and rising trend in responders and had not plateaued by seven months.

IGF-1 is a specific and reliable indicator of disease activity. It represents a time- integrated readout of the effect of growth hormone on the liver. A persistent IGF-1 > 1 times the upper limit of normal for age in an individual with a past history of acromegaly signals that the disease is active.

Serial GH measurements are sometimes used to monitor GH suppression with drug therapies that act to suppress GH secretion from the pituitary. A mean GH < 1 ng/mL after serial sampling is the recommended target in most therapeutic guidelines. This marker is less specific for disease monitoring since GH release is pulsatile and is less sensitive since the assessment of control is limited to the time window the sampling is performed.

The applicant used both IGF-1 and GH in their definitions of "responders". It considered all individuals with IGF-1 less than 1.3 time the upper limit of normal and a mean GH of < 2.5 ng/mL over two hours after a dose and right around the Mycapssa C_{max} to be "responder." This will be discussed below.

Pivotal STUDY CH-ACM-01: Maintenance of control in patients with Acromegaly who previously responded to and tolerated treatments with somatostatin analogs.

The efficacy of Mycapssa for the treatment of patients with acromegaly was evaluated in a single study. My review will focus on the core phase of the study (Months 0-7). I don't distinguish between the dose escalation or fixed dose phase because it varied for each patient, depended on whether the patient actually remained in the study, is exploratory and provides limited useful additional information (refer to figure 3 in Dr. Ketterman's review for a time to reach stable dose graph). Drs.

Ketterman and Abraham have discussed the voluntary extension study which only enrolled a subpopulation of participants who were eligible if they met specific response criteria at month seven (~50% of the original population). The exposure in this study is very limited (refer to Figure 2 in Dr. Ketterman's review). The applicant present analyses using subgroups of patients (e.g., those who stayed in the study and reached a fixed dose), these analyses are exploratory analyses of an exploratory study and are not considered to add value in estimating what the treatment effect of this drug will be in practice.

CH-ACM-01 CORE was an open-label, single arm, descriptive cohort study. Thirty seven sites were opened and 34 sites across Europe, Israel and Mexico enrolled at least one patient. No sites in the United States participated in the study.

The primary and secondary objectives of the trial per the end of phase 2 protocol were:

- To determine the effect of Octreolin (i.e., Mycapssa) therapy on Insulin-like Growth Factor 1 (IGF-1) levels (primary objective)
- To determine the effect of Octreolin (i.e., Mycapssa) therapy on Growth Hormone (GH) levels
- To assess the safety and tolerability of Octreolin (i.e., Mycapssa) in subjects with acromegaly
- To compare the effect of Octreolin (i.e., Mycapssa) therapy on IGF-1 levels with that of parenteral therapy with somatostatin analogs

The primary endpoint and secondary endpoints were:

- IGF-1 concentration at the end of the Core treatment period (refer to end of phase 2 protocol).
- In an amendment dated August 2011 the applicant added the following secondary efficacy endpoints
    - proportion of subjects with a mean GH concentration of < 1.0 ng/mL
    - proportion of subjects with both normalized IGF-1 levels (adjusted for age) and mean integrated GH over 2 hours < 2.5 ng/mL;
- In an amendment dated December 2013 the applicant changed the primary endpoint to
    - IGF-1 <1.3 times the upper limit of normal for the subject's age group and integrated GH levels over 2 hours <2.5 ng/mL. This coincided with the near completion of study and the submission of the "statistical analysis plan" to the Agency.

Eligibility Criteria

Patients were eligible to participate in the study if they were adults between 18 and 75 years, had a past diagnosis of acromegaly and were responding to (defined by biochemical eligibility criteria) and tolerating somatostatin analog therapies for at least three months prior to study entry.

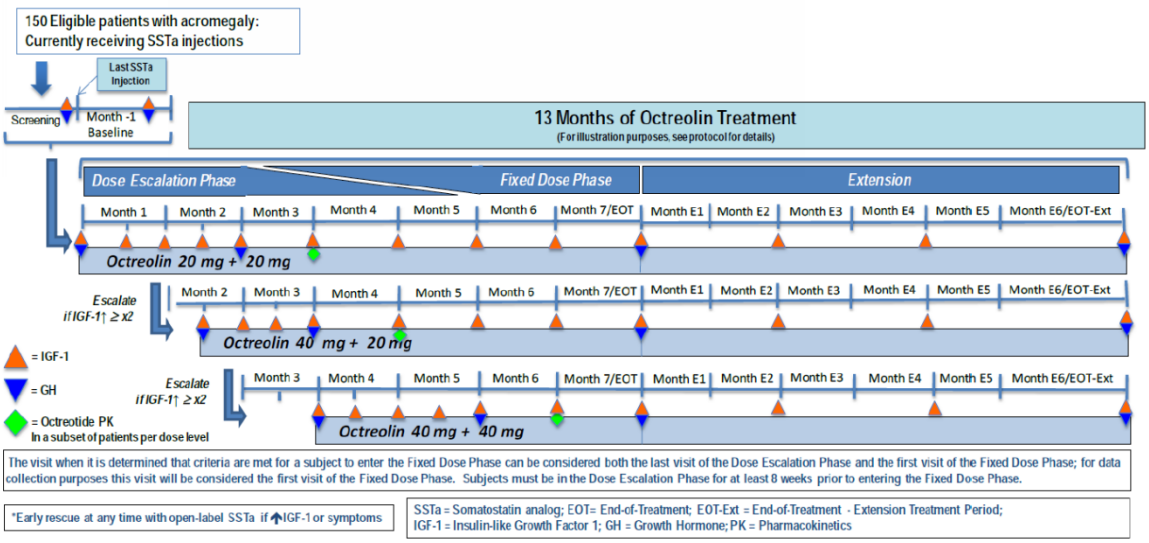
Seventeen patients were also enrolled on a multidrug regimen to control acromegaly (somatostatin analog + bromocriptine or pegvisomant) at baseline. Although exclusion criteria 20 and 21 apparently excluded current or recent therapy with cabergoline or pegvisomant (see Page 33 of Dr. Abraham's review).

The study excluded patients with: symptomatic cholelithiasis, radiotherapy within ten years prior to screening, pituitary surgery within 6 months, high risk pattern of pituitary tumor location on pituitary magnetic resonance imaging and active gastrointestinal, renal, hepatic, and cardiac disease.

Study Periods and Schematic

The study included a Screening Period of up to 4 weeks, a Baseline Period of up to 4 weeks, a Core Treatment Period of at least 7 months, an optional/voluntary Extension Treatment Period for eligible "responders" of up to 6 months, and a Follow-up Period of 2 weeks after last dose. The last injection of pre-trial somatostatin analog was to occur within four weeks of the baseline evaluation visit.

Figure 1: Study Schematic (Octreolin in the figure refers to Mycapssa)



During the Core Treatment Period (months 0 to 7), subjects received open-label oral Mycapssa twice daily for 7 months with individual dose titration based on IGF-1 levels. The Core Treatment Period consisted of a variable Dose Escalation Phase of 2 to 5 months in order to identify a therapeutic dose regimen for each individual subject and a Fixed Dose Phase of 2 to 5 months.

Dose Titration Algorithm

All subjects initially received Mycapssa 20 mg BID (40 mg per day). Subjects were to be titrated per protocol to 60 mg per day (40 mg in the morning and 20 mg in the evening and night respectively) or 80 mg per day (40 mg in the morning and the evening) depending on their IGF-1 levels. Mycapssa dose escalations were permitted if after two successive visits, IGF-1 levels were inadequately suppressed on a stable dose of Mycapssa. Inadequate IGF-1 suppression was defined as a "clearly rising" level and/or less suppression than that documented at baseline. "Clearly rising" levels were defined as at least a 20% increase over the prior level or smaller increases plus emergence of typical symptoms. On a case-by-case basis, after discussion with the study Medical Monitor, dose escalation could be considered under other circumstances.

Demographic and Baseline Disease Characteristics

The majority of participants in both studies were female (57%), White (88%), or identified as "others" for race (~10.3%) and were not Hispanic or Latino (87%). The mean age of participants was ~54 years. Most participants had disease diagnosed for more than ten years (52%), had a past microadenoma (33%) or an intrasellar macroadenoma (34%), and had had surgery alone (78%), radiation alone (8%)

or a combination of surgery and radiation (6%) to treat the tumor at the time of diagnosis. All participants were receiving either long acting octreotide (sandostatin LAR) or long acting lanreotide (somatuline), most for greater than 1 year (>80%) and on average for 6 years. Aproximately 60% were receiving the lowest recommended dose of the SSAs. The median (interquartile range) IGF-1 levels at baseline was 0.85 (0.76, 1.07).

Disposition

There were 155 participants enrolled. A large number of participants (34%) did not complete all study visits to seven months. The most common reasons for discontinuation were drug related and categorized as efficacy related (Discontinuation due to Treatment Failure: 24 subjects) or tolerability-related (Discontinuation due to Adverse Reactions n=21).

Twenty eight patients who discontinued early for issues listed as unrelated to efficacy and who had biochemical control at the time of discontinuation were counted as having responded at month seven in the applicant's analysis because the last on-treatment evaluation for these patients was carried forward to represent the seven month value (i.e., LOCF method was used to impute missing evaluation at specified trial endpoint). I agree with the statistics reviewer that this is likely to result in overestimating the drug's efficacy at seven month in these patients.

From a clinical standpoint, an analysis that treats patients who discontinue early as non-responders for the purpose of representing drug response at month 7 is very reasonable because most premature discontinuations were due to treatment failure or would have been expected to result in treatment failure at trial end in patients with active disease who discontinued early. In addition, using last observed data prior to discontinuation (i.e., LOCF) to represent efficacy at month 7 is not appropriate in this study because participants were not fully washed out from pre-trial therapies before month seven.

There are two main analysis populations used to descriptively present efficacy results. These populations were

- The ITT population which includes All subjects who were enrolled (N=155 individuals)
- The mITT population which includes All subjects who were enrolled and who had at least one post-baseline biochemical assessment referred to as the mITT population (N=151 individuals). At least three out of the four individuals who are in the ITT population but were excluded from the mITT population discontinued because of a product related issue (i.e., GI tolerability) prior to the assessment (see page 51 in Dr. Abraham's review). Since the discontinuations were likely attributed to poor product tolerability, I agree that the least biased estimate of the drug's efficacy at seven month is captured in the ITT population and not the mITT population.

Results

Since the study was descriptive, open-label and the hypothesis, endpoint and analysis plan evolved and changed with time as the trial was ongoing; I am presenting results in a descriptive fashion. There

are no primary or secondary endpoints to speak of and no inferences that were pre-specified in the strict sense of the term. My review focuses on data only for the ITT population and treats pre-mature discontinuations as non-responders for the reasons cited above.

Choice of Primary Endpoint to Capture Mycapssa Effect

The primary endpoint selected by the applicant artificially inflates the efficacy estimate.

I do not use the term "responder" to refer to what the applicant has designated as the main biochemical cutoff criterion for their efficacy assessment because it is a clinical misnomer. The applicant includes patients who have active disease in the response criterion. Patients with a persistent IGF-1 level greater than 1-fold the upper limit of normal (ULN) normalized for age have active disease and are not "responders" in a strict clinical sense.

The magnitude of response achieved using the applicant's definition of response appears more impressive than it is based solely on the biochemical criteria selected to define response. Had the applicant selected a more clinically relevant definition of response (e.g., one that includes normalized IGF-1 for age) for their "primary analysis", the response would be much lower (see table #15 below).

In the clinical care setting, patients with a history of acromegaly who have an IGF-1 persistently above the upper limit of normal and are symptomatic would not be left untreated for years if the patient could benefit from an alternative and available drug. The goal of therapy is to normalize IGF-1 for age and I don't really see the clinical value of describing the efficacy of this product using "partial response". The applicant stated that they selected the criterion because of issues with IGF-1 assay variability. I believe this is an overstatement of the problem. Patients had serial IGF-1 values in the trial (so it should have been easy to confirm a spurious high) and the assay was centrally run. In fact, for dose increase they did just that and recommended a dose increase if the IGF-1 rose by 20%. I note that they likely picked 20% because a sustained 20% increase in IGF-1, to the clinical advisors responsible for study protocol development represented a significant change in disease activity.

Although a "partial response" criterion similar to the one below has been used in some other acromegaly programs, this has usually been a secondary endpoint in the setting where the direction of change in IGF-1 was from higher at baseline to lower at trial end and not, as in this case, from lower at baseline to higher at trial end. It has also been in the setting where the IGF-1 levels had likely stabilized to the best achievable level.

In the end, I disagree with the response criterion that they ultimately selected for the primary efficacy analysis for the reasons cited in section 2 and repeated here for emphasis. The criterion is insensitive to detecting small but clinically meaningful changes in disease control. A full responder at baseline who goes from an IGF-1 level of 0.8 times the upper limit of normal for age to 1.2 times the upper limit of normal for age within a 7 month time frame would be considered a "responder" with the criterion selected by the applicant. However, this same patient, with the same IGF-1 trajectory,

would be considered a "non-responder" with the criterion used by current professional society guidelines to define disease control [i.e., a criterion that uses an IGF-1 level less than 1 times the upper limit of normal for age (+/-sex)]. From a clinical standpoint, it is likely that a sustained 50% increase in IGF-1 levels within a 7 months' timeframe, in the example patient described above who had stable disease at baseline, would represent a clinically meaningful change in disease activity. Furthermore in a study designed to evaluate "loss of control" choice and use of a more conservative failure criterion to estimate drug effect is more likely to represent substantial evidence.

Efficacy Estimates for the Applicant Selected Response Criterion and Primary Endpoint (i.e., proportion of patients meeting that criterion at trial end)

Table 1: Proportion of Individuals with an IGF-1 level less than 1.3 times the ULN for age and a mean serial GH less than 2.5 ng/mL at Month 7 (Source: Adapted from Table 7 in Dr. Ketterman's review)

	Mycapssa 40, 60 or 80 mg per day % (95% CI)
ITT population (N=155) Early Discontinuation Handled as Treatment Failures	53 (45-61)

It is interesting to note that in 2012 and based on key opinion leader advice and on a biochemical criterion that is still unclear to me at the time of this review[19], it was decided that a 50% responder rate after seven months of therapy would be viewed to represent a clinically meaningful effect (although the minutes in contrast to the study report state to "support prescription" of Mycapssa and purely based on mathematical average the effect that key opinion leader suggested is closer to 60 than 50 percent). Even with a liberal criterion to define "response" the estimate does not exclude a less than 50% response. As Dr. Kettermann shows in table 7 of her review, imputation method used to handle missing data did significantly affect the estimate of efficacy (increasing the response by ~12%).

Dr. Ketterman in her review did not assess response using an alternative, more appropriate, criterion [i.e., proportion of individuals with an IGF-1 level less than 1.0 times the ULN for age and a mean serial GH less than 2.5 ng/mL (or less than 1 ng/mL]. The applicant provided efficacy assessments for other responder definitions. The table[20] which follows presents data for the mITT population (N=151 and not N=155) and uses the last biochemical assessment before product discontinuation to represent response at month seven (i.e., LOCF). As reviewed above, these estimates erroneously inflate efficacy at month seven for the reasons cited[21] and should be interpreted with this caveat in

[19] Refer to redacted summary minutes from the 2012 advisor meeting submitted in response to an information request to the NDA on 4/13/2016: The minutes read "*Advisors were asked about the percentage of complete or partial responders in the phase 3 trial (study primary end-point) that will be sufficient to support prescription of Octreolin, in their own clinical practice, to patients already stabilized on parenteral somatostatin analogs. The advisors response ranged from 30-80%, while most advisors agreed that 50% will be sufficient Biller 30%-50%, Melmed 50%, Katznelson 50%, Casanueva 50%, Bonert 50%, Molitch 50%, Thorner 66%, Strasburger 70%, Popovitch 70%, and Clemmens - 80%.*"

[20] Refer to Table 15 in Dr. Abraham's review

mind. The most clinically relevant definitions of control are outlined in red. Even before the issues of analysis population and method of missing data handling are addressed, the efficacy in the study is estimated to be in the mid to low 30% range.

The table also describes differences in responder rates between baseline and last-on treatment biochemical assessment. Considering the change between baseline and end-of-treatment, the table shows that ~ 40% of individual controlled at baseline loose control between baseline and last on-treatment biochemical assessment. This endpoint (change from baseline) suffers from the same biases due to data missing after early discontinuation as the primary endpoint and 40% may underestimate the product true loss of efficacy vis a vis baseline.

Table 15. IGF-1 and growth hormone suppression at End of Treatment compared to Baseline, mITT, CORE phase, LOCF

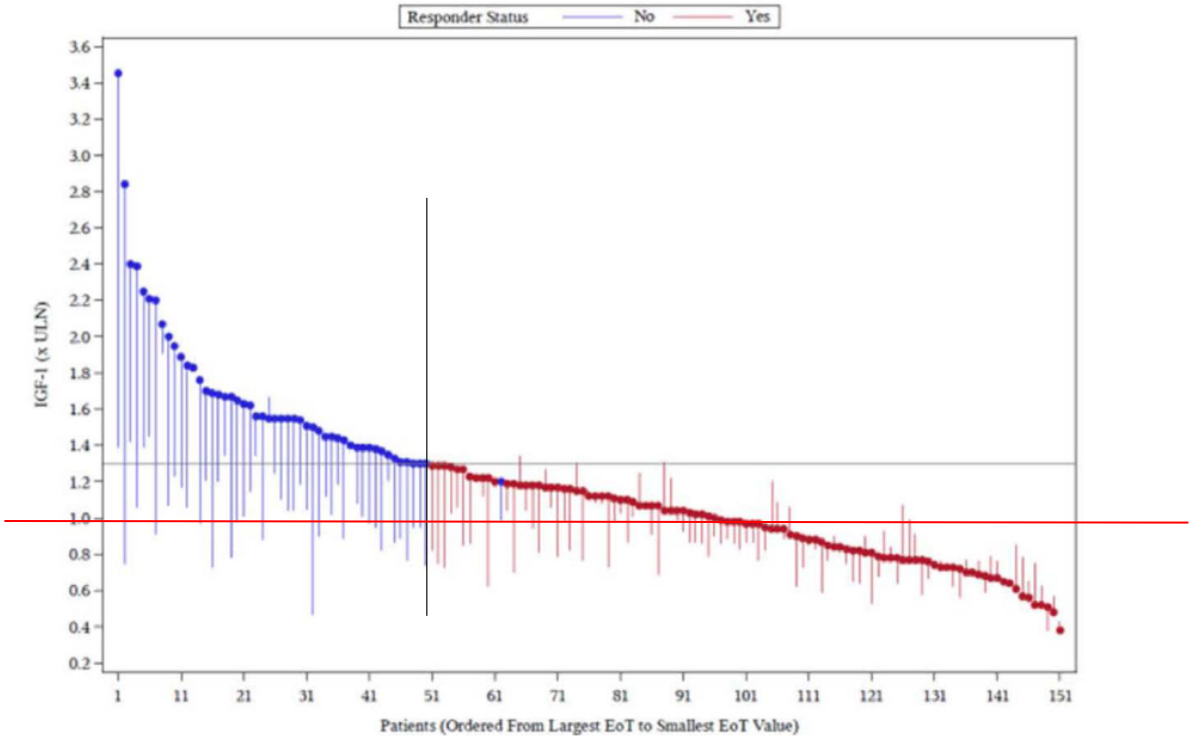
Response Category	Baseline n (%)	End of Treatment n (%)
mITT Population (N=151)		
IGF-1 < 1.3 times ULN and GH < 5.0 ng/mL	138 (91.4)	99 (65.6)
IGF-1 < 1.3 times ULN and GH < 1.0 ng/mL	95 (62.9)	80 (53.0)
IGF-1 ≤ 1.0 times ULN and GH < 5.0 ng/mL	96 (63.6)	54 (35.8)
IGF-1 ≤ 1.0 times ULN and GH < 2.5 ng/mL	93 (61.6)	54 (35.8)
IGF-1 < 1.0 times ULN and GH < 1.0 ng/mL	65 (43.0)	48 (31.8)
IGF-1 < 1.3 times ULN	138 (91.4)	101 (66.9)
IGF-1 ≤ 1.0 times ULN	96 (63.6)	56 (37.1)
GH < 5.0 ng/mL	151 (100.0)	147 (97.4)
GH < 2.5 ng/mL	145 (96.0)	143 (94.7)
GH < 1.0 ng/mL	100 (66.2)	117 (77.5)
IGF-1 ≥ 1.3 times ULN and GH < 2.5 ng/mL	11 (7.3)	45 (29.8)
IGF-1 < 1.3 times ULN and GH ≥ 2.5 ng/mL	4 (2.6)	1 (0.7)
IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL	2 (1.3)	3 (2.0)

Source: CSR, Table 27, modified
mITT, modified Intention to Treat; LOCF, last observation carried forward
*four patients had missing post-baseline assessments; therefore, End of Treatment (CORE) response not evaluable in these patients for all response categories.

The loss of control in IGF-1-levels can be appreciated in the following waterfall plot which graphs IGF-1 levels (Y-axis) for each individual patient (X-axis) between baseline (beginning of the line) and last on-treatment assessment prior to discontinuation (filled circle). The red horizontal line marker denotes IGF-1 level equal to 1 times the upper limit of the normal range. The majority of patients saw their IGF-1 levels rise and very few patients saw their IGF-1 levels fall.

[21] E.g., the biochemical assessment of a participant who discontinues on Day 2 due to a side effect is carried forward to represent Month 7.

Figure 6. IGF-1 levels at Baseline and End of Treatment by responder status, mITT population



Source: Clinical Overview, page 46
Filled circle is the End of Treatment value
Solid black line discriminates between non-responders to the left of the line and responders to the right of the line

The table below summarizes some possible reasons to explain the rise IGF-1 based on two end-of tiral IGF-1 categories; patients with IGF-1 greater than the upper limit of normal at trial end and patients with an IGF-1 less than the upper limit of normal at trial end. This is done for illustrative purposes and I define "active disease" as tumor activity that causes a rise in circulating IGF-1 to greater than 1 times the upper limit of normal for age.

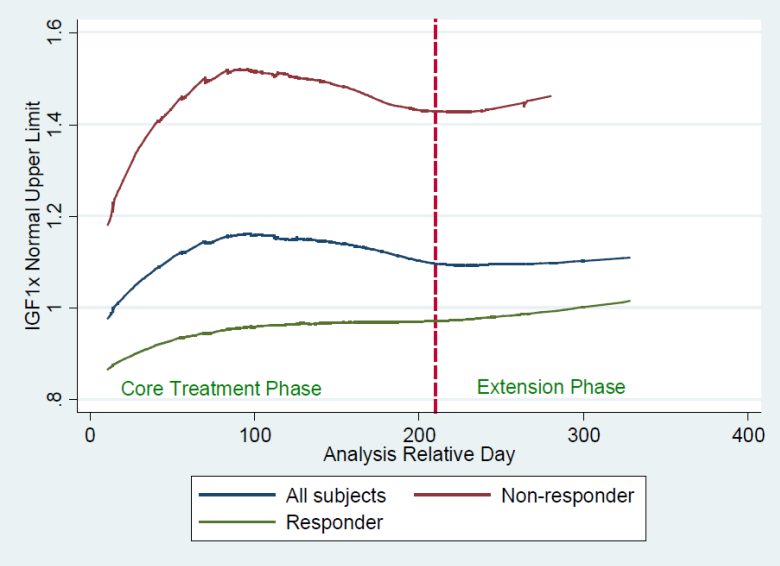
IGF-1 Category at Last On Treatment Biochemical Assessment	Possible Reasons to Explain IGF-1 rise
IGF-1 greater than the upper limit of normal for age at Last On Treatment Biochemical Assessment	Active disease and loss of PD effect from long acting somatostatin analog with duration of time in trial
IGF-1 less than the upper limit of normal for age at Last On Treatment Biochemical Assessment	Active disease and early discontinuation (insufficient time in trial to allow washout of pre-trial long acting somatostatin PD effect)
	Inactive disease and withdrawal of a drug that suppresses GH and IGF-1 (i.e., release of inhibition of pituitary GH release in a normal patient). Refer to the 3 patients who never had diab

Dr. Abraham examined shifts from baseline status for the subgroups controlled at baseline, partially controlled at baseline and not controlled at baseline in Table 16 and 17 of her review.

Dr. Kettermann examined the trend in IGF-1 levels (x-axis) over time (y-axis) for the entire trial population (blue line), the responder subgroup (green line) and the non-responder subgroup (red line) in the trial (see figure 6 reproduced below) in a purely exploratory fashion. The graph plots all available IGF-1 values across all time points for all patients (missing data points are not imputed). The applicant's graph of IGF-1 concentration over time in contrast does not include all IGF-1 values and uses LOCF to impute values missing for a specific time point (i.e., the graph is misleadingly suggesting the IGF-1 stabilized because patients who are no longer in the study have the same value represented at every serial time point).

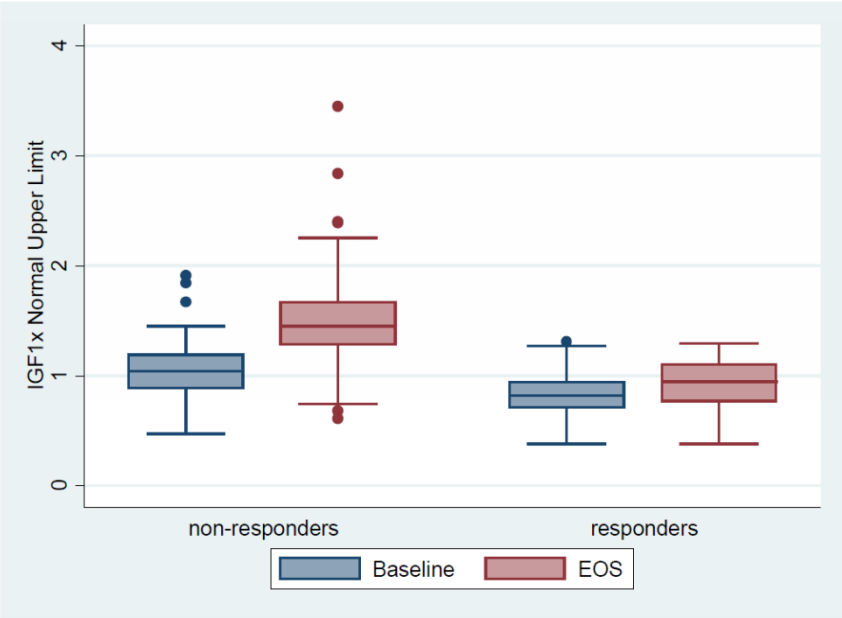
Dr. Kettermann cautioned that this is purely an exploration of all the available data submitted in the datasets and is not the most informative way to examine rate of rise in IGF-1. She cautioned against over-interpreting the figure because it is still subject to important limitations (early discontinuation of treatment failures, early discontinuation of poorly tolerant patient, loss of patients between core treatment phase and extension phase). Another way to explore the rate of rise in IGF-1 levels in the data available in the application is to consider only the change in IGF-1 over time for two time points (i.e., between the baseline and the last on-treatment biochemical assessment for each patient). This was not done but from the data in the waterfall plot above and figure 7 below it is clear that it would be directionally upward.

Figure 6. Lowess lines for IGF-1



Dr. Ketterman shows the median IGF-1 levels (interquartile range) at baseline and last on-treatment assessment prior to discontinuation in figure 7 of her review for the responders and non-responders. The overall direction of change in IGF-1 levels was qualitatively similar between responders and non-responders. These data do not suggest that the response to Mycapssa was qualitatively different between responders and non-responders (i.e., both subgroups fared worse and both had higher IGF-1 levels at the end of the study than at the beginning).

Figure 7. Boxplots for IGF-1



All other secondary and tertiary endpoint data (symptom score or pituitary MRI) are discussed by Dr. Abraham in her review. These endpoints are exploratory, subject to the same limitations of the primary endpoint and are less sensitive than IGF-1 to detect a clinically meaningful change. They provided limited useful additional information to address efficacy question related to Mycapssa.

8. Safety

Drs. Abraham and Zemskova have reviewed the safety information in this NDA and the reader is referred to these reviews for a detailed description of the findings. I concur with their overall safety assessment of the application and highlight the key findings from these reviews.

The safety assessment served, in part, to characterize the impact of the novel excipients in the product formulation and novel route of administration on clinical safety parameters in this population. The safety assessment was derived from a single arm and determining product relatedness in this setting is particularly challenging.

As shown in the table below, taken from Dr. Abraham's review, exposure to Mycapssa in the pivotal study informing intended use was limited.

Table 2. Summary of drug exposure in CH-ACM-01, safety population

Category/statistic	**CORE and Extension Treatment Periods**
N	155
Mean Exposure (Weeks) (SD)	42.4 (19.4)
Patient years	131.7
Number of months n(%)	
<3 months	15 (9.7)

3 to < 6 months	24 (15.5)
6 to < 9 months	28 (18.1)
9 to < 12 months	6 (3.9)
≥12 months	82 (52.9)

Source: Table 55, CSR
Exposure was calculated as date of last dose – date of first dose +1
SD, standard deviation

Gastrointestinal (GI) related adverse events including nausea (30%) and diarrhea (17%) were commonly experienced during the CORE treatment period of CH-ACM-01. GI-related adverse events were also the most common reason for discontinuation due to adverse event. The rate of GI adverse reaction in a patient population selected on the basis of being able to tolerate a somatostatin analog appears high and are therefore likely product related.

Other common treatment-related common adverse reactions that were frequently reported included headache (34%), arthralgia (27%), peripheral edema (21%), asthenia/fatigue (22%) and hyperhidrosis (22%) could be related to loss of disease control and are therefore likely product related in light of the efficacy results discussed above.

Two deaths occurred during CH-ACM-01, one death was due to a bile duct obstruction and the other to pancreatic tumor. It is likely that the death due to bile duct obstruction was related to MYCAPSSA use (gall bladder disease is a known risk associated with the drug class); whether the bile duct obstruction was related to the class effect of SSA therapy on gallbladder related disease or specific to MYCAPSSA use is not known. It is unlikely that MYCAPSSA use was associated with the pancreatic tumor.

In addition to a hepatobiliary related death, four of 16 patients experienced six hepatobiliary related serious adverse events (SAEs) in the CORE treatment period. Thus, in total 5/16 (31.3%) experienced a hepatobiliary related SAE.

I concur with Dr. Abraham's recommendations italicized below.

"With the known SSA class effect on hepatobiliary disorders and what appears to be a high rate of hepatobiliary SAEs with MYCAPSSA, close monitoring for these disorders will be needed.

Taken together, there does not appear to be a new safety signal associated with MYCAPSSA use. However, given the high discontinuation rate due to treatment failure in this study, AEs and SAEs might be underestimated both in number and severity. Also, the lack of an adequate PK and PD profile for MYCAPSSA imply that the dosing might not be correct in which case the safety results will not be a true reflection of chronic therapy with MYCAPSSA. In addition, while the new TPE formulation used in MYCAPSSA appears to be safe, we must be cognizant of the fact that increased exposure to TPE might reveal unanticipated safety signals."

9. Advisory Committee Meeting

Efficacy and safety issues identified in the application did not rise to the level of requiring the input from an advisory panel. Therefore no advisory committee was convened.

10. Pediatrics

Not applicable

11. Other Relevant Regulatory Issues

Refer to reviews by Dr. Zemskova and Abraham for financial disclosure information, inspections, and other relevant regulatory issues.

12. Labeling

Not applicable

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend a complete response.

- Risk Benefit Assessment

The two specific deficiencies to be conveyed in the CR letter are:

1. During a recent inspection of [redacted] (b) (4) located at [redacted] (b) (4) our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application can be approved

2. The data in the application do not provide substantial evidence that Mycapssa is effective as the effect captured in study CH-ACM-01 cannot be purported to represent the effect of Mycappsa. Satisfactory resolution of this deficiency is required before this application can be approved.

The basis for issuing deficiency number 2 is explained in the CR letter and key points are repeated below.

The data in the application demonstrate that Mycapssa and Sandostatin IR (listed drug) are not bioequivalent. Specifically, the relative systemic exposure, based on the least squares means for AUC0-t, of octreotide from the single-dose 20 mg fasted dose of Mycapssa relative to the 0.1 mg s.c. dose of octreotide was 0.97 with very wide confidence intervals of 73% – 128% for AUC0-t. Similarly, the Cmax with a point estimate of 0.64 and 90% confidence intervals of 45.29% - 89.78% failed to meet the bioequivalence criteria. A comparative pharmacokinetic (PK) study evaluating the proposed twice daily (BID) dosing regimen of Mycapssa compared to the three times daily (TID) dosing of Sandostatin was not conducted. The applicant did not characterize the Mycapssa dose-response relationship or the pharmacodynamic (PD) comparability (growth hormone and IGF-1) between Mycapssa and Sandostatin injection in your application.

Although meeting strict criteria for bioequivalence is not required for products reviewed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, absence of bioequivalence between

Mycapssa and the listed drug necessitated that the applicant demonstrate the safety and effectiveness of Mycapssa with data generated in study CH-ACM-01.

Study CH-ACM-01 was a single arm, open-labeled, cohort study with a planned primary efficacy endpoint assessment that was to take place 7 months after a baseline assessment. There were no formal inferences pre-specified and the study was purely descriptive in nature. Patients enrolled in the study were eligible if they had a past history of acromegaly and were controlled on and tolerated somatostatin analog therapies at the time of study screening. The intervention consisted of switching pre-trial therapies to Mycapssa and observing the biochemical response to the switch. The majority of patients enrolled had received surgery alone or surgery with a combination of radiotherapy as the initial treatment for acromegaly. The majority of patients had been treated for years with long acting somatostatin analogs with or without pegvisomant and/or bromocriptine prior to the baseline assessment. The study did not require confirmation of disease activity prior to the baseline assessment to account for the cumulative effects of past therapies on disease activity (e.g., pituitary surgery, drug therapy, radiation or a combination of the above). Drugs (long acting somatostatin analogs) known to be effective at suppressing growth hormone (GH) and insulin like growth factor-1 (IGF-1) were withdrawn close to the baseline assessment and had a lingering pharmacodynamic effect during a large portion of the efficacy phase of the study.

After reviewing the data from study CH-ACM-01, I conclude that the estimate of efficacy derived from study CH-ACM-01 does not distinguish the effect of Mycapssa from other effects such as inactive disease at the endpoint visit due to the cumulative effect of past therapies (e.g., pituitary surgery, drugs, radiation or a combination of these) or due to differences in the biological effect of individual tumors or due to confounding from the residual effects of pre-trial therapy (ies) used to control disease activity. At least some responders in the 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. Due to important biases in the estimate of efficacy derived from study CH-ACM-01, I cannot determine whether Mycapssa had a clinically important effect on disease control or the magnitude of the Mycapssa-attributable effect on the efficacy estimate in this study.

In our review of the data from study CH-ACM-01 we noted an overall worsening of control in the majority of patients, as evidenced by rising IGF-1 levels between baseline and last on-treatment assessment. For patients with active disease these finding would not be consistent with “maintenance of response” or “maintenance of control”. It did not appear that the rate of rise in IGF-1 had stabilized by the final biochemical assessment used to represent Month 7. This is concerning because a subject classified as a responder and whose IGF-1 trajectory is on a rising trend may reveal himself to be a treatment failure at a later assessment time point.

We noted in our review of the application that applicant had not pre-specified or selected which responder criterion to use to define response for the purpose of presenting the primary efficacy results in the protocol submitted to the Agency at the end of phase 2 meeting. I disagree with the response criterion that the applicant ultimately selected for the primary efficacy analysis because the criterion is insensitive to detecting small but clinically meaningful changes in disease control. A fully controlled individual at baseline who goes from an IGF-1 level of 0.8-fold the upper limit of normal for age to 1.2-fold fold the upper limit of normal for age within a 7 month time frame would be considered a “responder” with the applicant’s selected criterion. However, this same patient, with the same IGF-1 trajectory, would be considered a “non-responder” with the criterion used by current professional society guidelines to define disease control [i.e., a criterion that uses an age normalized

IGF-1 level (i.e., less than or equal to 1-fold the upper limit of normal for age)]. From a clinical standpoint, it is likely that a sustained 50% increase in IGF-1 levels in 7 months in the example patient described would represent a clinically meaningful change in disease activity. Furthermore in a study designed to evaluate "loss of control" choice and use of a more conservative failure criterion to estimate drug effect is more likely to represent substantial evidence.

We also noted in our review that the endpoint criterion selected for the primary efficacy analysis of Mycapssa was selected near the time of study completion (b) (6) Statistical Analysis Plan) close to the date of the last patient last visit (b) (6)). We further noted that content of Chiasma power point presentations used to support the open session discussions with the Data Monitoring Committee (DMC) for the 13 May 2013 (75% subject accrual meeting) and 22 August 2013 (100% subject accrual meeting) meetings contain slides showing individual level patient data and aggregate data at a time when the study was ongoing (i.e., prior to study database lock, prior to specifying the primary endpoint for efficacy analysis and prior the finalizing the analysis plan). Finally, we also noted that the DMC was getting routine aggregate efficacy updates with each DMC meeting reports (i.e., not for cause and not for the purpose of determining futility per the charter). Although we recognize the trial was open label, we find this level of access to accruing data during the conduct of a study to be problematic as it may have affected the study findings in ways that cannot be assessed for retrospectively.

To address this deficiency, the applicant will need to provide substantial evidence that Mycapssa will have the effect it purports to have under the conditions of use recommended in labeling for patients with acromegaly in a new clinical trial. The study design, conduct of the study and primary analysis should minimize biases to the extent possible to ensure the effect size captured is attributable to Mycapssa and not to a confounder. We strongly recommend that the study be randomized, double-blind and controlled. Randomized placebo controlled trials have been carried out for other products seeking an indication for acromegaly in patients who are not controlled at baseline. Drug withdrawal in patients with long acting disease for the purpose of determining disease activity is advocated by profession guidelines. Thus a placebo controlled trial in this setting would be feasible and ethical provided adequate safeguards (i.e., rescue) to ensure participant safety. The trial should enroll patients from the United States and be of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable

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
04/15/2016

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	208232
Priority or Standard	Standard
Submit Date(s)	June 12, 2015
Received Date(s)	June 15, 2015
PDUFA Goal Date	April 15, 2016
Division / Office	DMEP/ODE II
Reviewer Name(s)	Smita Baid Abraham
Review Completion Date	April 12, 2016
Established Name	Oral octreotide acetate
(Proposed) Trade Name	Mycapssa®
Therapeutic Class	Somatostatin analogues
Applicant	Chiasma
Formulation(s)	Oral
Dosing Regimen	20 mg po BID
Indication(s)	Long-term maintenance treatment for acromegaly
Intended Population(s)	Acromegaly patients in whom prior treatment with somatostatin analogues has been shown to be effective and tolerated.

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I do not recommend approval of MYCAPSSA for long-term maintenance treatment in acromegaly patients (b) (4) he quality of the data is insufficient to recommend approval. A study to adequately characterize the pharmacokinetic and pharmacodynamic effects of MYCAPSSA followed by a confirmatory efficacy trial that includes an appropriate washout period and control population is recommended.

1.2 Risk Benefit Assessment

In the phase 3 clinical development program, Chiasma conducted one single-arm, historical control, open label trial to demonstrate the safety and effectiveness of MYCAPSSA in the treatment of patients with acromegaly. The primary objective and endpoint was to show maintenance of biochemical control in acromegaly patients previously treated with somatostatin analogues. Biochemical control was defined as IGF-1 <1.3 x upper limit of normal (ULN) adjusted for age and sex and integrated GH levels over 2 hours < 2.5 ng/mL.

The efficacy results of CH-ACM-01 do not support the proposed indication: for long-term maintenance treatment (b) (4) At Baseline 88.4% of enrolled patients were defined as responders. By the end of the CORE phase, 52.9% (using "worst case imputation[1]" analysis for missing data) were considered responders. This is a significant loss in response over the course of the trial considering that patients were well controlled on an approved therapy at the start of the trial. The loss of response over time during the trial makes it challenging to conclude that MYCAPSSA provides long-term maintenance. Review of the data showed a high drop-out rate during the CORE treatment period (53/155, 34.2%) with a large proportion of drop-outs because of adverse events (21/53, 39.6%) and treatment failure (24/53, 45.2%). Furthermore, there is a significant loss of biochemical control in the majority of patients, including those who are responders (Figures 5 and 6).

Chiasma proposed an efficacy response rate of approximately (b) (4)% (b) (4) in their statistical analysis plan submitted October 21, 2013 (approximately 18 months after study start). Although the observed response rate is slightly greater than (b) (4)% using worst case imputation analysis for missing data, numerous issues identified within the review cycle put into question the efficacy result. These issues are listed here and discussed in detail throughout this clinical review:

[1] Worst case imputation is the statistical term used in this review to treat any patient who discontinued from CH-ACM-01 as a non-responder.

1. No pharmacokinetic bridge between Sandostatin® immediate-release and MYCAPSSA
    a. Lack of bioequivalence between single dose pharmacokinetic data between Sandostatin® immediate-release and MYCAPSSA
    b. No data to support transition from three times daily dosing for Sandostatin® immediate-release to twice daily dosing for MYCAPSSA
    c. No characterization of MYCAPSSA dose-response or PD comparability, i.e. growth hormone or IGF-1 levels, between MYCAPSSA and Sandostatin immediate-release
2. Single-arm, historical control, open label study design
    a. Inability to distinguish study results from biased observation
        i. Statistical analysis plan and final protocol with defined primary efficacy endpoint upon which efficacy results were calculated not submitted to FDA until at least 18 months after study start
    b. Historical control is best used in diseases with high and predictable mortality and in which the effect of the study drug is self-evident. The effect of MYCAPSSA is not self-evident
3. Lack of a washout period to identify patients with active disease
    a. Inability to differentiate the effect of MYCAPSSA from spontaneous change within the course of disease
        i. Three patients did not need to resume therapy as they were deemed to have adequate biochemical control or mild disease at End of Treatment in CH-ACM-01, suggesting biochemical control regardless of MYCAPSSA therapy
        ii. Medical literature suggests that withdrawal of injectable somatostatin analogue monotherapy in well-controlled patients might result in remission of 12-18 months: Similarly, patients can have a carryover effect of up to 9 months before losing biochemical control and resuming therapy, which suggests that some patients in CH-ACM-01 might have remained controlled without therapy for several months.
        iii. No evidence that in patients with a history of pituitary irradiation, there was withdrawal of somatostatin analogue therapy at regular intervals to reassess growth hormone and IGF-1 levels to ensure active disease

While an oral medical treatment would be a welcome addition to therapies available for acromegaly patients, given the concerns presented above I do not have confidence in the efficacy of MYCAPSSA.

Review of the safety data for CH-ACM-01 did not identify any new safety signals overall. However, given the high discontinuation rate due to treatment failure in this study, adverse events and serious adverse events might be underestimated both in number and severity. Also, the lack of an adequate pharmacokinetic and pharmacodynamic profile for MYCAPSSA imply that the dosing might not be correct in which case the safety results will not be a true reflection of chronic therapy with MYCAPSSA. Last, while the new Transient Permeability Enhancer

formulation used in MYCAPSSA appears to be safe, we must be cognizant of the fact that increased exposure to TPE might reveal unanticipated safety signals.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Octreotide is a long-acting acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin. Octreotide is a first generation somatostatin analogue (SSA), currently only available as an injectable medication. Chiasma has developed an oral formulation of octreotide, oral octreotide acetate, by use of a new technology, "Transient Permeability Enhancer" (TPE®). TPE enhances intestinal absorbance of drug molecules that have limited oral bioavailability. TPE facilitates paracellular transit across the intestinal wall via transient and reversible opening of the tight junctions between cells, allowing intact octreotide to be absorbed.

The oral formulation is an enteric-coated capsule designed to pass through the stomach intact and disintegrate when it reaches the higher pH of the small intestine where the octreotide-TPE formulation is released into the lumen.

Previously referred to as Octreolin™, the proposed trade name for oral octreotide acetate with this new drug application (NDA) is MYCAPSSA™.

Chiasma seeks the following indication for MYCAPSSA: For long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)

The dosing regimen of MYCAPSSA is 20 mg given twice daily (at least 1 hour prior to a meal or at least 2 hours after a meal) with doses being titrated upward to a maximum of 80 mg/day based on measured levels of IGF-1.

2.2 Tables of Currently Available Treatments for Proposed Indications

Acromegaly is a rare disease with a reported prevalence of 38-69 per million[2]. Acromegaly is most commonly caused by excess growth hormone secretion from a pituitary adenoma (somatotropinoma). The signs and symptoms have an insidious onset causing diagnosis of the

disease to be delayed over the course of years. The chronic elevation of GH and IGF-1 levels is responsible for the long term complications of acromegaly, and is associated with premature mortality, although the pituitary adenoma itself is generally benign[2]. The goal of therapy is to reduce GH and IGF-1(adjusted for age and sex) to normal levels. GH and IGF-1 normalization has been associated with a reduction in morbidity and mortality[3].

Transsphenoidal surgery (TSS) is the treatment of choice when chance of cure is high, i.e. size and location of tumor are amenable to complete resection. Medical therapy is an effective alternative option for those in whom adenoma resection either is contraindicated or has a low chance of cure. With the advent of effective medical therapies, the indications for radiation therapy are limited. However, in instances where surgery and radiation therapy are the primary treatment, medical therapies help to bridge the gap between surgery and the full effect of radiation therapy. The table below describes the available treatments for acromegaly.

Table 1. Available treatments for acromegaly

Name	Mechanism of action	Major side effects	Comments
Non-drug therapies			
Transsphenoidal surgery (TSS)	Removal of adenoma	Surgery related complications; pituitary hormone loss, vision damage	Higher cure rates with microadenomas; lower cure rates with macroadenomas. Experience of surgeon critical.
Radiation therapy	Adenoma cell death	Pituitary hormone deficiencies; rare cranial nerve palsies, blindness	Now used as supportive therapy in resistant cases as medical therapies have become more efficacious and with better safety profiles.
Approved drug therapies			
Octreotide	1st generation SSA	Diarrhea, nausea, gallbladder abnormalities	Hyperglycemia occurs in approximately 15% of patients. Tumor shrinkage observed with short and long acting formulations.
Lanreotide	1st generation SSA	Diarrhea, nausea, gallbladder abnormalities	
Pasireotide LAR	2nd generation SSA	Hyperglycemia and diabetes, diarrhea, gallbladder abnormalities	May have positive treatment effect in patients inadequately controlled on other SSAs.

[2] Sherlock M, et al. Medical therapy in acromegaly. Nat. Rev. Endocrinol, 2011
[3] Melmed S, et al. Guidelines for acromegaly management: An update. J Clin Endocrinol Metab, 2009

Pegvisomant	GH receptor antagonist	Liver toxicity; Concerns of adenoma growth	GH levels increase and not used for monitoring. As monotherapy or in combination with SSAs, has high rate of normalization of IGF-1.
Other drug therapies			
Dopamine receptor agonists -bromocriptine* -cabergoline*	Inhibition of GH secretion	Nausea, lightheadedness, mental fogginess	Suggested as initial adjuvant therapy after TSS in mild disease[4]; used in combination with SSAs.

TSS, transsphendoidal surgery; SSA, somatostatin analogue; GH, growth hormone
* Bromocriptine (Parlodel®) has an approved indication for the treatment of acromegaly; however, cabergoline does not have an approved indication for acromegaly

For reference, the trade names, NDA numbers, and dates of approval of approved injectable SSAs for acromegaly are listed in Table 2.

Table 2. Approved drug treatments for acromegaly

Trade Name	Active Ingredient	NDA	Approval
First generation somatostatin analogues			
Sandostatin® IR	Octreotide	19,677	1992
Sandostatin® LAR	Octreotide	21,008	1998
Somatuline® Depot	Lanreotide	22,074	2007
Second generation somatostatin analogues			
Signifor ®LAR	Pasireotide	203,255	2015

2.3 Availability of Proposed Active Ingredient in the United States

Octreotide acetate is available as Sandostatin immediate release (IR) and Sandostatin LAR Depot, for subcutaneous (s.c.) and intramuscular (IM) injection, respectively.

2.4 Important Safety Issues With Consideration to Related Drugs

The major safety concerns with octreotide LAR and lanreotide ATG, first generation SSAs, as listed in the "WARNINGS AND PRECAUTIONS" section of their labels include:

- Gallbladder: Gallstones may occur.
- Glucose metabolism: Hypo- or hyperglycemia may occur.
- Cardiac function: Bradycardia, arrhythmias, or conduction abnormalities may occur.

[4]Katznelson L, et al. Acromegaly: An Endocrine Society Practice Guideline. J Clin Endocrinol Metab, 2014

• Thyroid function (octreotide LAR only): Hypothyroidism may occur.

In addition to the gallbladder and cardiac warnings above, the Signifor® and Signifor® LAR labels also include the following safety issues in the "WARNINGS AND PRECAUTIONS" section of their labels:

• Hypocortisolism (Signifor® only): Decreases in circulating levels of cortisol may occur resulting in biochemical and/or clinical hypocortisolism. Signifor® dose reduction or interruption and/or adding a low-dose short-term glucocorticoid may be necessary.
• Hyperglycemia and Diabetes (occurs with initiation): Intensive glucose monitoring is recommended and may require initiation or adjustment of anti-diabetic treatment.
• Liver Test Elevations: Evaluate liver tests prior to and during treatment.

However, hypocortisolism, hyperglycemia and diabetes and liver test elevations are not major safety concerns with oral octreotide acetate.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Investigational new drug application (IND) 108,163 for oral octreotide acetate was submitted in 2010 and orphan drug designation granted on June 17, 2010. Oral octreotide acetate is not being studied under any other active U.S. IND.

The original proposed proprietary name for oral octreotide acetate was Octreolin; however, Chiasma withdrew this request on March 25, 2013. The new proposed proprietary name is MYCAPSSA. Similarly, in various submitted reports Chiasma has referred to somatostatin analogues as somatostatin receptor ligands (SRLs); however, in this review the abbreviation SSA will be used.

Three presubmission regulatory meetings took place prior to submission of this NDA 208232 for oral octreotide acetate. The clinical highlights of the meetings are described.

End-of-Phase 2 meeting, August 9, 2011

- Established that phase 3 trials will enroll patients eligible for maintenance therapy. Eventually Chiasma will also seek indication for initial therapy.
- The NDA will follow the 505 (b)(2) pathway with reliance on FDA's finding of safety and effectiveness for Sandostatin immediate-release (IR). To also rely in part on the FDA's findings of efficacy and safety for Sandostatin LAR will require Chiasma to establish a "bridge" between Octreolin and Sandostatin LAR, which might be challenging given the very different pharmacokinetic profiles of Octreolin and Sandostatin LAR.
- Two healthy volunteer studies (CHI-001 and CHI-002) show that exposure of oral 20 mg Octreolin under fasting condition seems comparable to the exposure of subcutaneous 0.1 mg Sandostatin. It is noted that Chiasma does not seek bioequivalence between Octreolin

and Sandostatin IR. The comparative bioavailability studies are to establish the "bridge" between Octreolin and Sandostatin IR [redacted] (b) (4)

- Agreement that one single-arm, open-label, pivotal trial for safety and efficacy is acceptable for NDA submission. Overall plan for proposed phase 3 trial acceptable.
- Number of patients (N = 150) reasonable; however, FDA stated that it is not clear if this number along with duration of exposure at proposed dose will be informative with respect to safety.
- No further QT studies needed.
- Sponsor confirmed that formulation used in the Phase 3 trial was the intended commercial formulation.
- In response to several clarification questions asked by the FDA, the following answers were provided by the sponsor:
    - No formal washout period for any of the subjects enrolled in the Phase 3 study.
    - There will be a carryover effect [from injectable SSA] early in the study, but, it should not raise any safety concerns because: 1) it overlaps with the Octreolin titration period and, 2) wide therapeutic index and safety margins of octreotide.
    - Carryover effect will not influence efficacy because efficacy of Octreolin will be measured at seven months, long after any effect of the pre-trial SSAs disappeared.
    - Evaluation of efficacy at seven months (versus one full year) was chosen as a balance between the shortest time required for 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. Chiasma is planning an open-label extension phase (six months).
        - FDA recommended that sponsor encourage patients to continue in extension trial and collect as much safety and efficacy data as possible. FDA indicated that the patient exposure should be comparable to that obtained with other somatostatin analogue programs.
    - IGF-1 values are assay- and lab- dependent and age-dependent. The 30% ULN threshold was chosen to ensure that any observed IGF-1 levels are clinically relevant changes and not simply due to inter- and intra-assay variability.
        - *The IGF-1 values discussed were with regard to general responder analyses and not with specific reference to the definition of a responder for the primary efficacy analysis. A specific definition of "responder" for CH-ACM-01 was not provided at this meeting.*
    - Chiasma's expert indicated that the decision to change the Octreolin dose if two consecutive IGF-1 levels confirm and an increase > 15% is clinically relevant and, in his opinion, can be implemented in clinical practice.
    - Regarding acromegaly biochemical control, the growth hormone (GH) threshold of 2.5 ng/mL versus 1 ng/mL was chosen because it is still an important criterion of acromegaly control and is also described in the acromegaly labels for the other somatostatin products. In addition, a GH level of < 2.5 ng/mL is associated with reduction in mortality rate to background levels. Chiasma agreed to also submit

data for GH levels < 1 ng/mL and would make this part of their statistical analysis plan.
    - The patient satisfaction is endpoint is exploratory and is intended for publication only.
- Chiasma stated that they plan to proceed directly to the phase 3 trial without submitting a special protocol assessment.

Pre-NDA meeting, May 21, 2014

Chiasma, Inc. was the original sponsor of this application until it was transferred to Genentech on March 11, 2014.

The FDA stated that since the phase 3 study (CH-ACM-01) is a single arm trial and interpretability and efficacy and safety data from such a trial will be challenging, Chiasma should address and clarify several questions. Chiasma's responses and any relevant discussion are summarized.

- Current diagnostic standards for acromegaly and those used to determine eligibility in CH-ACM-01 are based on AACE acromegaly guidelines[5].
- Although the listed drug is Sandostatin IR, the eligibility criteria for CH-ACM-01 allowed for patients to be on either Sandostatin IR or long-acting SSAs. None of the enrolled patients were on Sandostatin IR reflecting the current standard of care. A pharmacokinetic (PK) bridge to Sandostatin IR was established to support the 505(b)(2) application. The phase 3 study was not designed to establish a bridge to Sandostatin IR.
- There was no washout period in this study. The baseline visit occurred in most patients within approximately two weeks following their last injection of long acting SSA.
- Complete washout from long-acting SSA use is expected to occur within 8-12 weeks from withdrawal in a patient with active acromegaly. It is unlikely that residual effects of SSAs would have been observed. This statement is corroborated by the fact that 90 patients in CH-ACM-01 had elevated IGF-1 levels requiring an increase in the dose of oral octreotide to achieve biochemical control.
- The comparable PK between oral octreotide acetate and Sandostatin IR would predict that most patients controlled on an effective dose of injectable octreotide would also be controlled on oral octreotide acetate.
- A number of factors help explain why the observed response rate in the phase 3 study is not 100%
    - Variability in absorption of oral octreotide acetate (OOA)
    - Food effect
    - Early dropout due to GI adverse events

[5] Katznelson L et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update: executive summary. Endocr Pract 2011.

    - Observed biochemical fluctuation over time as observed for patients on stable injectable long acting SSAs (100% response rate at screening versus 88% response rate at baseline)
- The sponsor stated that the timing of the primary endpoint at seven months reflects chronic use of OOA, which 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 study.
- The sponsor believes that the response observed in the trial is due to treatment with oral Octreolin and not due to spontaneous improvement as the eligibility criteria were designed to only include patients who were not expected to have spontaneous improvement (e.g. newly diagnosed patients, SSA therapy less than every 4 weeks, etc.)
- FDA expressed concern that there was a reduction of almost 50% in the number of responders when patients were switched from SSAs to oral octreotide. Given that the dose selected had been shown to provide similar drug exposure as a therapeutic Sandostatin dose, such a loss of efficacy was odd. Genentech cited the aforementioned factors along with fluctuations in IGF-1 serum levels as reasons for this observation. Genentech reiterated that those patients who achieved control on oral octreotide also maintained control. All patients were responders with respect to GH reduction.
- FDA commented that a single-arm study is not as informative as a controlled study such as an active control using a non-inferiority design. There is always a concern in interpreting data from a single-arm trial wherein some patients may improve spontaneously.
- FDA questioned how much one can understand about the drug if exposure does not predict response, particular 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 (pharmacodynamic) relationship is not well known for octreotide, in general, and, therefore such predictions cannot be accurately made.
- FDA asked if the sponsor demonstrated bioequivalence. Genentech responded that they did not conduct a formal bioequivalence (BE) study as they believed a strict BE study was not necessary and a relative BE study was sufficient. FDA 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.
- PK data between responders and non-responders was not done as PK data was not collected in non-responders during the maintenance phase or at the end of the trial.
- The aim of the trial was not to target the therapeutic level of the drug as every patient is assumed to have a different therapeutic level.
- Include safety data from all studies conducted with oral octreotide acetate.

Type C Meeting, teleconference, December 8, 2014

(On August 8, 2014, IND 108,163 application was transferred from Genentech back to Chiasma, Inc., the original application holder. On October 3, 2014, Chiasma Inc. requested another pre-

NDA meeting to discuss their NDA submission plans. Since a pre-NDA meeting had already been held for this product, the Division re-classified this meeting as a type C guidance meeting to be conducted via teleconference.)

Much of the discussion emphasized the points made by FDA at the May 2014 pre-NDA meeting:

- Acceptance of the efficacy and safety data generated in the phase 3 study, as well as whether the PK studies and the phase 3 study conducted constitute an adequate bridge between MYCAPSSA and Sandostatin IR, will require full review of the data following the NDA submission.
- FDA reiterated concern about the reduction of approximately 60% in the number of responders at the end of the 7-month treatment period compared to baseline. The sponsor stated that they were surprised that they need to demonstrate a higher responder rate considering that a drug that offers a 50% responder rate and even as low as a 30% responder rate would be acceptable based on the Global Advisory Board Meeting in 2012. FDA clarified that the main concern was mostly with the loss of biochemical control when switching from an approved product to oral octreotide.
- The sponsor cited two published trials that both included a placebo arm in acromegaly patients. Both studies demonstrated no GH and/or IGF-1 control in placebo patients supporting the fact that the effect seen in the current phase 3 study was due to oral octreotide and not to a placebo effect.
- Sponsor noted that previous FDA approvals of somatostatin analogs were based upon demonstration of GH suppression alone.
- FDA stated that data from extension trial(s) is typically unreliable due to loss of randomization and assumptions that handle the response for patients who were originally randomized but no longer in the trial.
- FDA stated that based on the first pre-NDA meeting and this meeting, no issue had been identified that would preclude the sponsor from submitting an application for review.

2.6 Other Relevant Background Information

The listed drug for this 505(b)(2) application is Sandostatin IR (Sandostatin®). Chiasma does not seek bioequivalence between MYCAPSSA and Sandostatin® as they have performed their own clinical trial (CH-ACM-01); however, based on two comparative bioavailability studies, CHI-001 and CHI-002 does seek to (b) (4)

Sandostatin IR is indicated to reduce blood levels of growth hormone and IGF-1 (Somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses. The goal is to achieve normalization of GH and IGF-1 levels.

Sandostatin IR was chosen as the listed drug because, per the sponsor, the pharmacokinetics of MYCAPSSA mimic that of Sandostatin IR. However, Sandostatin IR for treatment of acromegaly is not the standard of care. Should a patient be treated with a somatostatin analogue,

Sandostatin LAR and Somatuline Depot are most commonly used as evidenced by the fact that all patients were on one of these two drugs prior to enrollment into CH-ACM-01.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA 208232 for MYCAPSSA was submitted in eCTD format. The quality and integrity of the submission was adequate.

3.2 Compliance with Good Clinical Practices

The applicant conducted the Phase 3 program in accordance with Good Clinical Practices (GCP).

As part of FDA's assessment of GCP, three foreign clinical sites (sites 1201, 0402 and 0602) as well as the sponsor's site were inspected. The preliminary classification for sites 1201 and 0402 is "No Action Indicated" (i.e. no deviations from regulations). The preliminary classification for site 0602 and the sponsor site is "Voluntary Action Indicated" (i.e. deviation(s) from regulations). Although regulatory violations were noted at two sites, overall, the Office of Scientific Investigations (OSI) concluded that these violations were unlikely to have affected the primary efficacy and safety analyses. For further details, please see the OSI review by Dr. Cynthia Kleppinger.

3.3 Financial Disclosures

In accordance with 21 Code of Federal Regulations (CFR) part 54 requirements[6], Forms 3454 and 3455 were submitted for all investigators.

Six investigators had disclosable financial arrangements and interests requiring reporting (Tables 3, 4, 5).

[6] Code of Federal Regulations, Title 21, part 54

Table 3. Disclosable financial arrangements: Consulting services

Year	(b) (6)						Total
	US $	US $	US $	US $	US $	US $	US $
(b) (6)	0	28,150	0	0	0	9,388	37,538
	6,712	0	0	3,520	0	14,060	24,292
	0	0	0	3,520	0	40,812	46,332
	19,566	0	0	0	0	31,400	50,966
	0	0	0	0	0	32,229	32,229
	19,317	0	0	0	0	77,000	96,317
	45,595	28,150	0	7,040	0	204,889	285,674

Source: Information request response received by FDA March 4, 2016

Table 4. Disclosable financial arrangements: Honorarium fees for participating in advisory meetings

Year	(b) (6)						Total
	US $	US $	US $	US $	US $	US $	US $
(b) (6)	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	1,000	0	1,000	0	2,000
	2,500	0	2,554	0	0	0	5,054
	0	0	0	0	0	0	0
	2,500	0	0	0	2,500	0	5,000
	5,000	0	3,554	0	3,500	0	12,054

Source: Information request response received by FDA March 4, 2016

Table 5. Stock options granted

Name	Grant Date	Options granted	Exercise price	Fair Value (on grant date)
(b) (6)		6,045	$1.92	$16,684
		27,353	$1.92	$35,012
		4,853	$8.13	$31,933
		4,853	$8.13	$31,933

Source: Information request response received by FDA March 4, 2016

Reviewer Comment: (b) (6) and (b) (6) received significant monetary contributions from the sponsor. (b) (6) was an investigator for (b) (6) at the (b) (6) (b) (6). This site was ranked (b) (6) of sites evaluated for risk, with (b) (6) being the (b) (6) according to the FDA site selection tool. (b) (6)

Similarly, (b) (6) served as the (b) (6) (b) (6). Chiasma states that any potential bias due to (b) (6) financial arrangements with Chiasma was mitigated by (b) (6) (b) (6) It is unlikely that the results of the study are biased because of (b) (6) financial arrangements with Chiasma.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry, manufacturing and controls team recommends approval. However, the Facility Review/ Manufacturing Inspection recommendation is a complete response.

Please refer to the reviews in Panorama by these two teams.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Chiasma is relying on previous nonclinical findings and comparability with Sandostatin IR to support the safety profile of MYCAPSSA. Data from nonclinical studies of MYCAPSSA

administered to Cynomolgus monkeys did not reveal any new drug-related toxicity. Overall, the nonclinical data are sufficient to support approval of the proposed dose of MYCAPSSA in acromegaly patients. For further details, please see the pharmacology/toxicology review by Dr. Jessica Hawes.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Somatostatin is a neuropeptide that exerts its metabolic effects via binding to somatostatin receptors (SSTRs). SSTRs are members of the G-protein-coupled receptor superfamily. There are five known SSTRs (1-5), each with a distinct activation profile and tissue distribution. Within the pituitary gland, somatostatin inhibits growth hormone (GH) release primarily via binding of SSTR 2 and 5. SSTR 2 and 5 are also found with high prevalence in pituitary tumors. Somatostatin has a short half-life (1-3 minutes) and therefore somatostatin analogues with longer duration of action have been developed for therapeutic purposes.

Parenteral formulations of octreotide acetate, currently marketed first generation injectable SSA therapy, are approved for human use worldwide. Octreotide acetate binds most strongly to SSTR2 and moderately to the other receptors.

Octreotide acetate is the active pharmaceutical ingredient in the sponsor's octreotide capsule product. The drug product incorporates the sponsor's new technology, Transient Permeability Enhancer (TPE®). TPE enhances intestinal absorbance of drug molecules with limited oral bioavailability. The TPE facilitates paracellular transit across the intestinal wall via transient and reversible opening of the tight junctions between cells, allowing intact octreotide to be absorbed.

The oral formulation is an enteric-coated capsule designed to pass through the stomach intact and disintegrate when it reaches the higher pH of the small intestine where the octreotide-TPE formulation is released into the lumen.

The octreotide capsule formulation does not cause any chemical or physical change in the active compound. Once octreotide reaches the systemic circulation after administration of the octreotide capsule, the metabolism and excretion of octreotide is expected to be identical to that of injected octreotide acetate (Listed Drug, Sandostatin IR).

4.4.2 Pharmacodynamics

For a detailed review of the pharmacodynamic and pharmacokinetic data of MYCAPSSA, please refer to the clinical pharmacology review by Dr. Sury Sista.

In this 505(b)(2) application, Chiasma did not conduct a study to characterize the pharmacodynamic (PD) effect of MYCAPSSA. Thus, there was no characterization of

MYCAPSSA dose-response or PD comparability, i.e. growth hormone (GH) or IGF-1 levels, between MYCAPSSA and Sandostatin IR.

4.4.3 Pharmacokinetics

Chiasma conducted studies CHI-001 and CHI-002 (see Appendix 1) as "comparative bioavailability" studies between MYCAPSSA and Sandostatin IR. Chiasma did not seek bioequivalence between MYCAPSSA and Sandostatin IR as Chiasma conducted its phase 3 clinical trial, CH-ACM-01 to show efficacy and safety of MYCAPSSA.

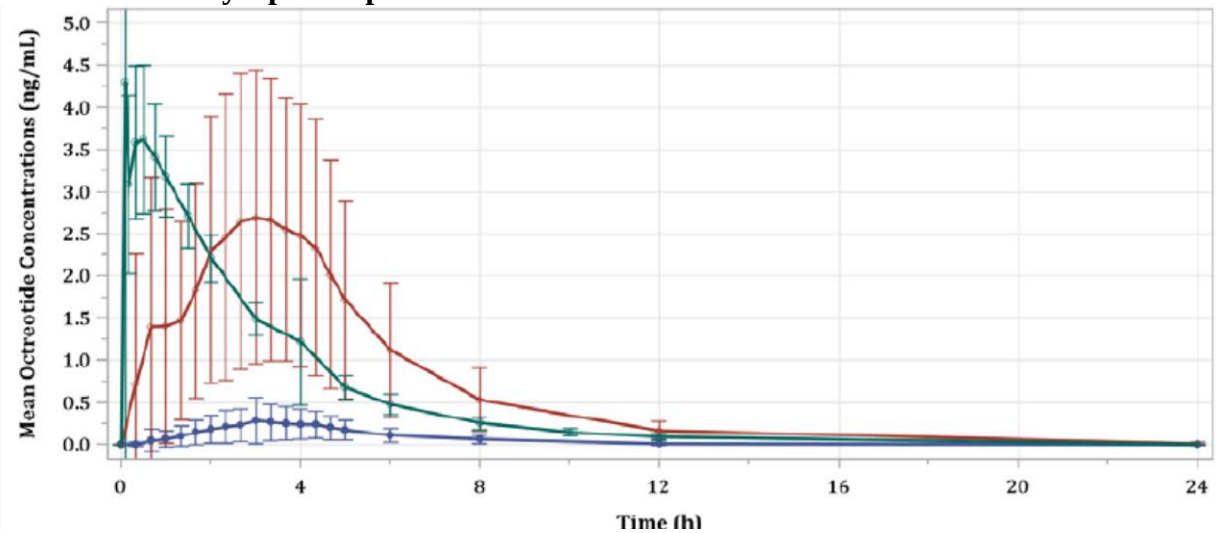
Pharmacokinetic (PK) properties of MYCAPSSA include:

- Relative bioavailability: 0.5%
- Median T_{max}: 1.67 – 2.5 h
- Half-life in healthy volunteers: approximately 2 – 4 h
- Half-life in acromegaly patients: 1.7 – 1.9 h
- Food effect: approximately 90% decrease in bioavailability with food effect, which is reduced to 60% when administered one hour before reduced-size high fat meal.

Reviewer comment: Patient instructions for taking MYCAPSSA state: "MYCAPSSA should be taken with a glass of water on an empty stomach (i.e., at least 1 hour before a meal or at least 2 hours after a meal). Drinking of water is allowed during these times." We noticed that the protocol allowed patients to drink juice before taking MYCAPSSA. Considering the significant food effect, it is not clear why juice was allowed during MYCAPSSA administration. Ingestion of juice might have further affected absorption of MYCAPSSA during the trial.

Figure 1 displays the mean serum concentration-time profile of octreotide following single-dose administration of MYCAPSSA and Sandostatin IR.

Figure 1. Study CHI-002: Single-dose, food effect and comparative bioavailability study of octreotide from Mycapssa capsules



Source: Dr. Sista's review, Figure 6, page 31
Green, Mycapssa 20 mg capsule (Fed)
Red, Mycapssa 20 mg capsule (Fasted)
Blue, 0.1 mg Sandostatin IR injection

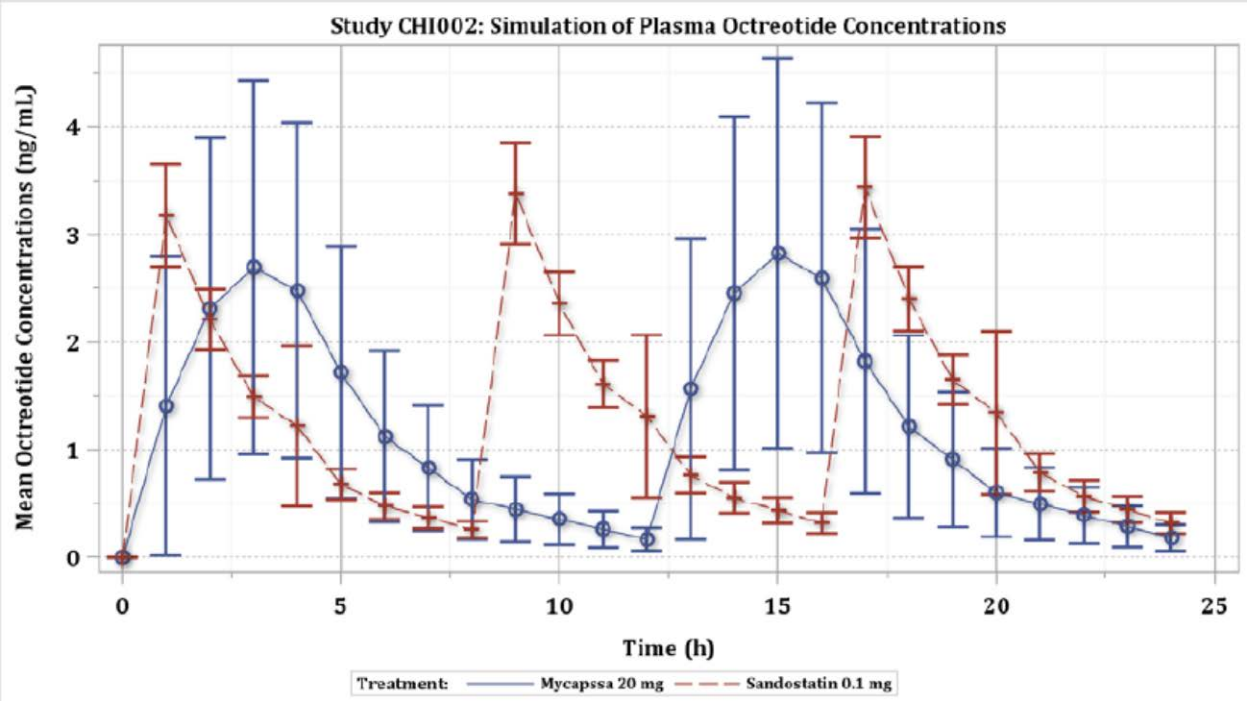
Figure 1 shows high intra-subject variability in octreotide concentrations with single-dose MYCAPSSA compared to single dose Sandostatin IR. High intra-subject variability leads to wide confidence intervals for AUC_{0-t}, which can make it more difficult to show bioequivalence between two products. To show that a test product is bioequivalent to a reference product, the 90% confidence interval around the point estimate of the ratio of least squares means (LSM) between the two products must be between 80-125% for the AUC_{0-t} and C_{max}.
The single dose PK data show that MYCAPSSA is not bioequivalent to Sandostatin IR as demonstrated by the LSM ratio between the two products:

- **AUC_{0-t}:** 0.97 (90% CI 73.03% - 128.37%)
- **C_{max}:** 0.64 (90% CI 45.29% - 89.78%)

In addition to the lack of bioequivalence by single-dose PK data between MYCAPSSA and Sandostatin IR, the difference in the dosing regimens between MYCAPSSA and Sandostatin IR raises concern. Sandostatin IR is administered three times daily compared to MYCAPSSA, which is proposed to be administered twice daily. In the Clinical Study Report (CSR), Chiasma states that the MYCAPSSA dose was selected based on "…results from clinical PK testing and modeling and was expected to yield circulating levels of octreotide similar to that of 0.1 mg subcutaneous octreotide (i.e. Sandostatin IR) given three times a day, the most commonly effective dose of the subcutaneous formulation." In Figure 2, Dr. Sista has simulated single dose PK data from study CHI-002 to a BID regimen for MYCAPSSA and TID regimen for Sandostatin IR. Figure 2 shows lack of bioequivalence between a BID regimen for MYCAPSSA and TID regimen for Sandostatin IR.

Although Chiasma stated that they are not seeking bioequivalence between MYCAPSSA and Sandostatin IR, the efficacy results of CH-ACM-01 are not robust (see section 6.0, Review of Efficacy). In addition, given the differences in the PK data, absent PD data, we cannot conclude that the PD characteristics, i.e. GH and IGF-1 levels over time, of MYCAPSSA are similar to those of Sandostatin IR.

Figure 2. Simulation of plasma octreotide concentrations



Source: Dr. Sista's review, Figure 12, page 40

Reviewer comment: In the December 8, 2014 Type C (Pre-NDA) teleconference FDA stated: "Acceptance of the efficacy and safety data generated in the phase 3 study as well as whether the PK studies and the phase 3 study conducted constitute an adequate bridge between MYCAPSSA and Sandostatin IR, will require full review of the data following the NDA submission."

The submitted PK/PD data do not establish an adequate bridge to Sandostatin IR.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In total, there are 12 completed studies that comprise the clinical development program for MYCAPSSA as summarized below:

- 1 clinical efficacy and safety study in patients with acromegaly (CH-ACM-01, pivotal trial) (N = 155) (Table 6)
- 1 clinical pharmacology study in healthy subjects (CHI-001) (N = 12)
- 1 clinical pharmacology study in hepatically impaired subjects (CH-PHT-01) (N = 18)
- 1 clinical pharmacology study in renally impaired subjects (CHI-007) (N = 6 severe renal, 6 end stage renal disease (ESRD) on dialysis, 12 healthy volunteers)
- 8 clinical pharmacology studies in healthy subjects evaluating drug-drug or drug-food interactions (CHI-002, Chi-004, CHI-005, CHI-006, OCT-01, OCT-02, OCT-03, OCT-04) (N = 160)

Table 6. Summary of pivotal trial for MYCAPSSA

Trial Description	Treatment duration	Dosing Regimen	Primary Endpoint	Efficacy Analysis set
Pivotal Trial to Support Efficacy and Safety: CH-ACM-01				
Phase 3, multicenter, single-arm, open-label, pivotal trial for safety and efficacy of MYCAPSSA in patients with acromegaly who are currently receiving parenteral somatostatin analogues.	Screening: up to 4 weeks Baseline: up to 4 weeks CORE treatment period: At least 7 months (includes dose escalation phase of ≥ 2 months and a fixed dose phase (CORE) of 2 to 5 months. Voluntary extension treatment period/fixed dose phase (extension): at least 6 months; follow-up period: 2 weeks.	MYCAPSSA 20 mg twice daily Dose escalation stepwise from 40 mg/day to 60 mg/day up to maximum 80 mg/day) based circulating IGF-1 levels and acromegaly related symptoms.	IGF-1 and mean GH levels[1] at the end of the CORE treatment period as a measure of responses in the modified intention-to-treat (mITT) population. Response defined as IGF-1 < 1.3 x ULN adjusted for age[2] and an integrated GH level < 2.5 ng/mL	Modified Intention-to-treat (mITT): All enrolled patients who received any amount of study drug and who had at least one IGF-1 or GH assessment post first dose with MYCAPSSA .

Source: Sponsor's clinical study report (CSR), pgs. 19 and 78-79
[1]blood samples for GH were collected every 30 ± 5 minutes for 2 hours (total 5 samples) beginning 2 hours following study drug dosing during the treatment period; source: schedule of assessments, Sponsor's CSR, pg. 58
[2]IGF-1 levels adjusted for both age and gender; source: response to information request received 08/25/2015

The remaining eleven studies are summarized in Appendix 1 of this document. These studies are reviewed in detail in the Clinical Pharmacology review by Dr. Sury Sista. Safety data from these studies is reviewed in section 7.0 of this clinical review as well.

5.2 Review Strategy

The primary focus of the efficacy and safety evaluation for this review was the phase 3, pivotal trial data (CH-ACM-01). The 120-day clinical safety update data was reviewed as well to ensure that no new safety signals emerged. In addition, several information request responses from Chiasma were reviewed.

The following reports were referenced during this review.

1) Phase 1 trial reports described in Table 41, Appendix 1.
2) Sandostatin® label
3) Sandostatin® LAR label
4) Somatuline® Depot label

5.3 Discussion of Individual Studies/Clinical Trials

The pivotal trial, CH-ACM-01, entitled "Efficacy and Safety of Oral Octreolin^{TM} in Patients with Acromegaly who are Currently Receiving Parenteral Somatostatin Analogs" is presented below. CH-ACM-01 is a phase 3, multicenter, single-arm, open-label, maintenance of response, baseline-controlled withdrawal study conducted in patients who were biochemically controlled on somatostatin analogue (SSA) therapy. The study was **initiated on March 13, 2012 and completed on May 30, 2014**. Patients were enrolled across 13 countries at 37 study centers. It is noted that there were no study centers within the United States.

Reviewer comment: 1) In the clinical inspection summary by Dr. Cynthia Kleppinger, it is reported that 34 sites, compared to the 37 reported above, were included in the summary. No subjects were screened at Sites 0401 and 0404. Site 1301 screened two subjects but neither was enrolled. Only sites that enrolled patients were evaluated in the clinical inspection summary.

2) The study completion date is not clear. In the synopsis of the CSR (page 3), the completion date is stated as May 30, 2014. However, on the title page of the CSR, the completion date is listed as November 26, 2013 – we believe this is the date of database lock.

The **primary objective** of CH-ACM-01 was to:

1. Determine the effect of MYCAPSSA therapy on IGF-1 and GH levels, as measures of response.

The secondary objectives were:

1. To assess the safety and tolerability of MYCAPSSA in patients with acromegaly
2. To compare the effect of MYCAPSSA therapy on IGF-1 levels and GH levels with that of parenteral therapy with somatostatin receptor ligands

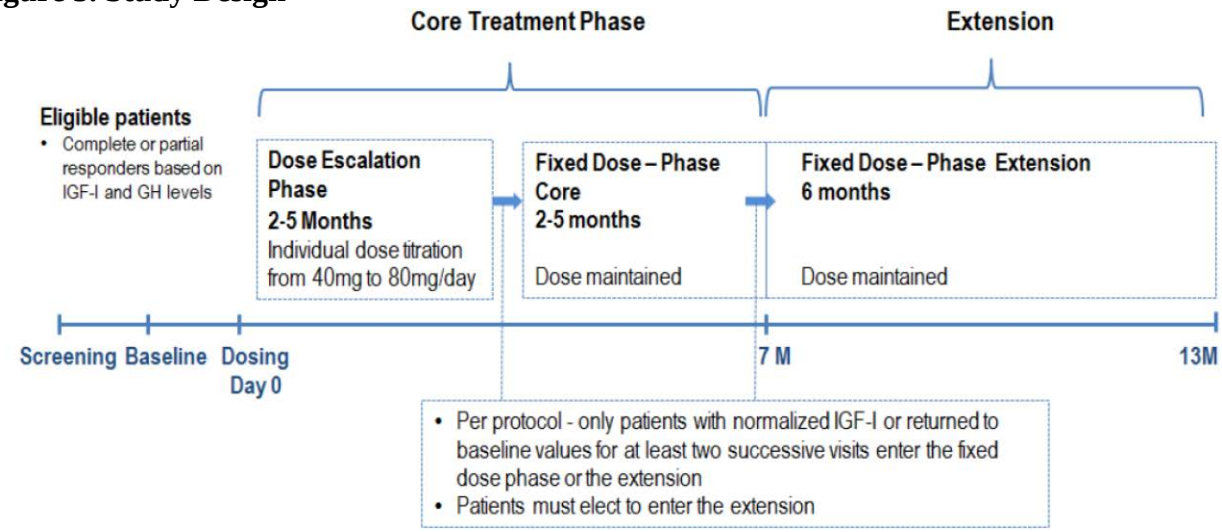
The exploratory objectives were:

1. To assess treatment satisfaction with parenteral vs. oral SSAs
2. To assess the rate of patients who need to return to parenteral therapy
3. To determine the pharmacokinetic profile of MYCAPSSA during chronic treatment

Study Design

The study consisted of a screening visit, baseline visit, dose escalation phase, and fixed dose (CORE) treatment phase and an optional fixed dose extension treatment period of six months (Figure 3).

Figure 3. Study Design



Source: Sponsor's CSR, pg 44

The study duration could be up to 16 months:

- Screening Period: up to 4 weeks (1 month)
- Baseline Period: up to 4 weeks (1 month)
    - At the beginning of a baseline period, lasting not more than 4 weeks and ending with the first dose of MYCAPSSA (visit TA1, see below), individual subjects will be receiving a stable dose (> 3 months) of one of the following somatostatin analogs: octreotide for injection (sc and LAR) or lanreotide for injection (LA, Autogel or Depot). Note that the

last dose of injectable somatostatin analog could have been given during the screening period (page 42/2245 of protocol, version 6.0 in 16-1-1-prot-amendments)

- CORE Treatment Period: at least 7 months
- Extension Treatment Period: 6 months
- Follow-up Period: 2 weeks

In an information request response received April 1, 2016, Chiasma reported that 142 patients had their last SSA dose prior to the TA1 visit (first dosing with MYCAPSSA) administered before the Baseline visit. For these patients, the mean number of days between the last injection of SSAs and the collection date for Baseline GH and IGF-1 was 17.5 days with a standard deviation of 13.85 days (range: 0 – 82 days). Fifty-nine (59) of these 142 patients had less than two weeks between their last injection of somatostatin analogue and Baseline GH and IGF-1 level collection. In nine patients the last SSA dose prior to the TA1 visit was administered after their Baseline visit.

In 51 patients the last SSA dose prior to the TA1 visit was administered before the Screening visit. For these patients the mean number of days between the last injection of SSAs and the collection date for screening GH and IGF-1 is 11.9 days, with a standard deviation of 10.14 days (range: 0 – 54 days).

Reviewer comment: There is significant variation as to when Screening and Baseline GH and IGF-1 levels were drawn relative to SSA injection. Ideally, the Screening and Baseline blood draw should have been a pre-specified number of days after the last SSA injection so that determination of response at both visits was consistent for each patient. In any given patient, response 1-2 weeks after injection might be different 3-4 weeks after injection.

For reference, throughout the remainder of this review the study visits are labeled as follows:

- Dose Escalation Phase, CORE Treatment Period: TA1 – TA15, occurs every two weeks.
- Fixed Dose Phase, CORE Treatment Period: TB1- TB6, occurs monthly.
- Extension Treatment Phase: TE1 – TE3, every second month.
- End of Treatment (EOT): last observation in the Fixed Dose Phase for patients who completed the CORE Treatment Period; or, the last observation during the CORE Treatment Period for patients who terminated the study early.
- End of Extension (EoE): last observation in the extension period
- Follow-up: two weeks after EOT or EoE.

The first dose of MYCAPSSA was administered no less than one month following the last dose of the patient's long-acting parenteral SSA.

Each patient received MYCAPSSA BID during the treatment period (dose escalation + fixed dose phase CORE + fixed dose phase extension). Titration was started at 40 mg (20 mg BID)

and increased step-wise (when required) to 60 mg (40 mg + 20 mg) and 80 mg (40 mg BID) daily.

To reduce the potential for a carryover effect from long-acting parenteral somatostatin analogs, subjects may not complete the Dose Escalation phase and enter the Fixed Dose phase until at least 3 months after their last dose of long-acting parenteral SSA.

Dose escalations were permitted after two successive visits with inadequate hormonal suppression of IGF-1 levels. Inadequate hormonal suppression was defined as at least 20% increase over the prior level or smaller increases plus emergence of typical symptoms and/or less suppression than that documented at baseline visit.

At the discretion of the Site Investigator, patients were allowed to revert back to their somatostatin analog therapy if they did not meet the definition of maintaining biochemical response.

Patients were allowed to enter the **Fixed Dose phase** if IGF-1 levels were normalized or maintained (IGF-1 $\leq$ 1.0 x ULN or < 20% increase compared to baseline), and the patient maintained symptomatic response for two consecutive visits.

The **CORE treatment period (CORE phase)** was completed for each patient when 1) the patient completed at least two (2) months of treatment in the fixed dose phase and, 2) a total treatment duration of at least seven (7) months.

The same criteria that allowed patients to enter the Fixed Dose phase (above) were used to determine eligibility to continue into the voluntary six-month Extension phase. Eligible patients who elected to continue into the Extension phase were maintained on their therapeutic dose. At study end, either in the CORE treatment phase or extension phase, there was a two week follow-up period for safety assessments.

Reviewer comment:
We have concern regarding this single-arm, baseline controlled trial. Chiasma states that the baseline comparison is an adequate study design to assess maintenance of response in a withdrawal trial, when an effective therapy (parenteral SSA) is withdrawn and patients are switched to an alternate therapy with the same proven mechanism of action. To further support their study design Chiasma made the following points in their Clinical Study Report (CSR pgs 47-48):

- *No tachyphylaxis to somatostatin analogs in patients with acromegaly. Maintenance of response to SSAs is well established in the literature and is reported to range between 80-100%.*
- *The duration of residual IGF-1 suppression after long-acting SRL withdrawal is not known, but, is not expected beyond 8-12 weeks from withdrawal in a patient with active disease (Stewart et al, 1999, Caron et al. 2000). GH levels may revert between 4 and 6 weeks after octreotide LAR withdrawal (Biermasz et al. 2003). In addition, the effect*

upon withdrawal of the somatostatin analogs is expected to wane by 8 weeks (Beirmasz et al. 2003). Therefore, the effect of maintenance measured at 7 and 13 months will be due to the therapeutic effectiveness of MYCAPSSA [OOA] and not the residual effect of prior somatostatin analog injections.

- *Spontaneous remissions are rare in acromegaly so the effect size at seven and thirteen months is due to MYCAPSSA [OOA].*
- *Study protocol excluded all patients who received pituitary radiotherapy (both conventional and stereotactic) within 10 years prior to screening to exclude treatment effects due to prior radiotherapy and similarly, excluded patients who underwent pituitary surgery within six months prior to screening.*
- *Therefore, adding a comparator arm of patients who continue treatment with long-acting somatostatin analogs, to evaluate maintenance of response of MYCAPSSA [OOA] controlled by somatostatin analogs was not necessary. Chiasma believes the addition of a comparator arm would not have added scientific value to the study in this regard. Adding a placebo-controlled arm was also not justified. The efficacy of octreotide is well established and adding a placebo arm to demonstrate that patients treated with placebo do not respond does not add to the assessment of MYCAPSSA [OOA] provided in the current trial design. The single-arm, baseline-control design comparing patients on injectable somatostatin analogs at baseline with MYCAPSSA [OOA] was an appropriate and conservative study design since this favors injectable somatostatin analogs because patients are preselected to be responding to injectable somatostatin analogs at screening.*

As per ICH guideline E10[7], the purpose of a control group is to allow discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment. In this case, the sponsor has used a baseline control, in which the subjects' status on therapy is compared with status before therapy. This is an uncontrolled study and therefore, at risk for bias in multiple areas including stage or severity of disease at time of treatment, concomitant treatments and observational conditions (such as methods of assessing outcome, investigator expectations). Typically, use of a baseline controlled study is used in situations where the effect of the treatment is dramatic and the usual course of the disease is highly predictable. Although, the course of acromegaly is relatively predictable, the effect of treatment in this case is not dramatic, and it is in fact, quite a bit less than that of the baseline control (use of injectable SSAs).

Subjects

At least 150 adult patients who were diagnosed with acromegaly and who, at screening, were receiving and responding to regular parenteral therapy at a stable dose of an SSA for at least 3 months were eligible for the study. Patients who met all of the inclusion criteria and no exclusion criteria were offered enrollment.

[7] ICH Harmonised Tripartite Guideline: Choice of control group and related issues in clinical trials E10, 2000.

Inclusion Criteria

1. Adult patients, 18 to 75 years of age, inclusive, at the screening visit.
2. Patients with acromegaly, defined as documented evidence of GH-secreting pituitary tumor that was abnormally responsive to glucose, and who were currently receiving regular parenteral injections at a stable dose for at least 3 months and were considered complete responders or at least partial responders to a SSA:
    - Eligible somatostatin analogues included: octreotide (subcutaneous and LAR), lanreotide (Autogel or Depot);
    - Complete response was defined as: IGF-1 normalized for age and integrated GH response over 2 hours < 2.5 ng/mL;
    - Partial response was defined as: IGF-1 < 30% above level normalized for age (i.e., < 1.3 times ULN and integrated GH response over 2 hours < 2.5 ng/mL;
    - Age-normalized IGF-1 was considered the 2.5th to 97.5th percentile range for the central reference laboratory. Local laboratory values were not to be used to qualify patients for the study;
    - Patients who took regular injections of SSAs less frequently than monthly were not eligible; and
    - Patients who took injections of octreotide on an as-needed basis to treat headaches were not eligible.
3. Patients who had received appropriate stable doses of hormone replacement therapy for ≥ 3 months.
4. Patients who were able and willing to comply with the requirements of the protocol.
5. Patients who were able to swallow capsules.
6. Patients who were able to understand and sign the written informed consent to participate in the study.

Exclusion Criteria

Patients were ineligible for enrollment into the study if they met any of the following criteria:

1. Symptomatic cholelithiasis.
2. Received pituitary radiotherapy within 10 years prior to screening.
3. Underwent pituitary surgery within the prior 6 months.
4. High-risk pattern of pituitary tumor location on pituitary magnetic resonance imaging (MRI).
5. Clinically significant gastrointestinal, renal, or hepatic disease as determined by the Principal Investigator. Conditions that could significantly affect gastric acidity or emptying would typically exclude patients (e.g., bariatric surgery). Current use (within 1 month) of proton-pump inhibitors (PPIs) and current chronic use of histamine 2 receptor-antagonists excluded patients.

6. Known allergy or hypersensitivity to any of the test compounds or materials.
7. Life expectancy of less than 2 years.
8. Known uncontrolled diabetes defined as having a fasting glucose > 150 mg/dL (8.3 mmol/L) or hemoglobin A_{1c} (HbA_{1c}) ≥ 8% (patients could be rescreened after diabetes was brought under adequate control); for Afro-Caribbeans, fructosamine (marker of glucose tolerance) level of > 288 mmol/L.
9. Known defects in visual fields due to optic chiasmal compression or other neurological signs, related to the pituitary tumor mass. Patients with long-standing (> 12 months), fixed, minor defects were to be considered on a case-by-case basis after consultation with the Medical Monitor.
10. Active, clinically significant cardiac disease, including sustained arrhythmia, at time of screening.
11. History of unstable angina or acute myocardial infarction within the three months preceding study screening.
12. Female patients who were pregnant or lactating.
13. Female patients who were of childbearing potential with a positive pregnancy test at screening or baseline or who were not practicing an acceptable method for birth control. Acceptable methods included intrauterine devices, or mechanical methods (e.g., vaginal diaphragm, vaginal sponge, or condom with spermicidal jelly), sexual abstinence, or a vasectomized partner. Contraception using oral contraceptives was not permitted. Women could be surgically sterile or at least 1 year post-last menstrual period.
14. Known history of immunocompromise, including a positive human immunodeficiency virus (HIV) test result (enzyme-linked immunosorbent assay [ELISA] and Western blot).
15. Underwent major surgery/surgical therapy for any cause within 4 weeks prior to enrollment.
16. Known hypothyroidism or hypocortisolism not adequately treated with a stable dose of thyroid or steroid hormone replacement therapy for ≥ 3 months.
17. Known history of alcohol or drug abuse.
18. Any condition that could jeopardize study participation (e.g., clinically significant abnormal screening clinical or laboratory finding during screening), interpretation of study results, or could impede the ability to obtain informed consent (e.g., mental condition).
19. Intake of an investigational drug within 30 days before patient inclusion in this study.
20. Current or recent (< 3 months) therapy with pegvisomant.
21. Current or recent (< 2 months) therapy with cabergoline.

Eligibility Criteria for the Extension Treatment Period

Patients were to be considered eligible to participate in the Extension Treatment Period if the following conditions were met after the CORE Treatment Period:

1. Patients had completed the full duration of the CORE Treatment Period and the End of Treatment visit according to the protocol.
2. Patients had levels of IGF-1 that were normalized, falling, or had returned to baseline levels documented during at least the prior 2 successive clinic visits, indicating that a therapeutic regimen had been reached.
3. Patients were not currently having study medication withheld for a study medication-related adverse event.
4. Patients did not have a clinically significant or unstable medical or surgical condition detected or worsen during the CORE Treatment Period, which would preclude safe participation and completion of the Extension Treatment Period.
5. Patients were willing and able to comply with the protocol requirements for the duration of the Extension Treatment Period.
6. Patients were able to understand and sign an additional written informed consent prior to entering the Extension Treatment Period.
7. On a case-by-case basis, after discussion and documentation between the Principal Investigator and Medical Monitor, patients with other safety and efficacy parameters could be entered into the Extension Treatment Period.

Reviewer comment: 1) While not a specific inclusion or exclusion criteria, patients on combination therapy, i.e. SSA and either a dopamine agonist or pegvisomant were allowed to participate in the trial. See section 6.1.2, Demographics for further details.
2) The Sandostatin LAR® label states that "In patients who have received pituitary irradiation, Sandostatin LAR Depot should be withdrawn yearly for approximately 8 weeks to assess disease activity…" It is not known if CH-ACM-01 patients with history of pituitary irradiation were withdrawn from therapy regularly to confirm activity of disease.
3) A washout period in these already biochemically controlled patients would have allowed for confirmation of active disease in this patient population. However, this was not done.
The inclusion, exclusion and withdrawal criteria are all otherwise reasonable.

Criteria for Drug Withdrawal

Patients could withdraw from the study at any time for any reason without prejudice to further treatment. Similarly, an Investigator could withdraw a patient if it was determined that continuing the study would result in a significant safety risk to the patient. Patients who did withdraw from receiving study treatment could still have agreed to further safety follow-up.

Patient withdrawal could occur for any of the following reasons:

1. Request of regulatory agency, or sponsor, or primary care physician, or Investigator;

2. Patient withdrew consent;
3. Adverse event;
4. Patient was unwilling or unable to continue the study or was lost to follow-up;
5. Patient was non-compliant with study procedures/study protocol;
6. Investigator decided that withdrawal from the study was in the best interest of the patient;
7. Patient needed medication not allowed in the protocol; or
8. Any clinically significant change in the patient's medical condition.
9. Pregnancy
10. Death

Chiasma also reserved the right to discontinue the study at any time and for any reason. The reasons for termination included but, were not limited to:

1. Inefficacy of the study medication
2. Occurrence of adverse events unknown to date in respect of their nature, severity, and duration, or the unexpected incidence of known adverse events; or
3. Medical or ethical reasons affecting the continued performance of the study.

Regulatory authorities also had the right to terminate the study at any time and for any reason. A patient who withdrew from the study could be replaced on a case-by-case basis.

Reviewer comment: No patient who prematurely withdrew was replaced.

Protocol Amendments

Over the course of the study Chiasma put forth five amendments. Some amendments were country specific; however, the majority were applied globally. Described below are global amendments of high relevance.

Original protocol (Protocol Version 1.2) was finalized on June 30, 2011. CH-ACM-01 was initiated on March 13, 2012 and completed on May 30, 2014.

Amendment 2 (Protocol Version 3.0) was finalized on May 22, 2012:

- Added a six-month Extension Treatment Period as an option to eligible patients and specified eligibility criteria
- Clarified the time of study visits so that the dose escalation phase and fixed dose phase of the CORE treatment period had a total duration of at least seven months
- Specified that the primary efficacy endpoint and analysis pertained to the CORE treatment period

Amendment 4 (Protocol Version 6.0) was finalized on December 6, 2013:

- Included modifications to study endpoints and response categories to allow more educated and informative data interpretation (some of which were requested by FDA). Changes were in line with the statistical analysis plan dated October 9, 2013.

Reviewer comment: The protocols submitted up to the time of study start indicated that the primary efficacy endpoint was "IGF-1 concentration at the completion of the treatment period". It was not until October 21, 2013 with submission of the statistical analysis plan that the primary efficacy endpoint was defined as IGF-1 and GH as a measure of response; and, response was defined as IGF-1 < 1.3 x ULN adjusted for age and sex and GH < 2.5 ng/mL. It is curious that CH-ACM-01 was over nearly completed when the definition of response was clarified in the protocol.

Special Safety Monitoring

None.

Pre-Specified Analysis Plan

There were separate statistical analysis plans (SAP) for the CORE Treatment Period and the Extension Treatment Period (SAP version 1.0 October 9, 2013 and version 1.0 June 23, 2014, respectively). Please also refer to the full statistical review by Dr. Anna Kettermann.

Key points to consider

- Patients were expected to have varying numbers of visits during the Dose Escalation Phase as well as the overall CORE Treatment Period.
- The duration that each patient would be exposed to each dose varied.
- Visits generally occurred every two weeks during the Dose Escalation Phase and monthly during the Fixed Dose Phase.
- For the analysis, summaries over time were performed because of the variability in therapy duration per patient.

Summaries over time by **Duration of Exposure**

To summarize data over time, Chiasma implemented visit windows based on the study day of the visit relative to the date the patient received the first dose of study drug. This approach was based on cumulative duration of exposure to study drug (i.e. Month 1, Month 2, etc.), irrespective of study treatment period or study visit label (e.g. TA1, TA2, TB1 etc.) Each patient was mapped to a specific month using the following algorithm:

Treatment Duration	**Target Day**	**Range**
Screening	Not Applicable	Not Applicable

Baseline	Not Applicable	Not Applicable
Visit TA1	0	0-0
1 Month	30	1-45
2 Months	61	46-75
3 Months	91	76-106
4 Months	122	107-137
5 Months	152	138-167
6 Months	183	168-198
7 Months	213	199-229
8[c] Months	243	230-258
End of Treatment[d]		

Source: Sponsor's CSR, pg 74.

During the Dose Escalation Phase, if a patient had multiple scheduled visits in a range, the visit closest to the target date was identified as the visit for that month for statistical summaries. Per Chiasma, this approach was expected to facilitate the assessment of safety as cumulative exposure to study drug increases, and was used to summarize both safety and efficacy data.

Summaries over **Time by Visit**

Efficacy data was also to be summarized for –

CORE Treatment Period
- Screening visit
- Baseline visit
- Visit TA1 (day 0)
- End of the dose escalation phase
- Beginning of fixed dose phase (TB1)
- End of fixed dose phase

Extension Treatment Period
- TE1
- TE2
- TE3
- End of Extension period
- Follow-up visit

Determination of Sample Size

At least 150 evaluable patients were to be enrolled in this study. While the sample size was considered to be adequate to assess safety and efficacy, inferential statistics were not used to test for efficacy results for significance or non-inferiority.

Chiasma determined that a clinically relevant response rate would be 50% based on expert opinions from the United States and Europe. With a sample size of 150, an exact 95% confidence interval (CI) would be ± 7 — 9%; therefore, at a response rate of 50% the 95% CI would be 42% - 58%.

Reviewer comment: The number of patients does not meet the ICH guidelines for exposure. However, Acromegaly is an orphan disease and the number of patients was agreed upon with the Division at the End-of Phase 2 (EoP2) meeting.

Analysis populations

Chiasma specified two sets of analysis populations including one set for the CORE phase analyses and one set for the extension treatment period.

CORE

1. Modified Intention-to-treat (mITT) Population: all enrolled (eligible and completed visit TA1) patients who received any amount of the study drug and who had at least one IGF-1 or GH assessment post first dose with OOA.

2. Per Protocol (PP) Population: subset of patients from the mITT population who had no eligibility criteria violations and/or no major protocol violations throughout the CORE Treatment Period.

3. Fixed-Dose (FD) Population: subset of patients from the mITT population who entered the Fixed Dose Phase of the CORE Treatment Period.

4. Intention to Treat (ITT) Population: all patients who enrolled in the study. This population was to be used in a sensitivity analysis for the primary endpoint in case there was a difference between the mITT and the ITT populations.

5. Safety Population: This population included all patients enrolled in the study that received any amount of the study drug and was used to generate summaries of safety data.

EXTENSION

1. Extension Intention-to-Treat (EXT-ITT) Population: This population included all patients who entered the Extension Treatment Period and received any amount of study drug during the Extension Treatment Period.

- Within the EXT-ITT Population, 2 subgroups were defined: responders at EXT-baseline and non-responders at EXT-baseline. All analysis using the EXT-ITT Population were performed by EXT-baseline response subgroups and for all EXT-ITT.

2. mITT Population: This population included all enrolled patients (i.e., patient was found

eligible and completed TA1) who receive any amount of study drug and who had at least one post-baseline efficacy assessment, as defined in the analyses for CORE Treatment Period, with n=151.

The definition for safety population in the Extension phase is the same as that used for the CORE phase.

Efficacy Analyses in the CORE Treatment Period (source: Sponsor's CSR pgs 63-66)

Primary efficacy endpoint
Concentrations of IGF-1 and mean integrated GH over 2 hours at the end of the CORE phase as a measure of response in the mITT population. Response was defined as IGF-1 <1.3x upper limit of normal (ULN) adjusted for age and sex and integrated GH levels over 2 hours < 2.5 ng/mL.

In patients who discontinued the study drug for any reason, the last concentration of IGF-1 and GH recorded for that patient was imputed as the End of Treatment concentration (last observation carried forward, LOCF).

However, based on FDA feedback (February 20, 2014), an additional analysis of the primary endpoint was performed using the ITT population and imputation method where all patients who were prematurely withdrawn were treated as non-responders, i.e. non-responder imputation.

Sensitivity analyses were also performed in the mITT population using a multiple imputation approach where missing data were to be imputed using the Markov chain Monte Carlo (MCMC) method. Sensitivity analyses were also performed in the ITT population.

Mean integrated growth hormone concentration was calculated from five samples taken over 2 hours beginning two hours after study drug dosing. If one or two samples were missing, the mean integrated growth hormone concentration was calculated from 4 or 3 samples, respectively. If more than 2 samples were missing, the mean integrated growth hormone concentration was not calculated and was considered missing. (page 42-43, clinical study protocol; page 11 statistical analysis plan)

Since IGF-1 levels change over days as opposed to hours, only the day and not the time of collection was specified in the protocol.

Neither the GH or IGF-1 assay was modified or changed during the study.

Reviewer comment: The definition of a responder as described above was not submitted to the FDA until October 2013, which is at least 18 months after study initiation. The medical literature consistently reports that one of the goals of treatment is normalization of IGF-1. Thus, if a patient were to have a confirmed level of IGF-1 of 1.3 x ULN, intensification of medical

treatment would be indicated. It is not clear why IGF-1 < 1.3 x ULN was chosen (please also see my comment below starting at the bottom of page 41).

The timing of the assessment of IGF-1 is appropriate. However, given the lack of PD data submitted with this application, it is not clear that GH measurements between two-four hours post dose is appropriate. The median T_{max} is 1.67 – 2.5 hours, thus GH levels were drawn near the time of maximal concentrations of octreotide, which might overestimate the effect of MYCAPSSA on GH. Please see Figure 2, which shows that there could be several hours during which GH rises while octreotide levels are low.

Secondary Efficacy Endpoints

1. Proportion of patients with the following IGF-1 and GH values at baseline and at the end of the CORE Treatment Period:

    - IGF-1 < 1.3 times ULN and GH < 5.0 ng/mL;
    - IGF-1 < 1.3 times ULN and GH < 1.0 ng/mL;
    - IGF-1 ≤ 1.0 times ULN and GH < 5.0 ng/mL;
    - IGF-1 ≤ 1.0 times ULN and GH < 2.5 ng/mL;
    - IGF-1 ≤ 1.0 times ULN and GH < 1.0 ng/mL;
    - IGF-1 < 1.3 times ULN;
    - IGF-1 ≤ 1.0 times ULN;
    - GH < 5.0 ng/mL;
    - GH < 2.5 ng/mL;
    - GH < 1.0 ng/mL;
    - IGF-1 ≥ 1.3 times ULN and GH < 2.5 ng/mL;
    - IGF-1 < 1.3 times ULN and GH ≥ 2.5 ng/mL; and
    - IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL.

2. Maintenance of IGF-1 response during the Fixed Dose Phase (CORE) — Proportion of patients with IGF-1 levels (adjusted for age) < 1.3 times ULN at the end of the CORE Treatment Period who also had IGF-1 levels (adjusted for age) < 1.3 times ULN at the first assessment in the Fixed Dose Phase.
3. Maintenance of IGF-1 and GH response during the Fixed Dose Phase (CORE) — Proportion of responders (IGF-1 levels [adjusted for age] < 1.3 times ULN and integrated GH < 2.5 ng/mL) at the end of the CORE Treatment Period who also had IGF-1 levels (adjusted for age) < 1.3 times ULN and GH < 2.5 ng/mL at the first assessment in the Fixed Dose Phase.

The exploratory efficacy endpoints were:

1. Shifts in response categories from baseline to the end of the CORE Treatment Period for the mITT Population, PP Population, and FD Population (shift from first assessment at the beginning of the Fixed Dose Phase) were to be summarized for the primary endpoint and all additional categories listed as secondary endpoints.
2. Treatment satisfaction as measured by the TSQM.

   Per Chiasma, the TSQM is a validated patient reported outcome measure consisting of 14 multiple-choice items. The questionnaire provides four scale scores, each focusing on a different domain by using selected questions: effectiveness, side effects, convenience, and overall satisfaction. Five supplemental (non-validated) questions were added to capture the incidence and bothersomeness of acromegaly symptoms (and recurrence towards the end of the injection cycle) and medication complications, and overall satisfaction on MYCAPSSA in comparison to previous treatments.
3. The number and percentage of patients (mITT Population) who required reversion to parenteral therapy (rescue); the time to rescue therapy was to be explored.
4. The number and percentage of patients who achieved a sustained IGF-1 response, defined as IGF-1 < 1.3 times ULN for at least the last 2 successive visits (end of Fixed Dose phase and the previous visit).

Baseline Biochemical Classification (source: sponsor's CSR pgs 77-78)

Each enrolled patient was classified as one of the following based on the patient's IGF-1 and GH levels at the baseline visit:

Complete responder (IGF-1 < 1 times ULN and GH < 2.5 ng/mL)
Partial responder (1< IGF-1 < 1.3 times ULN and GH <2.5 ng/mL)
IGF-1 responder only (IGF-1 < 1.3 times ULN and GH ≥ 2.5 ng/mL)
GH only responder (IGF-1 < 1.3 times ULN and GH < 2.5 ng/mL)
Non-responder (IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL)

These categories were further re-defined as follows:

Responder (IGF-1 < 1.3 times ULN and GH < 2.5 ng/mL)
Complete responder (IGF-1 ≤ 1 times ULN and GH < 2.5 ng/mL)
Partial responder (1 < IGF-1< 1.3 times ULN and GH <2.5 ng/mL)

Non-responder (IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL)
GH non-responder (GH ≥ 2.5 ng/mL)
IGF-1 non-responder (IGF-1 ≥ 1.3 times ULN); or
IGF-1 and GH non-responder (IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL)

Reviewer comment: It is noted that Chiasma defined "Responder" for the purposes of the efficacy analysis as IGF-1 < 1.3 times ULN and GH < 2.5 ng/mL. The GH levels for definition of response are overall the same and will not be discussed further. However, patients who were

considered complete responders on SSA therapy at baseline could still be considered a "Responder" in CH-ACM-01 even if their IGF-1 levels rose from ≤ 1 times ULN to < 1.3 x ULN, *i.e. the patient could go from being a complete responder at baseline to a partial responder at end of treatment and still be a considered a responder for the primary efficacy analysis. This is a concern if the trend in IGF-1 levels is to rise over the course of the study in which case, the data would need to strongly support stabilization of IGF-1 levels for an appropriate length of time.*

Chiasma reported that they wanted to use an IGF-1 level of 1.3 x ULN because of inter- and intra -assay variability. However, given that patients were getting labs drawn at the same center throughout the trial and the IGF-1 assay did not change throughout the trial, the level of 1.3 x ULN as a measurement of effectiveness is not clear. The medical literature consistently states that the goals of therapy in acromegaly include achievement of an age- and sex-adjusted normal IGF-1 [8,9].

Prior and Concomitant Medications

All medications taken within 30 days of the screening visit through the day of first dose of the study drug for the treatment of acromegaly were recorded, including prior injectable SSA.

In addition, all other prior and concomitant medications were recorded at each visit.

Regarding record of when medications were started and/or stopped, the following rule was implemented: If only the year was specified for start and stop dates of medications, January 1 was to be imputed for analysis purposes. If only the month and year were provided, the 1st of the specified month was to be imputed. Medications with missing start or stop dates were to be reviewed prior to database lock to determine whether the medication was to be considered as prior or concomitant.

6 Review of Efficacy

Efficacy Summary

The primary objective of CH-ACM-01 was to determine the effect of MYCAPSSA therapy on IGF-1 and GH levels, as measures of response. The primary efficacy endpoint was defined as concentrations of IGF-1 and mean integrated GH over 2 hours at the end of the CORE treatment phase as a measure of response in the mITT population. Response was defined as IGF-1 <1.3x upper limit of normal (ULN) adjusted for age and sex and integrated GH levels over 2 hours < 2.5 ng/mL.

[8] Melmed et al. Guidelines for acromegaly management. An update. J Clin Endocrinol Metab, 2009
[9] Katznelson L et al. Acromegaly: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metabl, 2014

The efficacy results of CH-ACM-01 do not support the proposed indication: for long-term maintenance treatment in acromegaly patients (b) (4) At Baseline 88.4% of enrolled patients were defined as responders. By the end of the CORE phase, 52.9% (using worst case imputation analysis for missing data) were considered responders. This is a significant loss in response over the course of the trial considering that patients were well controlled on an approved therapy at the start of the trial. The loss of response during the trial makes it challenging to conclude that MYCAPSSA provides long-term maintenance. Review of the data showed a high drop-out rate during the CORE phase (53/155, 34.2%) with a large proportion of drop-outs because of adverse events (21/53, 39.6%) and treatment failure (24/53, 45.2%). Furthermore, there is a rather striking rise in IGF-1 levels and loss of biochemical control (Figures 5 and 6) in both non-responders and responders.

Within the review process, several issues with regard to study design and the pharmacologic properties of MYCAPSSA became apparent putting into question the efficacy results of CH-ACM-01. These concerns are detailed below.

Study Design

CH-ACM-01 was designed as a single-arm, open-label pivotal phase 3 trial with use of a historical control. The regulations require that phase 3 pivotal trials be adequate and well-controlled[10,11]. CH-ACM-01 has inherent design flaws characterized as follows:

1) The "single-arm, open-label" design does not easily allow differentiation of the effect of OOA from other influences, such as spontaneous change within the course of the disease, placebo effect, or biased observation.

- The lack of a washout period reduces assurance that the enrolled patient population has active acromegaly. Review of CH-ACM-01 study results (see section 7.7) identified three patients that had mild disease activity and/or adequate biochemical control such that re-initiation of therapy for acromegaly post CH-ACM-01 completion was not needed. In addition, there is one patient who did not have documented elevated IGF-1 levels or an abnormal OGTT at study entry whose disease might not have been active based on biochemical markers and symptom assessment. These data suggest that some patients in CH-ACM-01 might not have had active disease, which confounds our ability to accurately assess the efficacy of MYCAPSSA. The question of active disease is highlighted in a small study published by Vilar et al.[12] showing that long-term remission, of 12-18 months, after withdrawal of parenteral somatostatin analogue monotherapy in well-controlled patients without a history of radiotherapy occurred in

[10] Code of Federal Regulations, Title 21, section 314.126
[11] ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports E3, 1995.
[12] Vilar et al. Can we predict long-term remission after somatostatin analog withdrawal in patients with acromegaly? Results from a multicenter prospective trial. Endocrine, 2014

(4/20) 20% of patients. Furthermore, in the remaining 80% of patients, recurrence occurred at 3, 6 and 9 months, i.e. GH and IGF-1 levels did not rise within 8-12 weeks in several patients after discontinuation of injectable SSA. Thus, without a washout period it is possible that in addition to the aforementioned patients, several other CH-ACM-01 patients considered "responders" might have remained biochemically controlled even without MYCAPSSA therapy.

- Use of a historical control is best used in diseases with high and predictable mortality and in which the effect of the study drug is self-evident, e.g. general anesthetics. In this study, the effect of MYCAPSSA is clearly not self-evident as shown by a nearly 40% reduction in efficacy compared to baseline, significant increases in IGF-1 levels and the need to rely on subgroup data to show maintenance of IGF-1 (see discussion on Fixed Dose population, section 6.1.5 of this review).

Pharmacokinetic and Pharmacodynamic Data

As discussed in section 4.4, the pharmacokinetic profiles of Sandostatin IR and MYCAPSSA are not sufficiently similar and no pharmacodynamic data were collected for MYCAPSSA. The major clinical pharmacology issues identified within this application are:

- Sandostatin IR is a TID drug in the majority of patients; MYCAPSSA is proposed as a BID drug without PK/PD data to support BID dosing.
- Mean integrated GH levels were drawn two to four hours post dose, when MYCAPSSA reaches its maximum concentration (C_{max}) ; thus, not considering what happens to GH levels over time and at trough levels of MYCAPSSA.
- Loss of IGF-1 control occurred in both non-responders and responders without strong evidence that these levels stabilize over time.

Overall, the efficacy results of CH-ACM-01 are not robust and given the PK/PD deficiencies, possibly unreliable. To overcome the aforementioned deficiencies, a proper PK/PD study will need to be completed followed by a new phase 3 trial that incorporates a washout period to confirm active disease in acromegaly patients and a control population.

6.1 Indication

Chiasma proposes its oral somatostatin analog, MYCAPSSA, for long term maintenance treatment in acromegaly patients (b) (4) (b) (4)

6.1.1 Methods

Chiasma seeks to prove their claim for efficacy with a single-arm, open-label pivotal trial, CH-ACM-01. For further details on the study design, please refer to section 5.2 of this review.

6.1.2 Demographics

In CH-ACM-01, 88.4% of enrolled patients were Caucasian with the next largest race group categorized as "other" with 10.3% of patients; 87% were not Hispanic/Latino. Mean age was 54.2 ± 11.4 years and percentage of females and males was 56.8% and 43.2%.

Baseline disease characteristics are presented for all enrolled patients in the CORE and Extension phases in Tables 7 and 8.

Table 7. Baseline disease characteristics, all enrolled patients, CORE phase

Baseline Characteristic Category/Statistic	Total (N=155)
Duration of acromegaly, n (%)	
< 10 years	74 (47.7)
10 – < 20 years	53 (34.2)
≥ 20 years	28 (18.1)
Pituitary tumor characteristic, n (%)	
Microadenoma	51 (32.9)
Intrasellar macroadenoma	53 (34.2)
Extrasellar macroadenoma	46 (29.7)
Other	5 (3.2)
Previous treatments for acromegaly any time in the past, n (%)	
Surgery	121 (78.1)
Medication, other than somatostatin analogs	61 (39.4)
Radiation	13 (8.4)
Surgery followed by radiation	8 (5.2)
Radiation followed by surgery	1 (0.6)
Previous somatostatin analog treatment, n (%)	
Octreotide (sandostatin LAR)	97 (62.6)
10 mg, 20 mg every 4 weeks	64 (66.0% of all patients on sandostatin LAR)
30 mg, 40 mg, 60 mg every 3-4 weeks	33 (34.0% of all patients on sandostatin LAR)
Lanreotide (somatuline)	58 (37.4)
30 mg, 60 mg, 90 mg every 3-4 weeks	25 (43.1% of all patients on somatuline)
120 mg every 3-4 weeks [5]	33 (56.9% of all patients on somatuline)
Length of time receiving parenteral somatostatin analogs	
Mean (SD) (months)	70.1 (58.65)
< 1 year	21 (13.5)
1 – < 5 years	63 (40.6)
5 – < 10 years	37 (23.9)
≥ 10 years	34 (21.9)
Time from last injection to first dose of oral octreotide acetate (days)	
Mean (SD)	32.6 (9.44)
Median (P25, P75)	31.0 (29.0, 35.0)

Source: CSR Table 14, modified
Duration of acromegaly indicates from time of diagnosis, not symptom onset
"Other", three patients had both intrasellar and extrasellar macroadenoma; one patient, no information available; one patient conflicting MRI results

Reviewer comment: In the May 21, 2014 Pre-NDA minutes, the sponsor suggests that the study was designed to enroll patients who would not likely have spontaneous improvement, i.e. newly diagnosed patients. Table 7 does not imply that many patients had newly diagnosed disease.

Table 7. Baseline disease characteristics, all enrolled patients, CORE phase, continued.

Baseline Characteristic Category/Statistic	Total (N=155)
At least one acromegaly symptom based on the AIS, n (%)	
Headache	64 (41.3)
Perspiration	65 (41.9)
Asthenia	68 (43.9)
Swelling of extremities	58 (37.4)
Joint pain	87 (56.1)
At least 1 symptom	125 (80.6%)
At least 2 symptoms	95 (61.3%)
At least 3 symptoms	67 (43.2%)
IGF-1 level (× ULN)	
Mean (SD)	0.94 (0.250)
Median (P25, P75)	0.89 (0.76, 1.07)
Min, Max	0.38, 1.91
Mean 2-hour GH level	
Mean (SD)	0.93 (0.716)
Median (P25, P75)	0.77 (0.44, 1.23)
Min, Max	0.07, 3.69
Baseline responder status, n (%)	
Responder (IGF-1<1.3*ULN, GH<2.5 ng/mL)	137 (88.4)
Complete responders (IGF-1≤1*ULN & GH<2.5 ng/mL)	95 (61.3)
Partial responder (1<IGF-1<1.3*ULN & GH<2.5 ng/mL)	42 (27.1)
Non-Responders (IGF-1≥1.3*ULN and/or GH≥2.5 ng/mL)	18 (11.6)
GH non-responders (GH≥2.5 ng/mL)	7 (4.5)
IGF-1 non-responders (IGF-1≥1.3*ULN)	13 (8.4)
IGF-1 and GH non-responders (IGF-1≥1.3*ULN and GH ≥2.5 ng/mL)	2 (1.3)

Source: CSR Table 14 continued
AIS, acromegaly index of severity; GH, growth hormone ng/mL

At screening, all enrolled patients met the criteria for responder. However, by the baseline visit (on average two weeks from last SSA dose), only 88.4% of patients met the criteria for responder.

Reviewer comment: As noted in section 5.3, page 29, Screening and Baseline labs were not completed at a pre-specified number of days after either visit, which might have accounted for the difference in the percentage of responders at the Screening and Baseline visits.

Although not provided in Table 7, 17 patients were receiving combination therapy for acromegaly. Sixteen patients were taking a dopamine agonist in addition to their SSA; and one patient took pegvisomant in addition to SSA therapy.

Table 8. Baseline disease characteristics, all enrolled patients, Extension phase

Baseline Characteristic Category/Statistic	Total (N=88)
Previous somatostatin analog treatment, n (%)	
Octreotide (sandostatin LAR)	49 (55.7)
10 mg, 20 mg every 4 weeks	36 (73.5% of all patients on sandostatin LAR)
30 mg, 40 mg every 3-4 weeks	13 (26.5% of all patients on sandostatin LAR)
Lanreotide (somatuline)	39 (44.3)
30 mg, 60 mg, 90 mg every 3-4 weeks	20 (51.3% of all patients on somatuline)
120 mg every 4 weeks	19 (48.7% of all patients on somatuline)
Acromegaly Symptoms based on the AIS, n (%)	
At least 1 symptom	69 (78.4)
At least 2 symptoms	54 (61.4)
At least 3 symptoms	38 (43.2)
IGF-1 level (× of ULN)	
Mean (SD)	0.86 (0.210)
Median (P25, P75)	0.86 (0.73, 0.98)
Min, Max	0.38, 1.67
Mean 2-hour GH level	
Mean (SD)	0.96 (0.686)
Median (P25, P75)	0.77 (0.48, 1.25)
Min, Max	0.11, 3.69
Baseline responder status, n (%)	
Responder (IGF-1<1.3*ULN, GH<2.5 ng/mL)	84 (95.5)
Complete responders (IGF-1≤1*ULN & GH<2.5 ng/mL)	67 (76.1)
Partial responder (1<IGF-1<1.3*ULN & GH<2.5 ng/mL)	17 (19.3)
Non-Responders (IGF-1≥1.3*ULN and/or GH≥2.5 ng/mL)	4 (4.5)
GH non-responders (GH≥2.5 ng/mL)	3 (3.4)
IGF-1 non-responders (IGF-1≥1.3*ULN)	2 (2.3)
IGF-1 and GH non-responders (IGF-1≥1.3*ULN and GH ≥2.5 ng/mL)	1 (1.1)

Source: CSR Table 16
AIS, acromegaly index of severity; GH, growth hormone ng/mL

Reviewer comment: Review of the baseline characteristics of those that entered the CORE phase versus those that continued into the Extension treated shows that the majority of characteristics are similar. While this is purely observational, it appears that a greater proportion of patients electing to continue into the extension were "responders" at baseline and, specifically, "complete responders".

Although the impact may be questionable, Chiasma should have reported that patients were allowed to be on combination therapy for acromegaly. The protocol and clinical study report give the impression that enrolled patients were on SSA monotherapy.

Per the inclusion criteria, patients with acromegaly were defined as"… having documented evidence of GH-secreting pituitary tumor that was abnormally responsive to glucose ….". In an information request, we asked Chiasma to explain why all patients did not have an oral glucose

tolerance (OGTT) to confirm a GH-secreting pituitary tumor that was abnormally responsive to glucose. Chiasma responded that either an OGTT or IGF-1 provide evidence of GH-secreting pituitary tumor as this is the current diagnostic standard for acromegaly as presented in the AACE acromegaly guidelines 2011.

Table 9 shows that 132/155 (85.2%) had a documented OGTT test and 128 patients (82.6%) had a documented IGF-1 to confirm acromegaly diagnosis. Eight patients did not have documented evidence of either OGTT or IGF-1 levels to confirm diagnosis.

Table 9. Cross tabulation of oral glucose tolerance (OGTT) and IGF-1 confirmation of diagnosis in all enrolled patients in the CH-ACM-01 study

Documented as diagnosed by OGTT (All Enrolled Patients, N=155)	Documented as diagnosed by IGF-1 (All Enrolled Patients, N=155)		
	Yes	No/Not recorded	Total
Yes	113 (72.9%)	19 (12.3%)	132 (85.2%)
No/Not recorded	15 (9.7%)	8 (5.1%)	23 (14.8%)
Total	128 (82.6%)	27 (17.4%)	155 (100%)

Source: Chiasma information request response received by FDA August 25, 2015

In the eight patients without OGTT or IGF-1 confirmation, a question arises as to whether these patients had active disease. Of the eight patients, three were non-responders (IGF-1 ≥ 1.3x ULN or GH ≥ 2.5 ng/mL) to MYCAPSSA suggesting active disease. Of the remaining five patients, three patients had dose titration to 80 mg and one to 60 mg implying a need to control increasing IGF-1 levels and thus active disease. In addition, these four patients that required dose titration also had active acromegaly symptoms with an acromegaly index of severity (AIS) score of at least two at the Screening, Baseline or TA1 visits.

The fifth patient (b) (6) remained on a dose of 40 mg and had an (AIS) score of "zero" at screening and baseline and "one" at visit TA1, implying milder or possibly inactive disease. This patient's reported duration of acromegaly was ≥ 20 years and it is not clear based on the provided data whether he/she had active disease at the time of enrollment. Per Chiasma, the local investigator assessed this patient as having a "confirmed diagnosis" of acromegaly. However, a confirmed diagnosis and active disease are two different issues for an efficacy study. The lack of OGTT and IGF-1 in these patients was not considered a protocol deviation.

Reviewer comment: Patient (b) (6) had a screening GH and IGF-1level of 0.64 ng/mL and 0.46 x ULN, respectively. At visit TB6, the patient (b) (6) had a GH and IGF-1 level of 0.15 ng/mL and 0.51 xULN, respectively. Given that this patient did not have a documented elevated IGF-1 level or OGTT as well as the fact that GH and IGF-1 levels were controlled at screening and at End of Treatment, it is possible that this patient did not have active disease. A washout period built in to the study design would have helped to eliminate uncertainty regarding whether or not enrolled patients had active disease.

Table 10 provides a summary of major medical disorders in the trial population.

Table 10. Major medical disorders, all enrolled patients

Disorder	Proportion of Patients (N = 155) n (%)
Hypertension	82 (52.9)
Cholelithiasis	39 (25.2)
Goiter	31 (20.0)
Type 2 diabetes mellitus	29 (18.7)
Hypothyroidism	26 (16.8)
Hypopituitarism	13 (8.4)
Nephrolithiasis	13 (8.4)

Source: CSR, page 108

The most common prior surgical procedure was cholecystectomy in 31 (20%) patients.

Of the 155 enrolled patients, 145 were taking concomitant medications. The most common concomitant medications used by ≥ 20% of the study population were:

- Thyroid hormones – 53 (34.2%)
- ACE inhibitors, plain - 44 (28.4%)
- Anilides – 35 (22.6%)
- HMG-CoA reductase inhibitors - 34 (21.9%)
- Glucocorticoids – 33 (21.3%)
- Biguanides – 31 (20.0%)

The majority of patients taking glucocorticoids were adrenally insufficient and taking physiologic replacement doses. Four patients required one glucocorticoid injection for diarrhea, vomiting and osteoarthritis (n=2), respectively. One patient required five days of intravenous glucocorticoids for acute sciatica (patient ID (b) (6), SAE, described in section 7.3.2). A few patients were taking intranasal or inhaled steroids as well.

Estrogens are known to lower IGF-1 levels. Five patients were taking an estrogen containing medication.

Reviewer comment: It is unlikely that the glucocorticoid injections had an effect on GH levels. Similarly, high dose intravenous glucocorticoids might have suppressed GH levels temporarily but, in these cases, we expect GH levels to reverse fairly quickly. Review of the screening and end of treatment GH and IGF-1 levels in the patients taking estrogen showed that in three patients IGF-1 levels increased during the study and in two patients IGF-1 levels remained approximately the same. Thus, it is unlikely that use of estrogen had any significant impact on the efficacy results.

6.1.3 Subject Disposition

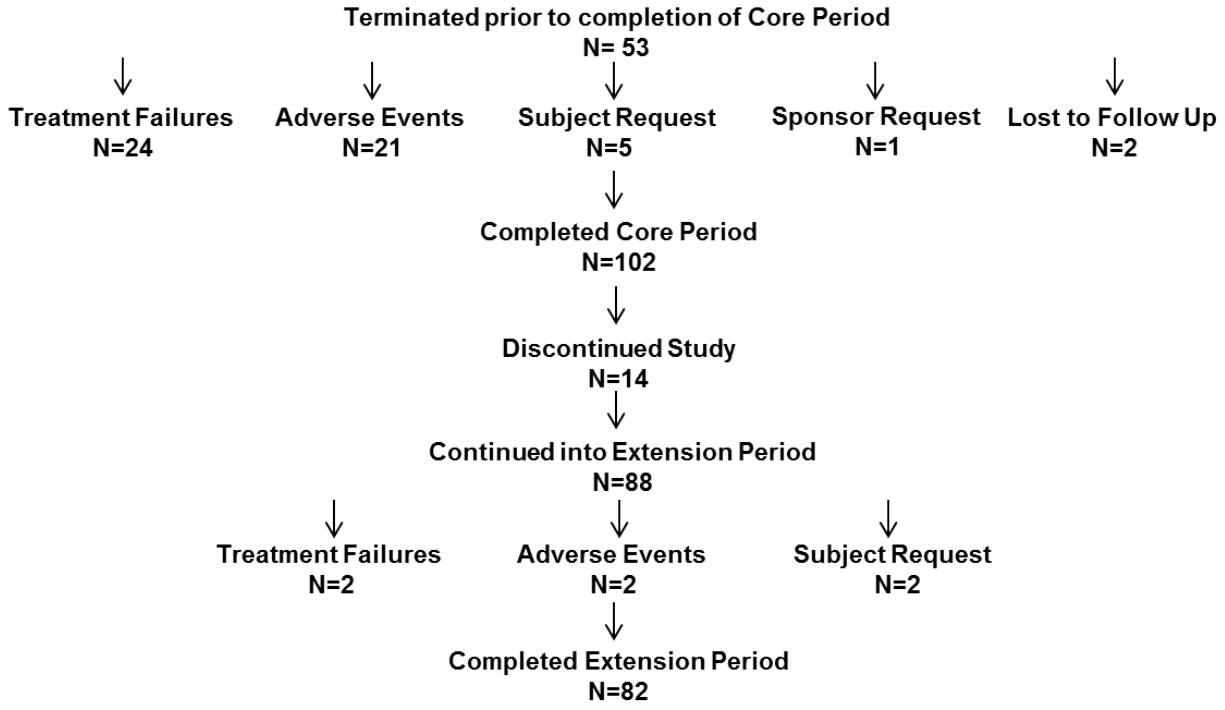
The CORE phase was completed by 102 patients (65.8%). Subject disposition through the CORE and Extension phases is detailed in Table 11 and Figure 4.

Table 11. Patient disposition, all enrolled patients, CORE phase

Category	Total n (%)
Screening	235
Failed Screening	80 (34.0)
-Did not meet eligibility criteria	69 (29.4)
-Patient request	8 (3.4)
-Non-compliance with protocol requirements	1 (0.4)
-Sponsor request	1 (0.4)
-Other	1 (0.4)
Enrolled	155
Completed CORE Treatment Period	102 (65.8)
Early terminated during the CORE Treatment Period	53 (34.2)
-Treatment failure	24 (15.5)
-Adverse event	21 (13.5)
-Patient request	5 (3.2)
-Lost to follow-up	2 (1.3)
-Sponsor request	1 (0.6)
Terminated prior to entry into Fixed Dose Phase	45 (29.0)
-Treatment failure	21 (13.5)
-Adverse event	16 (10.3)
-Patient request	5 (3.2)
-Lost to follow-up	2 (1.3)
-Sponsor request	1 (0.6)
Terminated during the Fixed Dose Phase	8 (5.2)
-Adverse event	5 (3.2)
-Treatment failure	3 (1.9)

Source: CSR, Table 8

Figure 4. Patient disposition throughout CORE and Extension phases



Source: Data from CSR, Tables 8 and 10

The ITT population included all 155 patients who were enrolled into this study. Four patients were excluded from the ITT population as they did not have an efficacy assessment post visit TA1. Therefore, Chiasma focused their efficacy results on the modified ITT (mITT) population. However, while they didn't have an efficacy assessment post visit TA1, three of these four patients who did not have a post TA1 efficacy visit dropped out because of adverse events.

(b) (6) – dyspepsia
- lost to follow-up
– abdominal pain, nausea, vomiting
– abdominal pain, flatulence, nausea

Dr. Anna Kettermann, FDA statistical reviewer, discusses the differences between the mITT and ITT population with regard to efficacy in her review.

Of the 102 patients who completed the CORE phase, 14 patients elected not to continue into the Extension treatment period. In an information request response, Chiasma reported that record of the reasons for not electing to proceed to the Extension was not required by protocol. However, in order to be eligible for the Extension, "Subjects have levels of IGF-1 that are normalized, falling or have returned to baseline levels documented during at least the prior two successive

clinic visits, indicating a therapeutic regimen had been reached" (section 4.3 protocol). Four of the 14 subjects had elevated IGF-1 on either one of the prior two successive visits, hence were not eligible to proceed into the Extension. These four patients were assigned a non-responder status for the CORE phase.

Detailed information on those subjects that prematurely terminated the trial is provided in section 7.3.3.

Protocol deviations

Table 12. Protocol deviations, all enrolled patients

Protocol Deviation	OOA (N = 155) n (%)
Any protocol deviation	45 (29)
Any inclusion criteria deviation	2 (1.3)
Any exclusion criteria deviation	7 (4.5)
Major protocol deviation	23 (14.8)
Other protocol deviation	13 (8.3)

Source: CSR, Tables 16.2.2.1 -3

The most common major protocol deviation (n=12/23, Table 12) was that the date of TB6/End of treatment visit was ≥ one day after date of last dose. Of these 12 patients, seven had only one day between their last dose and TB6/End of treatment GH and IGF-1 assessment; thus, these values were used in the mITT efficacy analysis. The remaining five patients had two or more days between their last dose and TB6/End of treatment GH and IGF-1 assessment, thus, for these patients the TB6/End of treatment values **were not used** and their last observation of GH and IGF-1 while taking MYCAPSSA was carried forward (LOCF). Please see my comments in section 6.1.5 regarding use of LOCF for missing data. Use of LOCF can overestimate the efficacy result.

The most common "other" protocol violation (n = 6/13) was use of a prohibited med, i.e. proton pump inhibitor (PPI) or H2 receptor antagonist (H2RA). Four of these six patients took PPI or H2RA for a short duration (1-4 days). The fifth patient took an H2RA for approximately 60 days during the trial; however, was a treatment failure and discontinued the study during the Fixed Dose phase. The sixth patient took a PPI for 1 month during the trial and completed the trial as a responder.

Two patients had "other" protocol deviations of concern. Patients (b) (6) and (b) (6) had their Baseline visit more than 56 days after their last SSA injection (82 and 56 days, respectively). These patients were both considered responders at their Baseline visit. While Chiasma reports that a three month carryover effect of injectable SSA therapy could be anticipated in patients, the fact that these two patients were still responding to SSA therapy at a delayed Baseline visit adds to the concern about patients not having active acromegaly during the trial.

As described on page 48, patients without documented acromegaly diagnosis by OGTT or IGF-1 levels were not considered to be protocol deviations.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint presents the proportion of responders in the mITT population at the End of Treatment. Response was defined as IGF-1 < 1.3 x ULN (adjusted for age and sex) and an integrated GH level over 2 hours < 2.5ng/mL.

The summary of responders at the End of Treatment is shown in Table 13. This analysis was conducted using the mITT population and the last observation carried forward (LOCF) method for missing data.

Table 13. Summary of responders at End of Treatment, mITT, LOCF, CORE phase

Category Statistic	Dose at the End of Treatment			Total (Primary Endpoint)
	OCT 20 + 20 (N=61)	OCT 40 + 20 (N=33)	OCT 40 + 40 (N=57)	(N=151)
Responders				
n	53	22	23	98
%	86.9	66.7	40.4	64.9
Exact 95% CI for %	83.0 – 98.1	48.2 – 82.0	27.6 – 54.2	58.4 – 74.2

Source: CSR, Table 20
mITT, modified Intention to Treat population; LOCF, last observation carried forward; OCT, oral octreotide acetate

Based on input from the FDA, Chiasma also performed the primary efficacy analysis on the ITT population using the worst-case imputation method in which all patients who prematurely withdrew from the study were considered non-responders (Table 14)

Table 14. Summary of responders at End of Treatment, ITT, CORE phase, worst-case imputation

Category Statistic	Dose at the End of Treatment			Total (Primary Endpoint)
	OCT 20 + 20 (N=65)	OCT 40 + 20 (N=33)	OCT 40 + 40 (N=57)	(N=155)
Responders				
n	48	19	15	82
%	73.8	57.6	26.3	52.9
Exact 95% CI for %	61.5 – 84.0	39.2 – 74.5	15.5 – 39.7	44.7 – 61.0

Source: CSR, Table 21
ITT, Intention to Treat population; Oct, oral octreotide acetate

Reviewer comment: The original statistical analysis plan Version 1.0, dated October 9, 2013, was submitted to IND 108163 October 21, 2013 and states in Section 6, page 20:

"*Based on a planned sample size of 150 subjects in the study, the observed efficacy response rate in subjects receiving Octreolin in the current study would have an exact 95% confidence interval of approximately ±7-9% (see table below). For example, an observed response rate of 50% on*

Octreolin would be clinically relevant and would yield an exact 95% confidence interval of 42% - 58%. The precision of this confidence interval would likely be acceptable from both a scientific and regulatory perspective."

While the calculated response rate matches the apriori response rate, we have concerns regarding the rising IGF-1 levels as well as the possibility that GH levels have been overestimated, thus falsely leading to a higher response rate. As will be detailed below, there is concern for continuing loss of IGF-1 control over time. Given the short CORE treatment period of seven months, we cannot conclude that this efficacy response rate represents "long term maintenance" as the proposed indication suggests.

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Fixed Dose (FD) Population

Chiasma presents several analyses regarding the FD population. The FD population consists of 110 patients who made it through the Dose Escalation phase of the study (2 – 5 months) and were able to enter the Fixed Dose phase (2 – 5 months). Eight patients terminated the study during the Fixed Dose phase. Five of the eight dropped out due to adverse events and three because of treatment failure (see section 7.3.3).

In the FD population, the proportion of responders was 87/110 or 79.1% (95% CI: 70.3 – 86.3) using LOCF for missing data.

Reviewer comment: The FD population is a subgroup of patients who were able to tolerate the drug and does not consider the 45 (29%) patients who dropped out due to adverse events or treatment failure in its assessment of efficacy. Chiasma considers this the "intended target population" for treatment with MYCAPSSA that is not confounded by early withdrawals. A few things to consider when interpreting the FD data:

1) Early withdrawals are not confounders and in this trial represent adverse events and treatment failures in response to MYCAPSSA therapy, which are important in assessing the overall efficacy of MYCAPSSA.

2) CH-ACM-01 was designed to include most patients with acromegaly who were biochemically controlled on injectable SSA therapy. While Chiasma states that the FD population is the "intended target population" in the real world, clinicians do not have a way of identifying which acromegaly patients will tolerate and/or respond to therapy.

3) The Fixed Dose phase was not a defined "fixed" time period within the trial. Since the dose escalation phase could take anywhere from 2-5 months and the total CORE period was not to be more than 7 months, the length of the fixed dose phase was different for each patient and could range from as little as two months (for a patient who did not reach their fixed dose until the 5 month mark) to five months (for a patient who reached their fixed dose by the 2 month mark). The indication for this drug includes the words "…long term maintenance"; however, some

portion of responders might have only been responding to a fixed dose for a period of two months. A fixed dose of two months or even three or four months does not imply long-term maintenance considering that the enrolled acromegaly patients had been requiring therapy for several years.

4) Analysis of the fixed dose data is exploratory at best.

Primary Efficacy Endpoint – Extension population

For completeness, a brief discussion of the efficacy data for the Extension population is provided here. The six month Extension period was voluntary. Please see Figure 4 for patient disposition in the Extension phase. Of 102 patients that completed the CORE phase, 88 elected to continue into the Extension phase. Of these 88, 74 were responders at the beginning of the Extension phase; thus 14 were non-responders. By the end of the Extension period, Chiasma reports that 69/88 (78.4%, 95% CI: 68.4 – 86.5) patients were responders using LOCF analysis for missing data (page 131, CSR). Six patients dropped out of the Extension period (Figure 4). Use of worst case imputation analysis for missing data shows that 66/88 patients were responders at the end of the Extension period. Please see Figure 10 in Appendix 3 as well.

Reviewer comment: The fact that 74 patients were responders at the beginning of the Extension and only 66 were responders by the end of the Extension (a 6 month period) imply there is continuing loss of efficacy, which confirms concern about lack of stabilization of biochemical control over time. These data confirm the need for better and adequate characterization of PK/PD data as discussed in section 4.4.

6.1.5 Analysis of Secondary Endpoints(s)

Data to inform each secondary endpoint is provided below.

Since the secondary endpoints focus on maintenance of effect, the discussion for section 6.1.9 regarding persistence and tolerance of effects will be presented here in section 6.1.5.

Secondary Efficacy Endpoints

1. Proportion of patients with various different measures of control by IGF-1 and GH values at baseline and at the end of the CORE phase (Table 15).

Table 15. IGF-1 and growth hormone suppression at End of Treatment compared to Baseline, mITT, CORE phase, LOCF

Response Category	Baseline n (%)	End of Treatment n (%)
mITT Population (N=151)		
IGF-1 < 1.3 times ULN and GH < 5.0 ng/mL	138 (91.4)	99 (65.6)
IGF-1 < 1.3 times ULN and GH < 1.0 ng/mL	95 (62.9)	80 (53.0)
IGF-1 ≤ 1.0 times ULN and GH < 5.0 ng/mL	96 (63.6)	54 (35.8)
IGF-1 ≤ 1.0 times ULN and GH < 2.5 ng/mL	93 (61.6)	54 (35.8)
IGF-1 ≤ 1.0 times ULN and GH < 1.0 ng/mL	65 (43.0)	48 (31.8)
IGF-1 < 1.3 times ULN	138 (91.4)	101 (66.9)
IGF-1 ≤ 1.0 times ULN	96 (63.6)	56 (37.1)
GH < 5.0 ng/mL*	151 (100.0)	147 (97.4)
GH < 2.5 ng/mL	145 (96.0)	143 (94.7)
GH < 1.0 ng/mL	100 (66.2)	117 (77.5)
IGF-1 ≥ 1.3 times ULN and GH < 2.5 ng/mL	11 (7.3)	45 (29.8)
IGF-1 < 1.3 times ULN and GH ≥ 2.5 ng/mL	4 (2.6)	1 (0.7)
IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL	2 (1.3)	3 (2.0)

Source: CSR, Table 27, modified
mITT, modified Intention to Treat; LOCF, last observation carried forward
*four patients had missing post-baseline assessments; therefore, End of Treatment (CORE) response not evaluable in these patients for all response categories.

The blue highlighted areas of Table 15 represent GH control from Baseline to End of Treatment. The data show that GH was well controlled on OOA, and some patients had improved GH control at End of Treatment compared to Baseline. Four patients had End of Treatment GH values ≥ 2.5 ng/mL and none had GH ≥ 5 ng/mL.

Reviewer comment: Again without the appropriate PK/PD assessment, the accuracy of the GH values is in question.

Unlike GH, IGF-1 values were less controlled on MYCAPSSA with several patients losing control from baseline (green highlighted rows, Table 15) to End of Treatment. Tables 16 and 17 display shifts in combined GH and IGF-1 response to therapy from Baseline to End of Treatment in the CORE phase treating missing data with LOCF and worst case imputation methods, respectively.

Table 16. Shift in IGF-1 and mean growth hormone response categories from Baseline to End of Treatment, mITT (N = 151), CORE phase, LOCF

Response Category	Baseline (N')	End of Treatment	
		Maintained/improved n (%)	Worse control n (%)
Complete Responder	93	48 (52)	45 (48)
Partial Responder	41	21 (51)	20 (49)
Non-responder	17	11 (65)	6 (35)
Total	**151**	**80 (53)**	**71 (47)**

Source: CSR, Table 30, modified
mITT, modified Intention to Treat; LOCF, last observation carried forward
Complete Responder = IGF-1 ≤ 1xULN & GH < 2.5 ng/mL
Partial Responder = 1<IGF-1<1.3xULN & GH < 2.5 ng/mL
% = n/N'

Table 17. Shift in IGF-1 and growth hormone response categories from Baseline to End of Treatment, mITT (N=151), CORE phase, worst case imputation

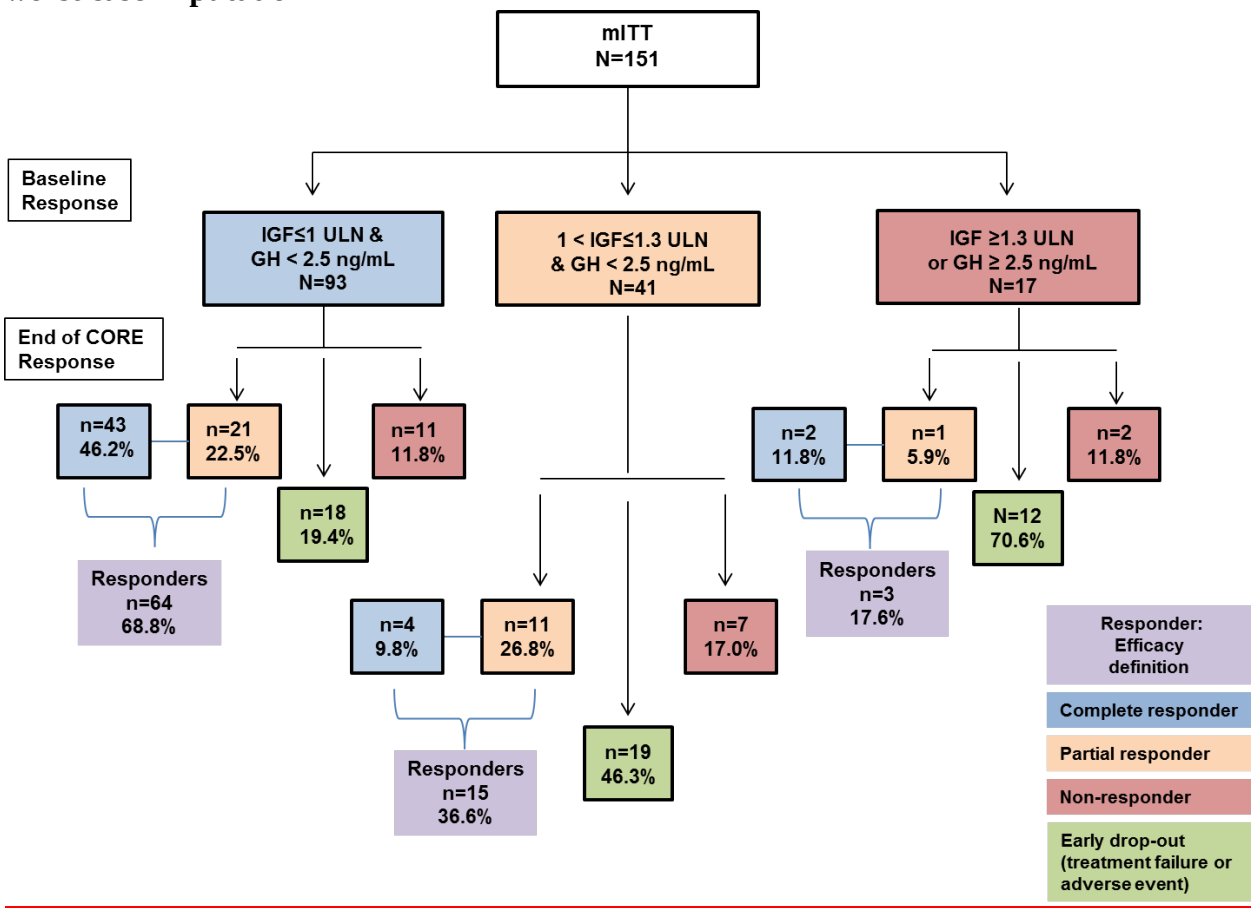
Response Category	Baseline (N')	End of Treatment		
		Maintained/improved n (%)	Worse control n (%)	Early drop-out
Complete Responder	93	43 (46.2)	32* (34.4)	18 (19.4)
Partial Responder	41	15 (36.6)	7 (17.0)	19 (46.3)
Non-responder	17	4^ (23.5)	1 (5.9)	12 (70.6)
Total	**151**	**62 (41.0)**	**40 (26.5)**	**49 (32.5)**

Source: Information request response received by FDA February 24, 2016, Table 19, modified
mITT, modified Intention to Treat; LOCF, last observation carried forward
% = n/N'
Complete Responder = IGF-1 ≤ 1xULN & GH < 2.5 ng/mL
Partial Responder = 1<IGF-1<1.3xULN & GH < 2.5 ng/mL
* Of the 32 baseline complete responders that lost control, 21 patients shifted to partial response at end of treatment and 11 became non-responders
^Three of four patients in the non-responder category became responders according to Chiasma's definition for efficacy

Reviewer comment: The shift tables are very helpful in understanding what happened to patients over time and are an excellent example of how the LOCF method for missing data can lead to misinterpretation of study results. As seen above, using LOCF it appears as if 53% of the population maintained or improved their response status with MYCAPSSA therapy compared to baseline. However, LOCF uses last on treatment values and carries them forward for any patient that dropped out; thus a patient who is "responding" to therapy but drops out early due to an adverse event gets counted in the "maintained/improved" category whereas in Table 17 these patients are counted in the early drop-out category. In this trial the majority of patients dropped out because of treatment failure or adverse events. A patient who maintained/improved their IGF-1 and GH response, but, who also dropped out because of an adverse event should not,

in this reviewer's opinion, be considered a responder and counted in the maintained/improved category. Figure 5 details even further how patients faired from Baseline to End of Treatment in the CORE phase.

Figure 5. Biochemical response from Baseline to End of Treatment, mITT, CORE phase, worst case imputation



Source: Data from information request response received by FDA February 24, 2016, Table 19
mITT, modified Intention to Treat
Responder definition in primary efficacy analysis includes complete AND partial responders

Similar to Figure 5, Figure 10 in Appendix 3 shows detailed data on patient disposition in the CORE and Extension phase. Effectively, Figure 10 shows that more patients dropped out by the end of the Extension phase. Patients who dropped out represent all responder categories, i.e. several complete and partial responders in addition to non-responders dropped out of the study.

Reviewer comment: Incorporating data from Table 17 and Figure 5 we can conclude, in the CORE phase:

a. Approximately 40% of patients who completed the study maintain or improve control in the

CORE period

b. Approximately 14% of patients lose control but remain biochemically controlled for purposes of the efficacy analysis (i.e. complete responder becomes a partial responder)

c. Approximately 28% lose control and prematurely terminate the study or become non-responders

d. Approximately 14% prematurely terminate the study because of adverse events.

e. The remaining patients (~4%) were lost to follow up or terminated the study because of personal or sponsor request.

2. Maintenance of IGF-1 response during the Fixed Dose Phase (CORE) — Proportion of patients with IGF-1 levels (adjusted for age) < 1.3 times ULN at the end of the CORE Treatment Period who also had IGF-1 levels (adjusted for age) < 1.3 times ULN at the first assessment in the **Fixed Dose** Phase.

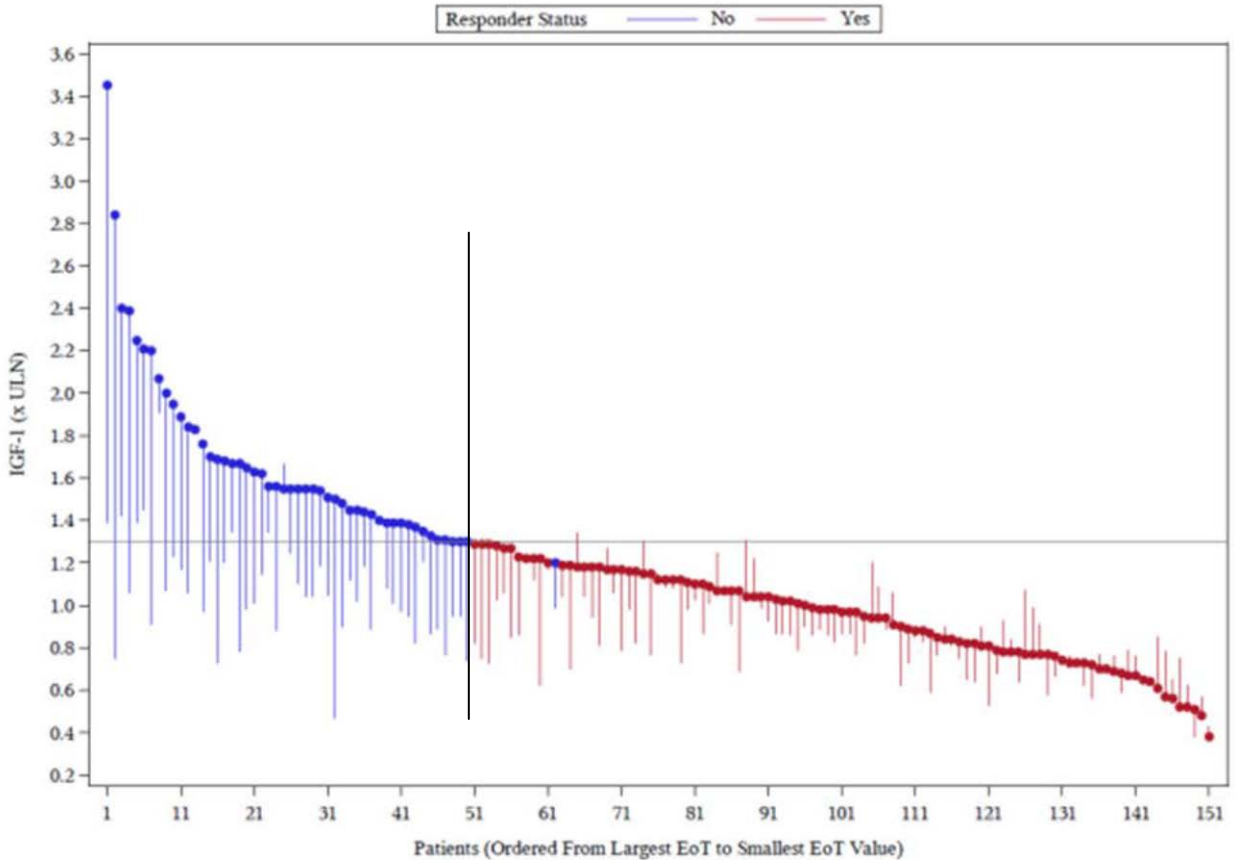
Table 18. IGF-1 response in Responders at end of Fixed dose/CORE phase compared to beginning of Fixed Dose phase, CORE phase, LOCF

Response Cohort	Beginning of Fixed Dose Phase n (%)	End of Fixed Dose Phase n (%)
Responders at First Assessment of the Fixed Dose Phase		N'=91
Response	91 (100.0)	82 (90.1)
Patients with IGF-1 < 1.3 times ULN at First Assessment in the Fixed Dose Phase		N'=91
IGF-1 < 1.3 times ULN	91 (100.0)	83 (91.2)

Source: CSR, Table 29
LOCF, last observation carried forward

Table 18 implies that patients maintained IGF-1 control from Baseline to End of Treatment. It is noted that this is again a subgroup analysis, i.e. Fixed Dose population. Regardless, Figure 6 shows that there is a significant loss of IGF-1 control even amongst patients who are considered responders.

Figure 6. IGF-1 levels at Baseline and End of Treatment by responder status, mITT population



Source: Clinical Overview, page 46
Filled circle is the End of Treatment value
Solid black line discriminates between non-responders to the left of the line and responders to the right of the line

3. Maintenance of IGF-1 and GH response during the Fixed Dose Phase (CORE) — Proportion of responders (IGF-1 levels [adjusted for age] < 1.3 times ULN and integrated GH < 2.5 ng/mL) at the end of the CORE Treatment Period who also had IGF-1 levels (adjusted for age) < 1.3 times ULN and GH < 2.5 ng/mL at the first assessment in the **Fixed Dose** Phase.

Table 19. IGF-1 and growth hormone suppression at End of Treatment compared to first assessment in Fixed Dose phase, Fixed Dose, CORE phase, LOCF

Response Category	First Assessment in Fixed Dose Phase n (%)	End of Treatment n (%)
FD Population (N=110)		
IGF-1 < 1.3 times ULN and GH < 5.0 ng/mL	91 (82.7)	88 (80.0)
IGF-1 < 1.3 times ULN and GH < 1.0 ng/mL	82 (74.5)	72 (65.5)
IGF-1 ≤ 1.0 times ULN and GH < 5.0 ng/mL	59 (53.6)	51 (46.4)
IGF-1 ≤ 1.0 times ULN and GH < 2.5 ng/mL	59 (53.6)	51 (46.4)
IGF-1 ≤ 1.0 times ULN and GH < 1.0 ng/mL	53 (48.2)	45 (40.9)
IGF-1 < 1.3 times ULN	91 (82.7)	88 (80.0)
IGF-1 ≤ 1.0 times ULN	59 (53.6)	51 (46.4)
GH < 5.0 ng/mL	109 (99.1)	110 (100.0)
GH < 2.5 ng/mL	109 (99.1)	108 (98.2)
GH < 1.0 ng/mL	97 (88.2)	90 (81.8)
IGF-1 ≥ 1.3 times ULN and GH < 2.5 ng/mL	18 (16.4)	21 (19.1)
IGF-1 < 1.3 times ULN and GH ≥ 2.5 ng/mL	0 (0.0)	1 (0.9)
IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL	1 (0.9)	1 (0.9)

Source: CSR, Table 28, modified
FD, fixed dose population; LOCF, last observation carried forward

Reviewer comment: Table 19 is similar to Table 15, however, represents the FD population. Chiasma is trying to show sustained response in the FD population. Again, the FD population results are not results from which we can draw a conclusion about efficacy. The results are presented here for completeness as well as possible understanding into the maintenance effect of MYCAPSSA. Table 19 uses the LOCF method for missing data. As noted above in my comment, use of LOCF in these analyses distorts the data. It is this reviewer's opinion that analysis of shift tables using the worst case imputation method is more useful in understanding what happens with biochemical control over time. Tables 20 and 21 provide shifts in combined IGF-1 and GH control in the FD population from Baseline to End of Treatment in the CORE phase as well as CORE and Extension phases using the worst case imputation method for missing data only.

Table 20. Shift in IGF-1 and growth hormone response categories from Baseline to End of Treatment, Fixed Dose (N = 110), CORE phase, worst case imputation

Response Category	Baseline (N')	End of Treatment		
		Maintained/improved n (%)	Lost control n (%)	Early drop-out
Complete Responder	59	41 (69.5)	17 (28.8)	1 (1.7)
Partial Responder	32	22 (68.8)	7 (21.9)	3 (9.4)
Non-responder	19	13^ (68.4)	2 (10.5)	4 (21.1)
Total	**110**	**76 (69.1)**	**26 (23.6)**	**8 (7.3)**

Source: Information request response received by FDA November 16, 2015, Table 11, modified
Fixed Dose, fixed dose population

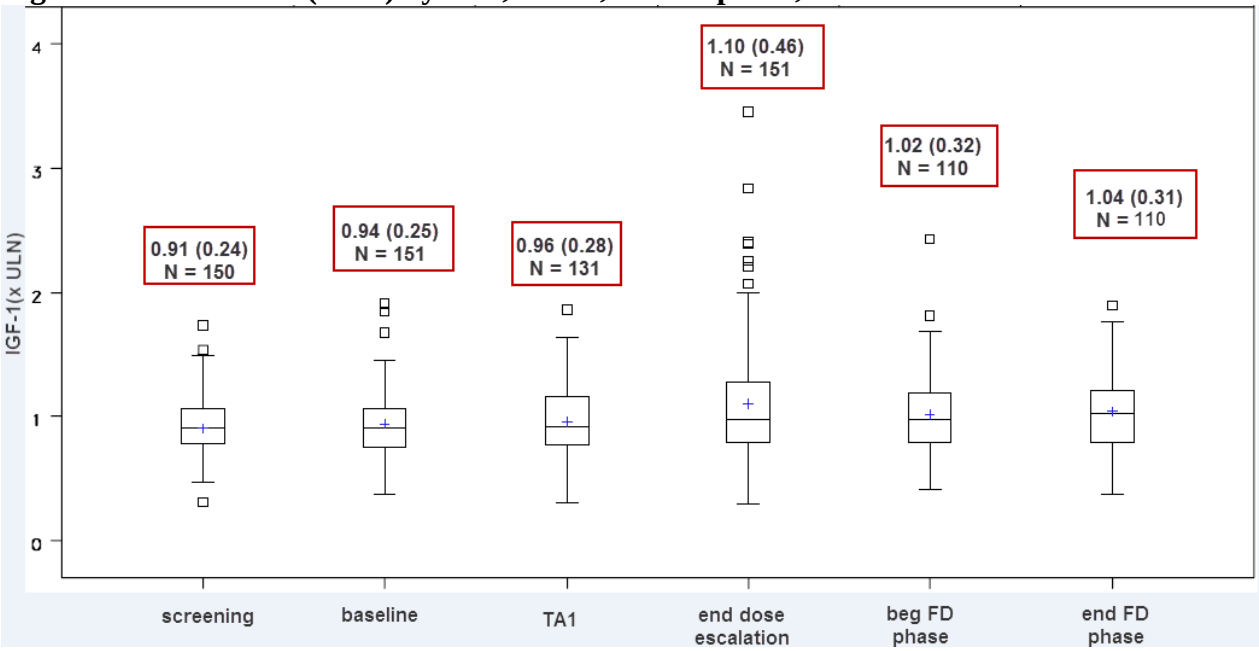
Complete Responder = IGF-1 ≤ 1xULN & GH < 2.5 ng/mL
Partial Responder = 1<IGF-1<1.3xULN & GH < 2.5 ng/mL
% = n/N'
* Of the 17 baseline complete responders that lost control, 15 patients shifted to partial response at end of treatment and two became non-responders
^Four of 13 patients in the non-responder/maintained/improved category became responders (complete responder, n =1 and partial responder n = 3) according to Chiasma's definition for efficacy

Table 21. Shift in IGF-1 and growth hormone response categories from baseline to end of treatment, Fixed Dose (N = 110), CORE and Extension phases, worst case imputation

Response Category	Baseline (N')	End of Treatment		
		Maintained/improved n (%)	Lost control n (%)	Early drop-out
Complete Responder	59	39 (66.1)	15 (25.4)	5 (8.5)
Partial Responder	32	21 (65.6)	7 (21.9)	4 (12.5)
Non-responder	19	13^ (68.4)	1 (5.2)	5 (26.3)
Total	**110**	**73 (66.4)**	**23 (21.0)**	**14 (12.7)**

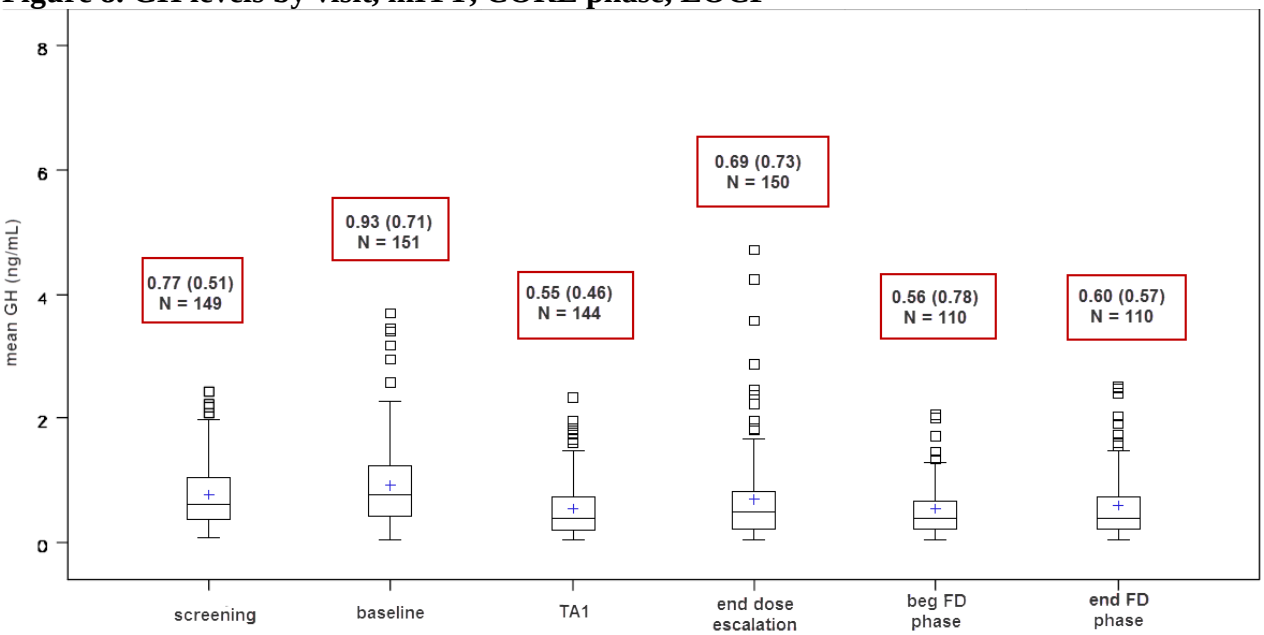
Source: Information request response received by FDA November 16, 2016, Table 12, modified
Fixed Dose, fixed dose population
Complete Responder = IGF-1 ≤ 1xULN & GH < 2.5 ng/mL
Partial Responder = 1<IGF-1<1.3xULN & GH < 2.5 ng/mL
% = n/N'
* Of the 15 baseline complete responders that lost control, 10 patients shifted to partial response at end of treatment and 5 became non-responders
^Four of 13 patients in the non-responder category became responders according to Chiasma's definition for efficacy

Figure 7. IGF-1 levels (ULN) by visit, mITT, CORE phase, LOCF



Source: CSR, Figure 7, modified
Boxplot of median and Interquartile range; Mean = "+" within the boxplot; mean values ±standard deviation presented in text box
LOCF, last observation carried forward; ULN, upper limit of normal; beg, beginning; FD, fixed dose

Figure 8. GH levels by visit, mITT, CORE phase, LOCF



Source: CSR, Figure 9, modified

Boxplot of median and Interquartile range; Mean = "+" within the boxplot; mean values ±standard deviation presented in text box
LOCF, last observation carried forward; ULN, upper limit of normal; beg, beginning; FD, fixed dose

The mean and median IGF-1 and GH absolute values reviewed in the CSR were similar. Figure 7 shows that IGF-1 levels increased slightly over time. The maximum mean IGF-1 level of 1.10 x ULN at the end of dose escalation includes IGF-1 levels of non-responders.

While the GH response to MYCAPSSA appears to be better than that of IGF-1, there is concern regarding the time of measurement of GH post dose such that the suppression in GH might have been overestimated.

The mean and median levels presented in Figures 7 and 8 were calculated by Chiasma using LOCF. However, these observations are confirmed by Dr. Kettermann's analysis (statistical review) in which she has analyzed IGF-1 and GH levels by responders (completers) versus drop-outs (completers and drop-outs) avoiding the LOCF method.

Mean (SD) GH and IGF-1 values for Baseline and End of Treatment in the CORE phase by responder status are provided in Table 22.

Table 22. Mean values of growth hormone and IGF-1 by responder status, CORE phase

Variable	N	Mean	Std Dev
Responder			
Baseline GH ng/mL	73	0.86	0.65
EoT GH ng/mL	73	0.56	0.51
Baseline IGF-1*ULN	82	0.83	0.19
EoT IGF*ULN	82	0.92	0.22
Non-responder			
Baseline GH ng/mL	18	1.23	0.87
EoT GH ng/mL	18	0.78	0.82
Baseline IGF-1*ULN	20	0.99	0.22
EoT IGF*ULN	20	1.49	0.17

Source: Data from analysis by Dr. Anna Kettermann, statistical reviewer, FDA
Responders, completed the study and IGF-1 < 1.3x ULN & GH < 2.5 ng/mL
Non-responders, completers and drop-outs and IGF ≥ 1.3 or GH ≥ 2.5
Std Dev, standard deviation; GH, growth hormone; *ULN, times upper limit normal; EoT, end of treatment

Reviewer comment: The data from Figures 7 and 8 and Table 22 imply that in the small group of patients that tolerates the drug, IGF-1 levels seem reasonably maintained, however, the increase over time is concerning. Mean and median IGF-1 levels are 8-12% increased at the end of treatment. In addition, Figure 7 shows a larger interquartile range at the end of treatment implying more variability in control.

6.1.6 Other Endpoints

1. Shifts in response categories from baseline to the end of the CORE Treatment Period for the mITT Population, PP Population, and FD Population (shift from first assessment at the beginning of the Fixed Dose Phase) were to be summarized for the primary endpoint and all additional categories listed as secondary endpoints.

   -Relevant shifts in response categories from baseline to end of the CORE phase are discussed in section 6.1.5.

2. Treatment satisfaction as measured by the TSQM.

   Per Chiasma, the TSQM is a validated patient reported outcome measure consisting of 14 multiple-choice items. The questionnaire provides four scale scores, each focusing on a different domain by using selected questions: effectiveness, side effects, convenience, and overall satisfaction. Five supplemental (non-validated) questions were added to capture the incidence and bothersomeness of acromegaly symptoms (and recurrence towards the end of the injection cycle) and medication complications, and overall satisfaction on MYCAPSSA in comparison to previous treatments.

   -In the mITT population, more patients reported deterioration (41%) in the Effectiveness scale than improvement (35%). A higher percentage (34.5%) reported an improvement in Side Effects than a deterioration (19.4%). Regarding Convenience, the percentage that reported an improvement versus deterioration was identical. The reported level of overall satisfaction deteriorated for 42.4% of patients and improved in 31.7% of patients.

   -In the FD population, more patients reported improvement (41.6%) in the Effectiveness scale than deterioration (35%). A higher percentage (38.7%) reported an improvement in Side Effects than deterioration (12.3%). A slightly higher percentage of patients reported an improvement (44.3%) in Convenience than deterioration (42.5%). The reported level of overall satisfaction was similar for those that improved or worsened, 34.9% versus 35.8%, respectively.

   -In the modified EXT-ITT population, more patients reported improvement (41.2%) in the Effectiveness scale than deterioration (28.2%). More patients reported an improvement (37.6%) in Side Effects than deterioration (12.9%), and more patients reported an improvement (48.2%) in Convenience than deterioration (38.8%). The reported level of overall satisfaction was higher for those that improved 38.8% versus those that deteriorated 29.4%.

   ***Reviewer comment**: Although this is an exploratory endpoint and not a validated patient reported outcome scale, the questionnaire results are mixed regarding overall satisfaction with MYCAPSSA use. This is in line with the biochemical efficacy results.*

3. The number and percentage of patients (mITT Population) who required reversion to parenteral therapy (rescue); the time to rescue therapy was to be explored.

   -This endpoint is not discussed in the CSR and will not be further discussed here.

4. The number and percentage of patients who achieved a sustained IGF-1 response, defined as IGF-1 < 1.3 times ULN for at least the last 2 successive visits (end of Fixed Dose Phase and the previous visit).

   -For this analysis, Chiasma utilized worst case imputation method for missing data. Of the 151 patients in the mITT population, 78 (51.7%) achieved a sustained IGF-1 response.

Baseline determinants of response to MYCAPSSA

In a post-hoc analysis , Chiasma reported that the degree of baseline control on injectable somatostatin analogs *predicted* subsequent response to MYCAPSSA (Table 23).

Table 23. Summary of responders at End of Treatment by Baseline status, mITT, LOCF

	Responders at End of Treatment	
Baseline response status	**n**	**%**
Responder (IGF-1 <1.3 x ULN & GH* <2.5) (N' = 134)	**93**	**69.4**
-complete responder (IGF-1<1.0 x ULN & GH <2.5) (N' = 93)	72	77.4
-partial responder (1 <IGF-1<1.3 & GH <2.5) (N' = 41)	21	51.2
Non-responder (IGF-1 ≥1.3 xULN &/or GH ≥2.5) (N' = 17)	**5**	**29.4**
-GH non-responder (GH ≥2.5) (N' = 6)	3	50.0
-IGF non-responder (IGF-1 ≥ 1.3 x ULN) (N' = 13)	3	23.1
-IGF-1 and GH non-responder (N' = 2)	1	50.0

Source: CSR, Posthoc 14.2.1.2a
*GH units, ng/mL

Reviewer comment: Although it is observed that the degree of response to OOA was greatest in complete responders > partial responders > non-responders; without a statistical analysis, e.g. logistic regression, it is not appropriate to say that baseline control on injectable somatostatin analogues predicted response to MYCAPSSA.

The data shown above in Table 23 is concordant with the observation from Table 8 (page 47) that that a greater proportion of patients electing to continue into the extension were "responders" at baseline and, specifically, "complete responders". In addition, Dr. Kettermann has noted that the mean time to fixed dose in responders is at an earlier time point in the study than non-responders (approximately 80 days versus 150 days).

6.1.7 Subpopulations

Chiasma presented responder analyses in the following subgroups:

- age (greater versus less than 65 y)
- gender (male versus female)
- renal function (eGFR greater versus less than 90 mL/min/1.73 m^2)

No significant differences within the subgroups were identified. These results are confirmed by Dr. Anna Kettermann's analysis as well. Please see her review for further details.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A dose ranging study was not performed for MYCAPSSA. Similarly, patients were not randomized to dose as this was a dose titration study. As described in section 4.4, there is a lack of adequate characterization of pharmacokinetic and pharmacodynamic properties of MYCAPSSA. Therefore, no further analysis can be provided.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See section 6.1.5 for this discussion.

6.1.10 Additional Efficacy Issues/Analyses

Chiasma evaluated compliance with MYCAPSSA administration. Patients were instructed to take the study medication on an empty stomach at least one hour prior or one to two hours after a meal. Compliance was assessed by pill count and diary cards. The results in Table 24 show relatively good compliance with MYCAPSSA.

Table 24. Study drug compliance and non-fasting doses, safety population, CORE phase

Parameter Statistic/Category	Assigned Dose at the End of Treatment			Total (N=155)
	OCT 20 + 20 (N=65)	OCT 40 + 20 (N=33)	OCT 40 + 40 (N=57)	
Overall compliance [1]				
n	64	33	57	154
Mean (SD)	105.8 (57.07)	99.6 (5.97)	98.5 (5.89)	101.7 (37.05)
< 75%, n (%)	2 (3.1)	0 (0.0)	1 (1.8)	3 (1.9)
75 – 90%, n (%)	2 (3.1)	2 (6.1)	3 (5.3)	7 (4.5)
> 90%, n (%)	60 (92.3)	31 (93.9)	53 (93.0)	144 (92.9)
Total number of non-fasting doses				
N′ [2]	62	33	57	152
Mean (SD) [3]	2.9 (7.86)	4.8 (10.83)	2.1 (3.50)	3.0 (7.44)

Source: CSR, Table 17
OCT, oral octreotide acetate; SD, standard deviation

Compliance = (number of capsules dispensed – number of capsules returned)/Expected number of capsules to be taken based on days of exposure and dose assignment) x 100
N' = number of patients who recorded the number of non-fasting doses

In addition to the pill counts and diary cards, later in the study via amendment 4, Chiasma added a questionnaire regarding general compliance with food restrictions. The questionnaires were collected at any dose escalation visit, TB1, and the end of the CORE and Extension phases. Thirty-nine patients completed the questionnaire of which 38 had sufficient data to calculate compliance: 16 complete responders, nine partial responders and 13 non-responders.

Of the 16 patients who achieved a complete response (IGF-1 within normal limits for age and sex and GH > 2.5 ng/mL), 15 patients were compliant with food restrictions and one patient was non-compliant.

Of the nine patients who achieved a partial response (1 < IGF-1 < 1.3x ULN and GH < 2.5 ng/mL), eight patients were compliant with food restrictions and one patient was non-compliant. Of the 13 patients who were non-responders, all patients were compliant with food restrictions.

Reviewer comment: Despite having only 38 questionnaires to assess compliance, this data along with the pill count and diary data suggest that efficacy was unlikely impacted by non-compliance with taking MYCAPSSA according to instructions.

7 Review of Safety

Safety Summary

Oral octreotide acetate, i.e. MYCAPSSA, is a first generation somatostatin analogue that has a safety profile similar in many respects to other drugs in its class. Gastrointestinal (GI) related adverse events including nausea (46 patients experienced 61 events) and diarrhea (27 patients experienced 37 events), were commonly experienced during the CORE treatment period of CH-ACM-01. GI-related adverse events were also the most common reason for discontinuation due to adverse event.

By systems organ class (SOC), GI-related adverse events were the most common; however, by preferred term the most common adverse event (AE) was headache (52 patients experienced 159 events). The number of headache events is high. Whether onset of headache is related to the oral formulation of octreotide or loss of biochemical control is not clear.

Two deaths occurred during CH-ACM-01, one death was due to a bile duct obstruction and the other to pancreatic tumor. It is likely that the death due to bile duct obstruction was related to MYCAPSSA use; whether the bile duct obstruction was related to the class effect of SSA therapy on gallbladder related disease or specific to MYCAPSSA use is not known. It is unlikely that MYCAPSSA use was associated with the pancreatic tumor.

In addition to a hepatobiliary related death, four of 16 patients experienced six hepatobiliary related serious adverse events (SAEs) in the CORE treatment period. Thus, in total 5/16 (31.3%) experienced a hepatobiliary related SAE. With the known SSA class effect on hepatobiliary disorders and what appears to be a high rate of hepatobiliary SAEs with MYCAPSSA, close monitoring for these disorders will be needed.

Similarly, 5/16 (31.3%) patients experienced a neoplasm related SAE; however, review of the neoplasm data does not raise a safety signal for association with MYCAPSSA. Cardiac and glucose related AEs, also known SSA class effect related AEs, were evaluated and no new safety concerns were identified.

Taken together, there does not appear to be a new safety signal associated with MYCAPSSA use. However, given the high discontinuation rate due to treatment failure in this study, AEs and SAEs might be underestimated both in number and severity. Also, the lack of an adequate PK and PD profile for MYCAPSSA imply that the dosing might not be correct in which case the safety results will not be a true reflection of chronic therapy with MYCAPSSA. In addition, while the new TPE formulation used in MYCAPSSA appears to be safe, we must be cognizant of the fact that increased exposure to TPE might reveal unanticipated safety signals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In this 505(b)(2) application, CH-ACM-01 is the only phase 3 clinical trial evaluated to assess the human safety of MYCAPSSA. The safety review applies to the use of MYCAPSSA therapy as a long term maintenance therapy in acromegaly patients in whom prior treatment with somatostatin analogues has been shown to be effective and tolerated.

It should be noted that 214 subjects were exposed to MYCAPSSA in 11 Phase 1 pharmacology studies (184 healthy volunteers, 18 patients with hepatic impairment, 6 patients with severe renal impairment and 6 patients with ESRD on dialysis). Safety data for these subjects has also been reviewed and are presented throughout the safety sections.

7.1.2 Categorization of Adverse Events

Within the Analysis Legacy Dataset for adverse events (ADAE), “AETERM” represented the reported adverse event term. AEDECOD represented the MedDRA 14.0 coded term.

All AE reported terms were compared to the MedDRA 14.0 coded term and appear to have been coded correctly.

As part of the safety evaluation, determination of symptom control was also evaluated. Chiasma employed the Acromegaly Index of Severity (AIS) tool to assess symptom severity during the

physical exam at pre-specified time points. Each individual symptom severity score was converted to a numeric score according the following algorithm: Absent – 0 point, Mild – 1 points, Moderate – 2 points, Severe – 3 points. For each assessment an overall score was calculated based on the sum of all individual symptoms numeric scores.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

CH-ACM-01 is a single, pivotal, clinical trial that evaluated the safety and efficacy of MYCAPPSA in acromegaly patients. All other phase 1 and 2 studies were completed in healthy volunteers or non-acromegaly patient populations. Thus, pooling of data across studies is not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, 214 subjects were exposed in 11 phase 1 pharmacology studies (184 healthy volunteers, 18 patients with hepatic impairment, 6 patients with severe renal impairment, and 6 patients with ESRD on dialysis). Drug exposure in these studies was typically one day and not more than six days.

Drug exposure in CH-ACM-01 is described in Table 25 followed by the demographics of the safety population for the CORE and Extension period shown in Tables 26 and 27. For more detailed information regarding the demographics of the trial population, please see Section 6 of this review, Review of Efficacy.

Table 25. Summary of drug exposure in CH-ACM-01, safety population

Category/statistic	CORE and Extension Treatment Periods
N	155
Mean Exposure (Weeks) (SD)	42.4 (19.4)
Patient years	131.7
Number of months n(%)	
<3 months	15 (9.7)
3 to < 6 months	24 (15.5)
6 to < 9 months	28 (18.1)
9 to < 12 months	6 (3.9)
≥12 months	82 (52.9)

Source: Table 55, CSR
Exposure was calculated as date of last dose – date of first dose +1
SD, standard deviation

The data in Table 25 show that 116 patients were exposed to MYCAPSSA for at least six months and 82 patients were exposed for 12 to 13 months.

Table 26. Demographics, CORE phase, safety population

Demographic Variable	Total (N = 155)
Age at Screening	
Mean (SD)	54.2 (11.5)
Gender, n (%)	
Male	67 (43.2)
Female	88 (56.8)
Ethnicity, n(%)	
Hispanic or Latino	20 (12.9)
Not Hispanic or Latino	135 (87.1)
Race, n(%)	
White/Caucasian	137 (88.4)
Asian	2 (1.3)
American Indian or Alaskan Native	0
Black/African or African American	0
Native Hawaiian or Pacific Islander	0
Other	16 (10.3)

Source: Table 13, CSR
SD, standard deviation

Table 27. Demographics, Extension phase, safety population

Demographic Variable	Total (N = 155)
Age at Screening	
Mean (SD)	55.0 (11.3)
Gender, n (%)	
Male	37 (42.0)
Female	51 (58.0)
Ethnicity, n(%)	
Hispanic or Latino	12 (13.6)
Not Hispanic or Latino	76 (86.4)
Race, n(%)	
White/Caucasian	78 (88.6)
Asian	1 (1.1)
American Indian or Alaskan Native	0
Black/African or African American	0
Native Hawaiian or Pacific Islander	0
Other	9 (10.2)

Source: Table 15, CSR
SD, standard deviation

Figure 4 in section 6.1.3 displays the patient disposition throughout the CORE and extension periods, which is also important in understanding the overall exposure to MYCAPSSA in CH-ACM-01.

Reviewer comment:

Given the rarity of acromegaly, the lack of racial diversity in this trial population is not surprising. The trial included slightly more females than males; however, gender distribution is fairly balanced overall.

With regard to the CH-ACM-01 data, of the 155 patients that were enrolled 102 (66%) patients completed the CORE phase (seven months); 88 (57%) patients voluntarily entered the extension of which 82 (53%) completed the six month extension for a total exposure of 13 months.
The active ingredient of MYCAPSSA is octreotide, which has a well-established safety profile; and, the pharmacology/toxicology team did not identify any safety signals with TPE.
Overall, the exposure to MYCAPSSA appears adequate to inform its safety profile.

7.2.2 Explorations for Dose Response

MYCAPSSA was titrated to biochemical control of GH and IGF-1. There were no explorations for dose response.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Routine clinical testing for CH-ACM-01 was adequate. See the detailed Schedule of Assessments in Appendix 2.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see section 4.4 of this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Chiasma's evaluation for potential adverse events for similar drugs in the somatostatin analogue drug class was appropriate. The adverse event profile, described below, is similar to that of other approved drugs in this class with common adverse events related to GI disorders and gallbladder abnormalities. Other adverse events of interest include cardiac disorders and metabolic and nutritional disorders, which were appropriately evaluated. QT interval studies were not required in CH-ACM-01 as per the well-characterized QT effects of other approved first generation somatostatin analogues.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in any of the clinical pharmacology studies.

Two patients died during the CORE phase of the study. No patients died during the Extension phase of the study.

Patient (b) (6) 36y old White male with a history of acromegaly for greater than 10 years due to an extrasellar macroadenoma that was not cured by transsphenoidal surgery. Relevant medical history included pituitary tumor apoplexy (b) (6) and pituitary deficiency. Concomitant medications included testosterone.

The patient was started on MYCAPSSA 40 mg BID. There is no report of dose titration. The patient's baseline IGF-1 ≤ 1 × ULN and GH < 2.5 ng/mL.

On Day 179, a serious AE of **suspected bile duct obstruction** was reported. The patient had mild, transient increases in ALT and AST (44 U/L and 64 U/L, respectively) on Day 112, which resolved by the next study visit. The patient experienced high fever and diarrhea and by Day 178, now also had significant jaundice associated with abdominal pain and vision abnormalities. On Day 180, an ultrasound of the abdominal cavity and peritoneal space was normal including normal gallbladder and no dilation of the common bile duct.

Laboratory sampling on Day 180 confirmed a white blood cell (WBC) count of 19.66 × 10^3/µL (reference range 4-10 × 10^3/µL), C-reactive protein (CRP) of 232 mg/L (reference range < 5 mg/L), aspartate transaminase (AST) of 112 U/L (NR 5-40 U/L), alanine aminotransferase (ALT) of 161 U/L (NR 5-40 U/L), alkaline phosphatase (ALP) of 212 U/L (reference range 40-129 U/L), and total bilirubin of 8.4 mg/dL (reference range 0.3-1.5 mg/dL).

MYCAPSSA was discontinued on Day 179. Subsequently, the patient developed an enlarged spleen with undefined parenchymal lesions. He then developed convulsions (etiology unknown), cardiac and respiratory failure and sepsis and died in the intensive care unit on Study Day 193. The autopsy revealed the following findings: enhanced inflammatory and necrotic changes in the brain, septic spleen with infarctions, massive damage of hepatic cells with necrosis of central part of lobules of liver, small-focal septic pneumonia, features of intravascular coagulation, hypertrophy of cardiac muscle, esophageal varices, and diffuse sclerotic changes of minor severity.

Following the review of the autopsy results, the Investigator considered the primary cause of death as sepsis and unrelated to study drug.

The patient did not have a baseline value of GH, therefore the sponsor used an average of the Screening visit and TA1 visit values of 0.618 ng/mL. There is also no baseline value of IGF-1, however, in this case the sponsor has designated the TA1 value of 0.77 x ULN, as the baseline value. The last available GH level was 0.812 on Day 112 and last available IGF-1 value was 1.15 x ULN on Day 168.

Reviewer comment: Given that this patient was young at 36y of age and had been doing well on his injectable somatostatin analogue, death due to sepsis is concerning. While it is puzzling that the abdominal ultrasound did not show evidence of bile duct obstruction and there is no mention of the pancreatobiliary anatomy on the autopsy, the patient's clinical symptoms and laboratory results are suggestive of bile duct obstruction. It is likely that the nidus for developing sepsis was the bile duct obstruction, which was most likely related to MYCAPSSA *use. Therefore, this patient's death is likely study drug related.*

Patient (b) (6)**:** 60 y old White male with a greater than 20 year history of acromegaly due to a microadenoma that was not cured by transsphenoidal surgery. Relevant past medical history included liver lesions (b) (6) hyperthyreosis, hypertension, and multinodular goiter. Patient was on multiple concomitant medications

This patient started MYCAPSSA at the 40 mg dose and over two months was titrated up to the 80 mg dose (Study Day 99).

The patient had a normal gallbladder ultrasound upon study entry. On Study Day 261, the patient complained of a two-day history of malaise, diarrhea, dark colored urine, mild dysuria and itchy skin and was found to be jaundiced. Laboratory results showed an ALT of 260 U/L and AST of 150 U/L (reference ranges not provided). Total bilirubin was 150 and direct bilirubin was 100 (units and reference range not provided), alkaline phosphatase not reported. Urinalysis showed 20-25 erythrocytes. Patient was hospitalized. Abdominal ultrasound on Day 267 showed enormous dilation of the gallbladder measuring 14 cm in diameter and dilation of the common bile duct, which measured 18mm in diameter. Liver function tests continued to rise and the patient also became hemodynamically unstable requiring intensive unit care. The patient **died of cardiac insufficiency on Study Day 270.**

Autopsy results revealed the primary cause of death as acute ischemic heart disease. However, an additional diagnosis of "**choledochus by tumour of the pancreas** with dilation of intrahepatic and extrahepatic bile ducts" was made as well. Cytological analysis of the pancreatobiliary tumor revealed a mildly differentiated, partially anaplastic carcinoma type, T3M0N0.

The patient's GH and IGF-1 levels at baseline of CH-ACM-01 were 0.22 ng/mL and 1.35 x ULN, respectively. The last available GH level from Day 211 was 0.16 ng/mL and last IGF-1 level from Day 246 was 1.56 x ULN.

Reviewer comment: *It seems unlikely that a pancreatic tumor would have developed after the start of* MYCAPSSA. *It is more likely that this patient already had an insidious pancreatic malignancy that worsened while the patient was on* MYCAPSSA. *Whether or not the patient's GH and IGF-1 levels contributed to the rapid growth and extension of the tumor is not known.*

7.3.2 Nonfatal Serious Adverse Events

As this is the first presentation of adverse events outside of Deaths, Table 28 provides an overview of adverse events in CH-ACM-01 followed by a discussion of nonfatal serious adverse events.

Of note, two serious adverse events (SAEs) occurred in the clinical pharmacology studies, which appear to be unrelated to MYCAPSSA use. These cases will not be discussed further.

Table 28. Overview of adverse events, CORE and Extension phases, safety population, N = 155

Category	CORE phase n (%)	Extension phase n (%)	Total n (%)
Deaths	2 (1.3)	0	2 (1.3)
Nonfatal SAEs*	~~13 (8.4)~~ 14 (9.0)	4 (2.6)	-
-nonfatal SAEs occurred in both CORE and Extension*	2 (1.3)		~~19 (12.3)~~ 20 (12.9) (total all nonfatal SAEs)
Discontinued due to AE	21 (13.5)	2 (1.3)	23 (14.8)
Discontinued due to SAE (including deaths)	6 (3.9)	0 (0)	6 (3.9)

Source: CSR, safety section
SAE, serious adverse event; AE, adverse event
*Addition of one SAE with 120 safety update that occurred during the CORE period, unknown if patient discontinued study; see text below.

Nineteen patients experienced a *nonfatal* serious adverse event within the CORE and Extension treatment periods. Of these 19 patients, 13 experienced an SAE during the CORE period; two experienced an SAE during the CORE and Extension periods; and, four patients experienced an SAE only during the Extension period. Table 29 lists each nonfatal SAE with relevant associated information.

With submission of the 120 day safety update, Chiasma reported an additional SAE of acute biliary pancreatitis that occurred during the CORE phase, which somehow was not reported to them earlier. Thus, 20 patients (12.9%) experienced a nonfatal SAE during the CORE and Extension treatment periods.

Table 29. Listing of patients with nonfatal serious adverse events, safety population

Patient Number	Preferred Term	Dose of OOA	Action taken with OOA
CORE treatment period			
(b) (6)	Cholelithiasis	60 mg	Continued
	Meningioma	80 mg	**Discontinued**
	Hyponatremia	80 mg	Continued
	Transient ischemic attack	40 mg	Continued
	Intervertebral disc protrusion	80 mg	Continued
	Urinary tract infection	80 mg	Continued
	Pulmonary embolism	80 mg	Continued
	Neoplasm, malignant	40 mg	**Discontinued**
	Corneal abscess	40 mg	Continued
	Breast cancer, recurrent	60 mg	Continued
	Herpes simplex, opthalmic	60 mg	Continued
	Hypoglycemia	60 mg	*Study drug interruption*
	Jaundice	60 mg	**Discontinued**
	Transaminases increased	60 mg	-
	Colon cancer	60 mg	**Discontinued**
	Sciatica	40 mg	Continued
	Seizure	40 mg	Continued
	Acute biliary pancreatitis	40 mg	Unknown
CORE and Extension treatment period			
(b) (6)	Bile duct stone (CORE)	60 mg	Continued
	Acute cholecystitis (Ext)	80 mg	Continued
	Delayed wound healing[1] (CORE)	40 mg	Continued
	Melena (Ext)	40 mg	Continued
Extension treatment period			
(b) (6)	Headache	80 mg	Continued
	Tinnitus	80 mg	Continued
	Vertigo	80 mg	Continued
	Polymyalgia rheumatica	40 mg	Continued
	Osteoarthritis	40 mg	Continued
	Syncope	60 mg	Continued
	Chronic sinusitis	40 mg	*Study drug interruption*

Source: Modified from Table 71 and post-text Table 14.3.2.3, CSR
(b) (6) added upon submission of 120 day safety update; not included in CSR

SAE narratives were reviewed. Of particular interest are those related to malignancy and hepatobiliary disorders, which are discussed below. The remaining SAE narratives were reviewed and do not appear related to MYCAPSSA use and will not be discussed further.

Narratives of SAEs presented below all occurred in the CORE phase except for one patient who experienced an SAE in the CORE and Extension treatment phases.

Neoplasm related SAEs
Five patients experienced five SAEs
One case (patient ID (b) (6)) described in "Deaths"

Note: All medical disorders and concomitant medications are not listed for the cases presented below unless they are relevant to the case.

As shown in Table 29, five patients experienced **neoplasms** during the CORE phase resulting in a serious adverse event. Patient (b) (6) died of a pancreatic tumor, which is discussed above on page 74 of this review. The four remaining patients had diagnoses of recurrent breast cancer, meningioma (benign), malignant neoplasm, and colon cancer. Brief narratives of these four cases are provided below.

Patient (b) (6): 53y White female with a less than 10 year history of acromegaly and a history of bilateral breast cancer with subsequent bilateral breast lumpectomy and radiotherapy. Patient experienced a SAE of recurrence of breast cancer reported on Study Day 99. Given this patient's history of breast cancer, the recurrence is unlikely related to MYCAPSSA use.

Patient (b) (6)**:** 55y White female with a greater than 20y history of acromegaly caused by an intrasellar macroadenoma not cured by transsphenoidal surgery, experienced an SAE of **alisphenoidal meningioma** (right side). Significant past medical history includes previous stereotactical radiation with gamma knife (b) (6), hypothyroidism post subtotal strumectomy, cholecystectomy, amaurosis left eye, prior compression of the optic nerve, arterial hypertension, hypopituitarism, post-menopausal, and polytrauma.

At baseline, this patient was defined as a responder with an IGF-1 $\leq$ 1 x ULN and GH < 2.5 ng/mL. The patient started MYCAPSSA at 40 mg daily on Day 1 (b) (6) and was titrated up to 60 mg daily by Day 118 and 80 mg daily by Day 183.

On **Day 209**, the patient experienced symptoms of increased headache described as "permanent pressure". MRI of the cranium on Day 254 showed a broad-based space-occupying parasellar lesion. The lesion had already been diagnosed in (b) (6) prior to the start of study drug, but, had grown in size since that time. The morphology was consistent with a rapidly growing meningioma. The patient underwent neurosurgery on Day 278; histology confirmed a

transitional meningioma (WHO Grade 1). The patient was later discharged from the hospital in a good general condition.

The patient **discontinued study drug** on Day 260. The severity of this adverse event was considered mild by the Investigator and possibly caused by previous stereotactical radiation with gamma knife. The patient's GH and IGF-1 levels at baseline were 0.732 ng/mL and 1.09 x ULN, respectively. The last available GH and IGF-1 levels were 0.442 ng/mL and 1.07 x ULN, respectively, on Day 246.

Patient (b) (6) 71y White female with a greater than 10y history of acromegaly caused by an intrasellar macroadenoma not cured by transsphenoidal surgery, experienced an SAE of **malignant neoplasm of pelvic bones, sacrum and coccyx.** Significant past medical history includes type 2 diabetes mellitus, diabetic retinopathy, diabetic nephropathy, hypertension, hyperlipidemia, osteoporosis, meningioma, right breast atheroma, carotid stenosis, and carotid plaque.

At baseline, this patient was defined as a responder with an IGF-1 $\leq$ 1 x ULN and GH < 2.5 ng/mL. The patient started MYCAPSSA at 40 mg daily on Day 1 (b) (6)

The patient's first reported complaint of back pain was Day 77 at which time a CT scan was performed but, of which the results are not reported. CT scan performed on Day 183 revealed a bone lesion at the sacrum suspected to be a chordoma. Sacral biopsy performed on Day 203 confirmed a diagnosis of malignant neoplasm of pelvic bones, sacral area and coccyx (chordoma; epithelial membrane antigen and pan-cytokeratin positive and S100, synaptophysin mildly positive). The patient underwent a partial ostectomy and wide resection of the pelvis and hip on Day 220. The patient was later discharged from the hospital and the malignancy was considered "resolved".

The patient **discontinued study drug on Day 220** (per CSR, this was in the fixed dose period of the CORE treatment period). The patient's GH and IGF-1 levels at baseline were 0.11 ng/mL and 0.76 x ULN, respectively. The last available GH level on Day 87 was 0.092 ng/mL and IGF-1 level on Day 213 was 0.74 x ULN.

→In the 120-day safety update, Chiasma reported that this patient had not resumed acromegaly treatment at follow-up, as this patient was reported to have "adequate biochemical and symptomatic control with no treatment".

→(Please see section 7.7 for other patients who did not re-initiate therapy for acromegaly)

Patient (b) (6) 54y White female with a greater than 10 year history of acromegaly caused by an extrasellar macroadenoma experienced an SAE of **colon adenocarcinoma**. Significant past medical history includes premature menopause, pituitary failure, gonadotropin deficiency, hypercholesterolemia, congenital hyperbilirubinemia, tuberculosis, sporadic goiter, and secondary osteoporosis.

At baseline the patient as defined as a responder, 1 < IGF-1 < 1.3 × ULN and GH < 2.5 ng/mL. The patient started MYCAPSSA at 40 mg daily on Day 1 (b) (6) and on Day 56 was titrated up to 60 mg daily.

The patient had complaints of rectorrhagia since (b) (6) at which time non-complicated hemorrhoidal disease was diagnosed and surgically treated. Rectoscopy was performed because of continued symptoms, which was negative for any pathological lesion. After several evaluations, colonoscopy was performed on Day 133. The pathology revealed a well-differentiated colon adenocarcinoma (grade 1). The patient underwent successful resection of the sigmoid colon and was later discharged from the hospital in general good condition.

Study medication was discontinued on Day 109. The patient's GH and IGF-1 levels at baseline were 1.332 ng/mL and 1.39 x ULN, respectively. The last available GH level from Day 56 was 3.558 ng/mL and last IGF-1 level at Day 90 was 2.25 x ULN. Both GH and IGF-1 levels rose significantly during the course of the study.

Reviewer comment: The narratives for patients (b) (6) suggest that these patients had undiagnosed malignancy prior to starting MYCAPSSA and will not be discussed further.

In our assessment of neoplasm association with MYCAPSSA, two mechanisms must be considered. First, MYCAPSSA might induce neoplastic growth as a drug. Second, inefficacy of MYCAPSSA and subsequent increases in GH and IGF-1 might also induce neoplastic growth.

The narrative for the remaining patient (b) (6) does not suggest any evidence that the malignancy was associated with MYCAPSSA use. Similarly, review of the "baseline" and last available GH and IGF-1 shows well-controlled levels in patient (b) (6) Taken together, it is unlikely that elevated levels of GH and IGF-1 contributed to the onset of malignancy in (b) (6).

Hepatobiliary related SAEs
Four patients experienced six SAEs
(includes one patient whose data was provided with the 120 day safety update)

Patient (b) (6): 73y White female with a greater than 10 year history of acromegaly caused by an intrasellar macroadenoma not cured by transshenoidal surgery experienced an SAE of **symptomatic cholecystolithiasis**. Significant past medical history includes asymptomatic cholecystolithiasis (b) (6) arterial hypertension, atrial fibrillation status post radiofrequency ablation, and pituitary insufficiency gonadotropic axis.

At baseline, this patient was defined as a responder with an IGF-1 ≤ 1 x ULN and GH < 2.5 ng/mL. The patient started OOA at 40 mg daily. On Day 41 the dose was increased to 60 mg and on Day 112 to 80 mg.

On Day 98, the patient complained of right upper quadrant pain radiating to the back and right shoulder without nausea or vomiting. Lab results on Day 100 showed an increased bilirubin (total versus direct, not specified) level of 1.8 mg/dl (normal ≤ 1.1 mg/dl); GGT 1176 U/l (normal ≤ 40); alkaline phosphatase 329 U/l (reference range 35-109); ALT 548 U/l (normal ≤ 35), AST 374 U/l (normal ≤ 35). The patient was hospitalized on Day 100 and abdominal ultrasound and ERCP confirmed a gallbladder full of stones; and, contrast filling defects typical of stones in the bile ducts and dilation of the common bile duct. Treatment included papillotomy and extraction of the stones from the bile duct during the ERCP procedure.

Lab results on Day 101 were improved. Bilirubin 1.5 mg/dl; GGT 1006 U/l, ALT 356 U/l, AST 164 U/l. The patient was clinically improving and discharged with a recommendation to have cholecystectomy as soon as possible. While awaiting a date for surgery, the patient was hospitalized a second time for symptomatic cholelithiasis. Diagnostic laparoscopy followed by cholecystectomy was performed on Day 135. The patient was discharged from the hospital on Day 138.

Baseline GH and IGF-1 levels were 0.86 ng/mL and 1.09 x ULN, respectively. The last available GH and IGF-1 levels from Day 324 were 0.582 ng/mL and 1.12 x ULN, respectively.

MYCAPSSA was continued during the event.

Patient (b) (6) **(SAEs occurred in both CORE and Extension phases):** 65y old White female with greater than 10 year history of acromegaly caused by a microadenoma experienced SAEs of **choledocholithiasis and acute cholecystitis**. Significant past medical history included asymptomatic cholelithiasis (b) (6) diabetes mellitus type 2, nodular thyroid disease/thyroidectomy, and menopause. There is no mention of transsphenoidal surgery or radiation therapy for the pituitary microadenoma.

At baseline, this patient was defined as a responder with an IGF-1 ≤ 1 x ULN and GH < 2.5 ng/mL. The patient started MYCAPSSA at 40 mg daily. On Day 42, the dose was titrated up to 60 mg daily and on Day 98 to 80 mg daily. The subject completed the Extension treatment period on Day 440.

On Day 28, the patient complained of right upper abdominal pain. Laboratory results showed significantly increased liver aminotransferases (see Table 30). By Day 31, aminotransferase values were improving and the Investigator concluded that the abnormal lab values were caused by a bile duct obstruction caused by bile stones that were excreted spontaneously. Day 56 lab results showed a second episode of increased liver aminotransferases associated with abdominal pain. Abdominal ultrasound revealed cholelithiasis and mild central intrahepatic bile duct dilatation as well as mild dilatation of the common bile duct. Although the patient's symptoms

resolved within 24 hours, the patient was hospitalized on Day 62 for choledocholithiasis. Lab results were improved compared to Day 56 (see Table 30). The subject recovered well and was discharged from the hospital on Day 64.

On Day 451, the patient was hospitalized following a 6-day history of epigastric and right hypochondrial pain with several episodes of vomiting and no associated fever. Abdominal ultrasound showed worsening gallbladder disease and possible perforation. Laboratory results revealed a slightly elevated white blood cell (WBC) count 15.2 x 10^9/L and absolute neutrophil count 12.35 x 10^9/L with an otherwise normal complete blood count (CBC). Cholecystectomy was performed and a closed empyemic gallbladder removed. The patient's hospital discharge was on Day 466.

Table 30. Patient 0503-01 liver function tests

Study Day	Bilirubin mg/dL (reference range)	ALT U/L (reference range)	AST U/L (reference range)	GGT U/L (reference range)
28	1.94 (0.10-1.10)	1482 (6-41)	1816 (9-34)	-
Not reported		566 (1-49)	191 (1-46)	-
30		417 (1-49)	101 (1-46)	-
56	1.34 (0.1-1.0)	550 (6-41)	483 (9-34)	-
62		149 (not specified)	33 (not specified)	
70*		33.2	19.4	192 (not specified)

*Day 70 labs were 'control labs'
Source: case narrative page 1611, CSR

Baseline GH and IGF-1 levels were 1.52 ng/mL and 1.1 x ULN, respectively. The last available GH and IGF-1 levels from Day 266 were 0.0.33 ng/mL and 1.55 x ULN, respectively.

Patient (b) (6)**:** 63y White male with a greater than 20 year history of acromegaly caused by an extrasellar macroadenoma not cured by transsphenoidal surgery and radiotherapy experienced the SAE of **icterus and significant aminotransferase elevation**. Significant past medical history includes surgical hypothyroidism (nodular goiter resection), hypertension, hypercholesterolemia, enlargement of the prostate, right-sided nephrolithiasis, cholecystectomy ((b) (6) diastolic chronic heart failure (NYHA I), recurrent abscesses of abdominal wall, anemia, leukopenia, and hepatitis A (date unconfirmed; not ongoing).

The patient was taking hydrocortisone likely for central adrenal insufficiency caused by neurosurgery and/or radiation. However, it should be noted that this diagnosis is not listed in the patient's past medical history.

At baseline, this patient was defined as a responder with an IGF-1 ≤ 1 x ULN and GH < 2.5 ng/mL. The patient started the study at MYCAPSSA dose 40 mg daily and was increased to 60 mg daily on Day 56.

On Day 67/68 the patient reported diarrhea and over the next month stomach aces. On Day 109, the patient reported symptoms of abdominal pain and dark urine and further symptoms of weakness, jaundice and chills on Day 111 requiring hospitalization. The patient reported performing long and intensive work removing ivy from his house and garden in temperatures above 35°C the week before hospitalization. Lab results on Day 111 were: ALT 428 U/; (normal ≤ 41), AST 288 U/l (reference range 5-40), GGT 452 (normal ≤ 60), total bilirubin 6.22 mg/dl (reference range 0.3-1.2), alk phos 225 U/l (reference range 40-130), and C-reactive protein 45.5 mg/L (0.0-5.0). **MYCAPSSA was discontinued**.

Abdominal ultrasound (Day 111) showed liver enlargement of 160 mm with homogenous increased echostructure. There were no signs of concrements in the gall ducts and no visualization of gallbladder (previous cholecystectomy).

On Day 112 patient was noted with serious weakness, yellowing of skin and hypotension (90/60 mmHg). All anti-hypertensives were temporarily discontinued and patient also diagnosed with dehydration. Laboratory results on Day 114 revealed ALT 205 U/L (reference range 0-55), AST 103 U/L (reference range 0-34), and GGT 322 U/L (reference range 12-62). Hepatitis viruses diagnostics performed on Day 114 were negative. Repeat ultrasound on Day 115 confirmed increased liver enlargement, increased echostructure and now showed lipid infiltration. Common bile duct and intrahepatic ducts were not dilated.

Patient was treated with ornithine, timonacic and ursodeoxycholic acid. Laboratory results on Day 127 (b) (6) revealed total bilirubin 0.86 mg/dL, ALT 41 U/L, AST 26 U/L and GGT 183 U/L. The patient was discharged from the hospital on Day 128.

By Day 148, GGT was still slightly elevated at 83 U/L (reference range 12-64) and IGF-1 was elevated at 1108 mg/mL (reference range 75 -112). Because of the elevation in IGF-1, somatuline autogel once every four weeks was started.

Baseline GH and IGF-1 levels were 0.082 ng/mL and 0.59 x ULN, respectively. The last available GH and IGF-1 levels from Day 99 were 0.828 ng/mL and 0.68 x ULN, respectively. Note that the IGF-1 value of 1108 mg/mL is not shown in the main the data analysis set ADLBEFF as this measurement was performed by the local investigator after the patient had discontinued the study.

Patient (b) (6) **(from 120 day safety update):** 41y old White male with greater than 10 year history of acromegaly not cured by transsphenoidal surgery. Medical history is not provided by patient's concomitant medications included hydrocortisone 30 mg BID, levothyroxine and nasal desmopressin acetate. *(Reviewer comment: the hydrocortisone dose is supraphysiologic).*

Approximately two months after starting MYCAPSSA, the patient was admitted to an outside hospital with acute biliary pancreatitis. Additional diagnoses included calculi of gallbladder. Laboratory findings: Total bilirubin – 5.4 mg/dL, ALT – 143 U/L, AST – 98 U/L and alk phos – 569 U/L (normal ranges not reported). Complete blood count, chemistry (except one elevated creatinine value which normalized) were otherwise normal. Abdominal ultrasound showed gallbladder concrements, common bile duct of 8mm, normal pancreas and also was otherwise normal. Patient was discharged from the hospital six days after admission; two months later had ERCP with endoscopic sphincterotomy and revision of bile ducts with Dormia's basket and finally underwent cholecystectomy approximately four months after the incident. No further information is provided and it is not known if the patient discontinued MYCAPSSA.

Reviewer comment: Cholelithiasis and cholecystitis are known complications of somatostatin analogue therapy. Thus, the aforementioned SAEs are not unexpected per se. However of the 16 patients (includes two who had SAE in CORE and Extension) total SAEs in the CORE treatment period, four patients (26.7%) experienced six SAES due to hepatobiliary disorders. In addition, one patient died due to a hepatobiliary event, which makes 5 patients (31.3%) who experienced any hepatobiliary SAE while on MYCAPSSA. This percentage of SAEs due to hepatobiliary disorders seems high. Given the high drop-out rate, overall number of AEs and SAEs might be underestimated. Also, given the new formulation of MYCAPSSA that includes TPE and MYCAPSSA first pass metabolism, increased exposure to drug via a longer CORE and/or Extension period would have helped to understand whether MYCAPSSA use presents an increased risk of hepatobiliary disease.

7.3.3 Dropouts and/or Discontinuations

Table 31 describes the reason for discontinuations throughout the CORE and Extension periods of the study. All treatment failures (n=24, CORE treatment period, see Table 43, Appendix 4 for subject IDs; n=2, Extension period;) occurred, per protocol, on the 80 mg dose, since each patient was titrated through all three dose levels of MYCAPSSA before being determined to be a treatment failure. Of the 24 patients who failed treatment in the CORE treatment period, 21 terminated the study in the Dose Escalation phase and three terminated the study during the Fixed Dose phase.

Twenty-three (14.8%) patients discontinued MYCAPPSA treatment because of an adverse event during the trial. Sixteen of the 23 discontinued during the Dose Escalation phase, five (21.7%) discontinued during the Fixed Dose phase of the CORE treatment period and two discontinued during the Extension Treatment Period. Of the 23 patients who discontinued: 12 were on MYCAPSSA 40 mg, seven on 60 mg and four on 80 mg.

Table 31. Adverse events leading to discontinuation of study drug in CORE and Extension phases (safety population; n=23)

Number of patients	Patient ID	Reason for Discontinuation	SOC	Category	Treatment Period	Dose
1.	(b) (6)	Death	Hepatobiliary	**Death**	CORE -dose esc	
2.		Death	Neoplasm	**Death**	CORE -fixed dose	
3.		Meningioma	Neoplasm	**SAE**	CORE -fixed dose	
4.		Neoplasm, malignant	Neoplasm	**SAE**	CORE -fixed dose	
5.		Transaminases increased	Hepatobiliary	**SAE**	CORE -dose esc	
6.		Colon cancer	Neoplasm	**SAE**	CORE -dose esc	
7.		Headache	Nervous System	AE	CORE -fixed dose	
8.		Depression	Psychiatric	AE	CORE -dose esc	
9.		Dyspepsia	Gastrointestinal	AE	CORE -dose esc	
10.		Diarrhea	Gastrointestinal	AE	CORE -dose esc	
11.		Sinus bradycardia	Cardiac	AE	CORE -dose esc	
12.		Rash	Skin and Subcutaneous	AE	CORE -dose esc	
13.		Diarrhea	Gastrointestinal	AE	CORE -dose esc	
14.		Nodal arrhythmia	Cardiac	AE	CORE -Fixed dose	
15.		Diarrhea, nausea	Gastrointestinal	AE	CORE -dose esc	
16.		Diarrhea, nausea, Peripheral edema	Gastrointestinal General	AE	CORE -dose esc	
17.		Abd pain, dyspepsia, GI motility disorder, nausea, rectal tenesmus, vomiting	Gastrointestinal	AE	CORE -dose esc	
18.		Abd pain, Nausea,	Gastrointestinal	AE	CORE -dose esc	

		vomiting				
19.	(b) (6)	Unknown[a]		AE	CORE -dose esc	
20.		Dry mouth, nausea, retching	Gastrointestinal	AE	CORE -dose esc	
21.		Abd pain, flatulence, nausea	Gastrointestinal	AE	CORE -dose esc	
22.		Erosive gastropathy	Gastrointestinal		Extension	
23.		Abdominal fullness with study drug; abdominal distension	Gastrointestinal		Extension	

*Source: Table 14.1.4 CSR; SAE, nonfatal SAE; dose esc, dose escalation phase; fixed dose, fixed dose phase
[a]Patient (b) (6) experienced gastritis and nausea that resolved with study drug interruption. Patient resumed therapy, yet, decided to discontinue treatment within one month of experiencing these adverse events. The site principal investigator insisted that this patient be listed as discontinuation due to adverse events; however, Chiasma felt that since the adverse events were resolved at the time the patient decided to discontinue the study, they did not list any specific adverse event term as part of the reason for discontinuation. Source: response to information request received by FDA 01/15/2016.

Five subjects requested to withdraw from the study during the CORE treatment period. An information request was sent to Chiasma for details surrounding the request. The data from Chiasma's response is provided in Table 32 below.

Table 32. Reason for patient requests to withdraw from the study

Patient#	Days on TX	Baseline IGF-1 (x ULN) GH (ng/mL)	EOT IGF-1 (x ULN) GH (ng/mL)	Comments
(b) (6)	42	1.17 0.954	1.2 1.002	The subject chose not to dose escalate due the AEs she was experiencing at the beginning of the study (disturbance in attention, dizziness and memory impairment). All AEs were resolved and the investigator assessment was that this subject could continue in the study. It was the subject choice to discontinue treatment. Last dose: 40 mg

(b) (6)				
	210	1.04 0.814	1.18 1.516	The subject discontinued treatment due to personal reasons (family issues), that could not allow him to continue and comply with study visits requirements. Last dose: 80 mg
	84	0.67 0.622	0.76 0.052	The subject had difficulties with the fasting requirements on octreotide capsules. Last dose: 40 mg
	73	1.12 0.438	1.22 0.908	The patient had an exacerbation of acromegaly symptoms, while on the mid dose of OOC. It was the subject's choice to leave the study while the investigator's impression was that the subject could continue in the study. Last dose: 60 mg
	133	0.75 0.068	2.84 2.24	Based on the investigator, the subject was not treated for sufficient time with the 80 mg dose. It was the patient's choice to leave the study, while the investigator thought that he should continue. Last dose: 80 mg

Source: Chiasma response to information request, received by FDA 11/16/2015 (SN0010)

Patient (b) (6) is listed as having discontinued CH-ACM-01 due to an adverse event in Table 14.3.3.3 and as described in the patient's narrative (page 1641, CSR) of Chiasma's clinical study report. Per these tables, the patient experienced increased frequency of bowel movements and nausea. This patient is **not** included in the n=23 patients who discontinued the study due to an adverse event (Table 31). However, according to Table 14.1.4 of the clinical study report the patient discontinued as per a "subject request". In response to an information request about this patient, Chiasma responded that the patient did experience the stated adverse events, which led to temporary discontinuation of study drug. Approximately two weeks later, the patient decided to permanently discontinue the study although the investigator thought that the patient could continue. It is not clear if the stated adverse events had resolved and Chiasma has no further information on why this patient decided to leave the study.

Review of the data in Table 32 shows that patient (b) (6) and (b) (6) might be better reclassified as discontinuation due to adverse event. Similarly, patient (b) (6) might be better classified as a treatment failure.

Patient (b) (6) was discontinued from the study by Chiasma ("sponsor request"). At baseline, this patient had elevated IGF-1 levels (1.91 x ULN) and elevated GH levels (2.96 ng/mL), thus a non-responder to injectable SSA therapy. In a response to information request by FDA (response received 01/15/2016), Chiasma reported that patient 1002-04 had been titrated up to the 60 mg MYCAPSSA dose and was in the dose escalation phase for 170 days (just under 6 months) and that the dose escalation phase should only consist of 2-5 months. Since patient

(b) (6) was on 60 mg MYCAPSSA for > 5 months and not responding to therapy, Chiasma requested that the patient discontinue the study. This patient might also be better classified as a treatment failure.

Taken together, it seems that a few patients from the "subject request" and "sponsor request" for discontinuation groups should be re-classified.

Subject Request Category

(b) (6)
– reclassify as discontinuation due to adverse event
– no change in classification
– no change in classification
– reclassify as discontinuation due to adverse event
– reclassify as treatment failure

Sponsor Request Category

(b) (6) – reclassify as treatment failure

Therefore modifications to the numbers in Figure 4 are shown in Table 33:

Table 33. Reason for discontinuation, CORE treatment period, reclassification, safety population, N = 155

Reason for Discontinuation	Before Reclassification CORE (Figure 4) n (%)	After Reclassification, CORE n (%)
Treatment failure	24 (15.5)	26 (16.7)
Adverse event	21 (13.5)	23 (14.8)
Subject request	5 (3.2)	2 (1.3)
Sponsor request	1 (0.6)	0
Lost to follow-up	2 (1.3)	2 (1.3)
Total (N)	53/155 (34.2)	53/155 (34.2)

During the Extension phase, two patients discontinued the study due to adverse events, two due to treatment failure and two because of subject request. The subject requests were:

- **Patient** (b) (6) – could not comply with drug-food instructions during the Ramadan fast
- **Patient** (b) (6) – Four days after entering the Extension phase, patient experienced exacerbations of acromegaly symptoms (joint pain, headache, swelling of extremities and perspiration) and discontinued treatment. Per the Investigator's clinical judgment, the patient could have continued in the study. Baseline IGF-1 levels were 0.75 x ULN and GH levels were 1.4 ng/mL. At end of treatment, IGF-1 level was 1.18 x ULN and GH 0.64 ng/mL.

7.3.4 Significant Adverse Events

Chiasma identified adverse events in the following SOCs as Adverse Events of Interest:

- Gastrointestinal Disorders
- Infections and Infestations
- Metabolism and Nutrition Disorders
- Cardiac Disorders
- Hepatobiliary Disorders
- Neoplasms

Gastrointestinal disorders

The majority of adverse events in CH-ACM-01 fall within this category as 88/155 (56.7%) patients had at least one gastrointestinal (GI) related AE. Nine of the 21 (42.9%) patients that discontinued MYCAPSSA due to an adverse event in the CORE phase had a GI related event (see Table 31). The most common adverse events under this SOC were:

Nausea	n=46 (29.7%)
Diarrhea	n=27 (17.4%)
Dyspepsia	n=13 (8.4%)
Abdominal pain	n=15 (9.7%)
Abdominal distension	n=10 (6.5%)
Vomiting	n=9 (5.8%)

Five patients reported nausea and one patient reported vomiting with OOA administration according to the reported AE term. This was coded as "nausea" or "vomiting" in MedDRA version 14.0 (AETERM column in ADAE, analysis legacy dataset).

One patient (b) (6) experienced a GI related SAE of melena during the study, which is unlikely to be related to MYCAPSSA. Neither of the two deaths that occurred in the study were GI related. GI disorders most commonly occurred in the first 3 months of the study and overall were mild to moderate in severity. The number of adverse events in the Extension phase of the study was considerably lower as only 88 (56.7%) patients entered the Extension. The patients entering the Extension likely tolerated MYCAPSSA well. However, when CORE and Extension phase adverse events are combined the distribution of events is similar.

Infections and Infestations

The adverse events in this system organ class were reviewed. Infections and infestations were reported in 61 patients (39.4%) during the CORE and Extension phases. The most common AEs were: nasopharyngitis (n=12, 7.7%); influenza (n=10, 6.5%); and upper respiratory tract infection (n=8, 5.2%). The majority of AEs in this SOC were mild, with a few moderate and

none that were severe. There were no SAEs or Deaths in this SOC. However, patient (b) (6) died from "sepsis", which could be considered an infection. The sepsis was likely because of bile duct obstruction, a nidus for infection.

Again, the number of events in the Extension period was considerably lower; however, when CORE and Extension phase adverse events are combined the distribution of events is similar.

Metabolism and Nutrition Disorders

Metabolism and nutrition disorders occurred in 20 patients (12.9%) during the CORE treatment period. While as a system organ class, all events combined, the number of patients who experienced AEs is ≥ 5%, each individual preferred term within this class is less than 5%, thus Metabolism and Nutrition Disorders does not show up in Table 40, Common Adverse Events.

The most common AE was hypoglycemia occurring in seven patients in the CORE phase (none reported in Extension phase). Three patients had a history of glucose abnormalities prior to study start. Narratives of the remaining four patients were reviewed. There does not appear to be any objective documentation of a low glucose value for any of these patients, thus the adverse event is based on subjective signs and symptoms. Glucose values by study visit were not low in any of these patients.

Ten (6.4%) patients experienced 13 adverse events of increased blood glucose, impaired fasting glucose and worsening/inadequate control of diabetes during the CORE treatment period. Of these 10, three patients had new onset of increased blood glucose while the remaining seven all had a history of a glycemia related disorder.

One patient experienced an AE of worsening diabetes control in the Extension treatment period.

There were no deaths, SAEs or discontinuations from hypoglycemia or increases in blood glucose.

Reviewer comment: Hypoglycemia and hyperglycemia are labeled adverse events for s.c. Sandostatin, Sandostatin LAR, lanreotide, and pasireotide s.c. and pasireotide LAR.

Cardiac Disorders

In the current study, CH-ACM-01, two patients, (b) (6) (43y, male) and (b) (6) (64, male), discontinued MYCAPSSA because of sinus bradycardia and nodal arrhythmia, respectively. Both patients had sinus bradycardia at baseline and screening. Upon request, Chiasma did provide narratives for these two patients and no further relevant information was identified. An association between sinus bradycardia, nodal arrhythmia and MYCAPSSA use is unlikely in these two patients.

The frequency of cardiac events, overall, was low as seen in Table 34. Associated adverse events, SAEs, available narratives and any ECG abnormalities were reviewed for the patients who experienced these cardiac disorders and no signal was identified. Many of the patients had baseline cardiac abnormalities.

Review of the Extension data shows two more patients with palpitations and two more patients with sinus bradycardia.

Table 34. Cardiac disorders, CORE phase, safety population

Cardiac Disorder	n (%)
Acute myocardial infarction	1
Myocardial ischemia	1
Bradycardia	1
Sinus bradycardia	2
Tachycardia	1
Sinus tachycardia	1
Bundle Branch Block (R or L)	2
Cardiac failure	1
Left ventricular hypertrophy	1
Nodal arrhythmia	1
Palpitations	4
Supraventricular extrasystoles	1
Ventricular extrasystoles	2

Source: ADAE, dataset, JMP version 11.0
CSR, Table 14.3.1.2;
R, right; L, left

Two patients died (narratives in section 7.3.1 of this review) in the CORE phase. Patient (b) (6) experienced SAEs of bradycardia and cardiac failure and patient (b) (6) experienced an SAE of acute myocardial infarction. However, these cardiac events were likely unrelated to study drug as described in the aforementioned narratives.

Reviewer comment: Overall, there is no new safety signal identified with MYCAPSSA and cardiac disorders.

Hepatobiliary disorders

Hepatobiliary disorders were reported in 13 patients who experienced 14 events during the CORE phase. Cholelithiasis was the most common adverse event under this SOC, with seven

patients experiencing seven events. Other events that occurred were less common with only one or two (0.6% and 1.3% of 155 patients) patients in each category: N=1 for acute cholecystitis; N =1 for bile duct obstruction, bile duct stone, gallbladder disorder, hepatic steatosis, hepatomegaly and jaundice.

The number of hepatobiliary events in the Extension phase was considerably lower; however, when CORE and Extension phase adverse events are combined the distribution of events is similar. Two patients were found to have a gallbladder polyp in the Extension period.

Gallbladder ultrasounds were scheduled to be completed in each patient at baseline and at follow-up. Since a patient's follow-up visit could have occurred during the CORE or Extension phase, Table 35 represents the CORE and Extension phases.

Table 35. Gallbladder Ultrasound Summary, CORE and Extension phases

	Assigned Dose at End of Treatment			
Category	**Oct 20+20 (N=64) n (%)**	**OCT 40+20 (N=33) n (%)**	**OCT 40+40 (N=58) n (%)**	**Total (N=155) n (%)**
Ultrasound on screening and post-screening	N'=47	N' =27	N' =37	N' =111
Ultrasound normal at screen	**N'' =22**	**N'' =16**	**N'' =20**	**N'' =58**
Ultrasound worse at follow-up	3 (13.6)	4 (25.0)	2 (10.0)	9 (15.5)
Hepatobiliary disorder reported as AE	3 (13.6)	3 (18.8)	2 (10.0)	8 (13.8)
Normal ultrasound at screen and follow-up	19 (86.4)	12 (75.0)	18 (90.0)	49 (84.5)
Ultrasound abnormal at screen	**N'' =25**	**N'' =11**	**N'' =17**	**N'' =53**
Ultrasound worse at follow-up	5 (20.0)	0 (0.0)	2 (11.8)	7 (13.2)
Hepatobiliary disorder reported as AE	3 (12.0)	3 (27.3)	2 (3.4)	8 (5.2)
Ultrasound improved at follow-up	1 (4.0)	1 (9.1)	2 (11.8)	4 (7.5)
Ultrasound no change at follow-up	19 (76.0)	10 (90.9)	13 (76.5)	42 (79.2)

Source: Response to information request received by FDA January 28, 2016, Table 17
OCT, Octreolin; AE, adverse event
N'', number of subjects with normal gallbladder ultrasound at screen and is used as the denominator for percentage calculations
Note: several of the percentages provided in the sponsor's table were incorrect if they actually used n/N" for the percentage calculations. The percentages shown in Table 31 have been corrected and represent n/N".

Forty-three patients did not have ultrasound on screening and post-screening and one patient only had a follow-up ultrasound. The reasons for lack of ultrasound at both screening and post-screening were: cholecystectomy (n=13), death (n=2), biliary MRI done instead (n=1), investigator opinion that ultrasound not needed at follow-up (n=14), patient refused (n=2), patient had ultrasound one month prior to end of treatment (n=1), discontinued study early (n=9), unknown (n=2).

Reviewer comment: Per protocol, gallbladder ultrasound was to be done at screening and follow-up visits, thus in the cases where it was not performed because the investigator decided it was not needed goes against the protocol. Given the known association of gallbladder disease

and SSA therapy, where possible, the ultrasound should have been completed. That being said, review of the hepatobiliary AEs associated with gallbladder as well as the data in Table 35 do not identify an increased safety signal in intensity or frequency compared to the known association of gallbladder disease with SSA therapy. However, please see my note regarding hepatobiliary related SAEs on page 83.

Neoplasms

Ten patients experienced malignancies during the CORE and extension treatment periods of CH-ACM-01. Five of these 10 patients experienced a SAE, which are described above in section 7.3.2. The five remaining patients experienced six events: hemangioma of the liver (N=2), lipoma, renal hemangioma, skin papilloma, and thyroid neoplasm. Overall, a neoplasm safety signal is not apparent from this data.

7.3.5 Submission Specific Primary Safety Concerns

Signs and Symptoms

Submission specific primary safety concerns include gastrointestinal, hepatobiliary and metabolic and nutrition related adverse reactions. These have been discussed in the above section 7.3.4.

In addition to the SOC safety concerns, there is concern about exacerbation of acromegaly symptoms with use of MYCAPSSA as many patients lost some degree of biochemical control with MYCAPSSA use when compared to their baseline response status to injectable SSAs. As described in section 7.1.2, Chiasma assessed symptoms of asthenia, headache, joint pain, perspiration and swelling of extremities with the Acromegaly Index of Severity. Chiasma has presented this data in the Safety section of their CSR, however, typically sign and symptom control is considered part of the Efficacy of a study drug. Regardless, the data will be presented here.

Within the safety population (N=155), the proportion of patients with at least 1, 2, or 3 acromegaly symptoms at Baseline and End of Treatment (CORE + Extension) is described in Table 36.

Table 36. Proportion of patients with 1-3 acromegaly related symptoms based on Acromegaly Index of Severity at Baseline and End of Treatment

Number of Symptoms	Baseline	End of Treatment	P-value
mITT population (N = 151)			

≥ 1 symptom	81%	74%	0.0705
≥ 2 symptom	61%	53%	0.0516
≥ 3 symptom	43%	35%	0.0578
Fixed Dose population (N = 110)			
≥ 1 symptom	79.1%	68.2%	.0186
≥ 2 symptom	62.7%	48.2%	.0017
≥ 3 symptom	44.5%	30.9%	.0053
Extension Intention-to-Treat population (N = 88)			
≥ 1 symptom	78.4%	64.8%	0.01
≥ 2 symptom	61.4%	43.2%	0.0006
≥ 3 symptom	43.2%	25.0%	0.0011

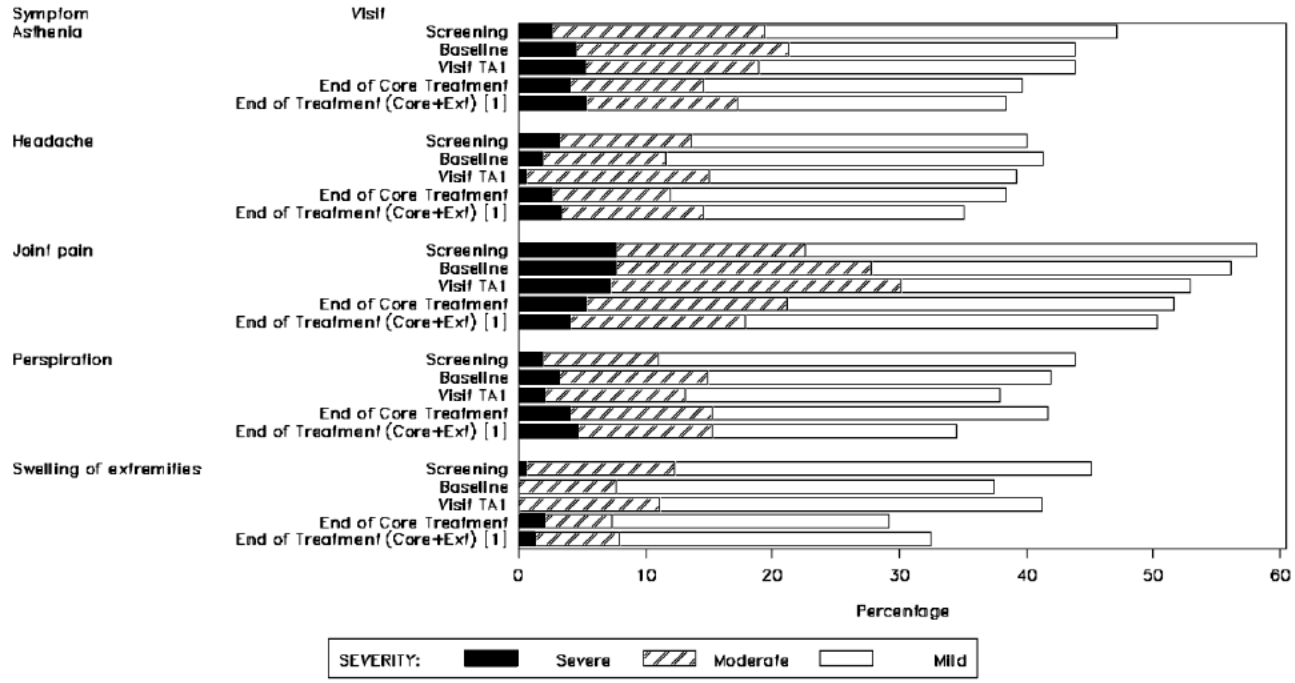
Source: Posthoc Table 14.3.5.8.2a

Review of Table 36 above shows that in the mITT population the number of symptoms did not change significantly (P > 0.05 in all) between baseline and end of treatment. However, in the fixed dose subpopulation (FD) there was a significant decrease in the number of symptoms from baseline to end of treatment. The FD consists of those patients (N=110) who entered the fixed dose phase of the CORE treatment period and excludes the 41 patients who dropped out of the study because of treatment failure or adverse events, subject or sponsor request. Although it appears that the FD population saw a significant reduction in the number of symptoms, this is a subgroup of the intention-to-treat population and not generalizable to the acromegaly population.

Similarly, the Extension population is a subgroup of patients who volunteered to participate in the extension and likely tolerated and likely felt well while taking MYCAPSSA. Thus, this subgroup also shows a significant reduction in symptoms between baseline and end-of-treatment; but, only represents a small population of acromegaly patients.

Figure 9 below shows the summary of overall AIS scores by visit in the safety population.

Figure 9. Proportion of patients with signs and symptoms related to acromegaly based on Acromegaly Index of Severity by Visit (CORE and Extension), Safety Population (N=155)



Source: Figure 18, CSR;
For patients not completing the CORE treatment period, the last assessment during the CORE treatment period was used. For patients not completing the Extension treatment period, the last assessment during the Extension Treatment Period was used.

The presentation of data in Figure 9 is challenging to interpret in its format. This graph style is better suited to display large changes in percentages over time. It appears that overall, there was minimal change in the percentage of mild, moderate and severe symptoms from screening to end of treatment. However, review of the percentage of severe symptoms from screening to end of treatment actually appears to have increased slightly for asthenia, perspiration and swelling of extremities.

Last, Table 37 shows the overall summary of AIS scores across visits.

Table 37. Summary of Acromegaly Index of Severity (AIS) score by visit, mITT population

AIS SCORE	Screening	Baseline	TA1	End of Treatment (CORE + Ext)	Change from Baseline to End of Treatment
N'	151	151	150	151	151
Mean	3.3	3.2	3.2	2.8	-0.4
SD	2.8	2.9	2.9	3.1	2.38
Min	0	0	0	0	-7
Max	12	11	11	14	8

Category	mITT (N = 151)
Improve	74 (49%)
No Change	35 (23.2 %)
Worse	42 (27.8)

Source: post-text, post hoc Table 14.3.5.8.1a; Includes only patients that completed all questions of the AIS at the specified visit.
For patients not completing the CORE treatment period, the last assessment during the CORE treatment period was used. For patients not completing the Extension treatment period, the last assessment during the Extension Treatment Period was used.

To better understand the symptom data, we asked Chiasma to further clarify the relationship between the AIS change from baseline to biochemical response and patient disposition status. The following tables display this information.

Table 38. Relationship between Acromegaly Index of Severity (Baseline to End of Treatment) to biochemical response and disposition, mITT population.

Category	Responder n (%)	Non-Responder n (%)	Number Completed CORE n (%)	Number Completed Extension n (%)	D/C Early n (%)	Adverse Event n (%)	Treatment Failure n (%)
Improvement (n=74)	45 (48.4%)	29 (53.7)	56 (54.9)	49 (59.8)	19 (34.5)	4 (20.0)	14 (53.8)
No change (n=35)	24 (25.8%)	10 (18.5)	28 (27.5)	22 (26.8)	9 (16.4)	3 (15.0)	4 (15.4)
Worsening (n=42)	24 (25.8%)	15 (27.8)	18 (17.6)	11 (13.4)	27 (49.1)	13 (65.0)	8 (30.8)
Total	93	54	102	82	5	20	26

Source: Response to information request received by FDA, 02/02/2016

Table 39. Relationship between Acromegaly Index of Severity (Baseline to End of Treatment) to biochemical response and disposition, Fixed Dose population (N=110)

	Responder n (%)	Non-Responders n (%)	Number Completed CORE n (%)	Number Completed Extension n (%)	D/C Early n (%)	Adverse Event n (%)	Treatment Failure n (%)
Improvement (n=59)	41 (50.0)	18 (64.3)	56 (54.9)	49 (59.8)	4 (28.6)	2 (28.6)	2 (40.0)
No change (n=29)	22 (26.8)	7 (25.0)	28 (27.5)	22 (26.8)	3 (21.4)	-	2 (40.0)
Worsening (n=22)	19 (23.2)	3 (10.7)	18 (17.6)	11 (13.4)	7 (50.0)	5 (71.4)	1 (20.0)
Total	82	28	102	82	14	7	5

Source: Response to information request received by FDA, 02/02/2016

Chiasma reports that the discrepant relationship between biochemical control and symptom control is well known among clinicians and reported in the literature (references not provided). Chiasma also pointed out that there is a similar lack of close association between biochemical

control and acromegaly symptoms at baseline when 88% of the enrolled population was considered a responder and experienced a range of symptoms as shown in the tables and figure above. Chiasma also stated that the benefit of MYCAPSSA is not captured by the tables above, but, is represented by the fact that patients taking long acting SSAs can suffer from breakthrough symptoms as the medication wears off. This is often treated by administration of subcutaneous short-acting octreotide (Sandostatin IR). Chiasma states that since the PK of OOA resembles the PK of subcutaneous octreotide, daily administration of MYCAPSSA can eliminate wear-off effects. However, as is discussed in section 4.4 (clinical pharmacology) as well as section 6.0 (efficacy), there are not insignificant differences between the PK of Sandostatin IR and MYCAPSSA. In addition, data showing that patients had improved symptom control because of decreased wear off effects was not reported in the clinical study report.

In conclusion, it seems that the proportion of patients who improved, had no change, or had worsening of symptoms was approximately the same in the responders compared to non-responders group. Given the lack of a control group, it is challenging to conclude the effect of MYCAPSSA on signs and symptoms acromegaly. However, as an observation, it does not appear patient signs and symptoms at end of treatment do not appear to be worse than their baseline status.

Pituitary MRI

Pituitary MRI was performed during the CORE treatment period only.

Pituitary MRI was completed in 106 patients. Of these 106, 103 had no evidence of pituitary tumor growth. Of the remaining three patients, two did not have a tumor volume increase of greater than 20% and for the third, it appears that maximum tumor diameter might have increased but data on one dimension is missing.

Reviewer comment: Overall, there does not appear to be a change in size in pituitary tumor growth; however, approximately 32% of patients did not have pituitary MRI (likely because of the dropout rate) making these results less reliable.

7.4 Supportive Safety Results

7.4.2 Laboratory Findings

Abnormal laboratory findings as presented in Tables 14.3.4.20 (Listing of laboratory safety parameters for subjects with notable laboratory abnormalities, safety population) and 14.3.4.22 (Listing of laboratory safety parameters for subjects with potentially clinically significant values, safety population) were reviewed. Notable laboratory abnormalities represent those levels that fall outside of the reference range. Potentially clinical significant values are values pre-specified by the sponsor to have potential clinical significance. Overall, no safety signal was identified for any laboratory parameter.

As expected, there were several mild, transient laboratory abnormalities that did not result in an AE or have any clinical correlation.

Several patients experienced elevated glucose levels (fasting, morning measurement) detected at the planned study visits. Glucose values > 160 mg/dL were flagged as potentially clinically significant. The majority of patients with elevated glucose levels during the study had elevated glucose levels at screening and baseline visits. The rise in fasting glucose levels seen in this group of patients could be expected in a patient with glucose intolerance or diabetes. In this population of patients with notable or potentially clinically significant glucose values, the maximum fasting glucose was a *baseline* value of 191 mg/dL in one patient. The majority of fasting glucose levels in this subgroup were 140-180 mg/dL. Review of mean and median hemoglobin A1c results across visits (Table 14.3.4.1) also did not identify clinically significant increases in this safety parameter.

Similarly, potentially significant values in occurred in at least 2.5% of patients from baseline to any post dosing visit for the following parameters: bilirubin (4 patients, 2.7%), potassium (5 patients, 3.4%), AST/SGOT (4 patients, 2.7%), creatine kinase, (7 patients, 4.7%), total cholesterol (3 patients, 2.5%), triglyceride (4 patients, 2.7%) and CRP (6 patients, 4%). This data has been reviewed and no safety signal identified. The following are reasons for why the abnormalities described are unlikely to be clinically significant and related to MYCAPSSA use:

- several patients had elevated but not flagged values at baseline such that further rise in the lab parameter would not be unexpected (i.e. total cholesterol baseline 282 mg/dL, high value 328 mg/dL and flag is for total cholesterol > 300 mg/dL)
- patient had one high value during the study but all other values normal
- no associated adverse events

Also, the elevations in AST and bilirubin values were not associated with each other and were not associated with elevated ALT values. These elevated AST and bilirubin values did not raise concern for Hy's law.

7.4.1 Common Adverse Events

Common adverse events are shown below in Table 40. While more patients experienced GI disorders compared to any other SOC, headache was the most common preferred term (AE) experienced in CH-ACM-01. Although, hepatobiliary disorders is an adverse event of special interest, the overall number of events under this SOC is lower compared to others and cholelithiasis is the only adverse event experienced by ≥ 5% of patients in this SOC.

Table 40. Incidence of most common (≥ 5% of total patients) adverse events in CORE phase, safety population

System organ class Preferred term	Dose at Onset of Adverse Event						Total (N=155)	
	OCT 20 + 20 (N=155)		OCT 40 + 20 (N=90)		OCT 40 + 40 (N=57)			
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAE	**116 (74.8)**	**586**	**61 (67.8)**	**257**	**38 (66.7)**	**245**	**134 (86.5)**	**1096**
Gastrointestinal disorders	71 (45.8)	131	30 (33.3)	60	15 (26.3)	32	88 (56.8)	223
Nausea	30 (19.4)	35	14 (15.6)	16	6 (10.5)	10	46 (29.7)	61
Diarrhoea	18 (11.6)	22	8 (8.9)	11	3 (5.3)	4	27 (17.4)	37
Dyspepsia	11 (7.1)	14	1 (1.1)	1	1 (1.8)	1	13 (8.4)	16
Flatulence	9 (5.8)	9	1 (1.1)	2	2 (3.5)	3	9 (5.8)	14
Abdominal pain upper	9 (5.8)	9	2 (2.2)	3	1 (1.8)	1	12 (7.7)	13
Abdominal distension	7 (4.5)	8	4 (4.4)	4	1 (1.8)	1	10 (6.5)	13
Vomiting	4 (2.6)	4	3 (3.3)	3	3 (5.3)	3	9 (5.8)	10
Nervous system disorders	53 (34.2)	96	23 (25.6)	44	21 (36.8)	62	62 (40.0)	202
Headache	41 (26.5)	70	18 (20.0)	37	19 (33.3)	52	52 (33.5)	159
Dizziness	7 (4.5)	8	1 (1.1)	1	2 (3.5)	4	8 (5.2)	13
Musculoskeletal and connective tissue disorder	32 (20.6)	61	26 (28.9)	37	19 (33.3)	44	58 (37.4)	144
Arthralgia	22 (14.2)	43	20 (22.2)	25	10 (17.5)	20	42 (27.1)	88
General disorders and administration site conditions	42 (27.1)	78	14 (15.6)	29	12 (21.1)	17	53 (34.2)	127
Asthenia	24 (15.5)	33	11 (12.2)	13	7 (12.3)	9	35 (22.6)	56
Oedema peripheral	18 (11.6)	27	8 (8.9)	10	5 (8.8)	5	25 (16.1)	42
Fatigue	5 (3.2)	6	1 (1.1)	1	1 (1.8)	1	8 (5.2)	9
Infections and infestations	31 (20.0)	47	17 (18.9)	19	16 (28.1)	22	53 (34.2)	89
Nasopharyngitis	5 (3.2)	8	4 (4.4)	4	5 (8.8)	5	12 (7.7)	17
Influenza	6 (3.9)	6	3 (3.3)	3	2 (3.5)	2	10 (6.5)	11
Upper respiratory tract infection	4 (2.6)	4	1 (1.1)	1	3 (5.3)	4	8 (5.2)	9
Skin and subcutaneous tissue disorders	28 (18.1)	51	11 (12.2)	17	8 (14.0)	10	42 (27.1)	80
Hyperhidrosis	20 (12.9)	36	9 (10.0)	14	6 (10.5)	6	34 (21.9)	57

Source: Table 58, CSR
N = number of patients assigned to specific dose at any time point
N = number of patients in a treatment group with event in specified category
OCT = oral octreotide acetate; TEAE = treatment-emergent adverse event

Reviewer comment: The values presented in Table 40 were confirmed by this reviewer analyzing Analysis Legacy Dataset ADAE with JMP version 11.0.

The number of patients with headache is significant. One could hypothesize that this is representative of rising IGF-1 levels and overall less biochemical control than what patients had experienced on long-acting injectable therapy.

7.4.3 Vital Signs

The summary of vital sign parameters provided in Table 14.3.4.23 was reviewed. No clinically significant values or patterns were identified.

7.4.4 Electrocardiograms (ECGs)

No significant ECG abnormal patterns or signals were identified. Table 14.3.4.26 shows that three patients experienced prolonged QTc interval > 500 msec. Review of dataset ADAE shows two patients ((b) (6) and (b) (6)) experienced prolonged QT interval that was reported as an adverse event, one of whom had this abnormality prior to first dose of drug.

There were no reports of ventricular tachycardia, ventricular fibrillation or torsades de pointes. Data on three patients with an AE of presyncope, one patient with syncope and two patients with seizure (convulsion) were reviewed: These AEs are unlikely related to OOA use.

See also "Cardiac Disorders" under Significant Adverse Events in section 7.3.4 of this review.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this NDA.

7.4.6 Immunogenicity

Per Chiasma, no patient developed antibodies (605 samples screened; 45 with confirmatory immune depletion analysis) against octreotide during the CORE and Extension treatment periods.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The proposed dosage administration is 40 mg per oral every day with titration up to 60 mg or 80 mg based on biochemical response and tolerability. CH-ACM-01 was not designed to compare safety issues between the doses and the sponsor has not provided any analyses in this regard. A dose dependent analysis for adverse events is inherently confounded in CH-ACM-01 as many

patients withdrew during the dose escalation phase prior to the establishment of an effective dose of MYCAPSSA.

Per the clinical pharmacology team, there does not appear to be any exposure safety relationship. For more detailed information, please refer to the clinical pharmacology review by Dr. Sury Sista.

7.5.2 Time Dependency for Adverse Events

Chiasma did not provide any analyses on time dependency to adverse events; however they did report that early discontinuations due to adverse events occurred in 80% of those treated with 40 mg within 2 months, and in all patients treated with 60 mg up to 4 months and with 80 mg from approximately 5 to 9 months.

Given the dose escalation period of two to five months and the end of the CORE period at seven months, patients who tolerated MYCAPSSA were on stable doses for a variable period and possibly short (as short as two months) of time. Of the 88 patients who tolerated the drug and entered the Extension, two dropped out because of adverse events compared to the 21 patients who dropped out of the study due to AE by the end of the CORE treatment period.

Reviewer comment: *As per the ICH guideline on exposure, most AEs first occur and are most frequent within the first few months of drug treatment. This pattern is seen in CH-ACM-01 as well.*

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not evaluated for CH-ACM-01.

7.5.4 Drug-Disease Interactions

MYCAPSSA has been studied in the acromegaly patient population (CH-ACM-01) as well as in clinical pharmacology studies of non-acromegaly patients with hepatic and renal impairment. A brief synopsis of the results of these studies is provided below. For further detail, please see Appendix 1, Table 41 describing the clinical pharmacology studies, as well as the clinical pharmacology review.

CH-PT-01 (hepatic impairment; single dose of 10 mg or 20 mg)
N = 18, patients with stable liver cirrhosis (Child-Pugh class A or B) and portal hypertension

- Hepatic venous pressure gradient reduction of at least 10%
- PK analysis indicated a dose-related but greater than dose-proportional increase in the mean plasma octreotide concentrations after OOA administration

CHI-007 (renal impairment; single dose of 40 mg)
N = 24 (n = 6, severe renal impairment, n = 6, ESRD on dialysis, 12 healthy subjects)

- Subjects with ESRD on dialysis had higher mean plasma concentrations than did those with severe renal impairment with higher mean values for C_{max}, AUC_{0-t}, AUC_{inf}, and t½, consistent with an effect of renal impairment on octreotide exposure.
- 2-fold longer Tmax in subjects with severe renal impairment compared to healthy subjects

7.5.5 Drug-Drug Interactions

Please see the clinical pharmacology review for a detailed discussion of drug-drug interactions in this study.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The non-clinical program did not identify evidence of carcinogenicity due to MYCAPSSA. For further details, please refer to Dr. Jessica Hawes' (nonclinical reviewer) review.

CH-ACM-01 was not of sufficient duration to assess for long-term carcinogenicity. A clinical safety signal for neoplasm was not identified within this NDA safety review.

7.6.2 Human Reproduction and Pregnancy Data

There were no reported pregnancies in CH-ACM-01. There are insufficient human data with MYCAPSSA and pregnancy to inform this topic. Chiasma is relying on information from the Sandostatin IR label on pregnancy, lactation and fertility for the MYCAPSSA label should it be approved.

7.6.3 Pediatrics and Assessment of Effects on Growth

MYCAPSSA is an orphan drug. The applicant was exempted from pediatric assessment and has provided appropriate documentation.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no specific reports of overdose or abuse with MYCAPSSA nor is there expected abuse potential for this drug.

7.7 Additional Submissions / Safety Issues

Chiasma submitted a 120 day clinical safety update. Since all of the clinical trials were closed at the time of NDA submission, no new safety information that has been generated. However, since the date of the NDA, Chiasma received note of a serious adverse event that was not

included in the original submission. Patient (b) (6) is a 41y White male that experienced the SAE of acute biliary pancreatitis. Please see the remainder of the narrative above in section 7.3.2 Nonfatal Serious Adverse Events.

In addition, Chiasma provided data on which patients from CH-ACM-01 re-initiated therapy for acromegaly. Of the 155 patients that enrolled in CH-ACM-01 (ITT population), 145 (93.5%) of patients continued treatment for acromegaly following the study. Treatment was initiated with SSA therapy, dopamine agonists, pegvisomant, and in one case, pituitary surgery. Three patients (b) (6) did not re-initiate therapy as it was determined that the patients either had mild disease activity or adequate biochemical and symptomatic control.

Reviewer comment: It is interesting that three patients did not require therapy by the end of CH-ACM-01. This supports the need for a washout period as some patients, although few, might not have active disease thus confounding the results.

8 Postmarket Experience

MYCAPSSA has not been marketed in any country at the time of this review.

9 Appendices

Appendix 1.

Table 41. Completed trials with MYCAPSSA

Study Number	Phase	Design of the study	Drug, doses	N	Patient population
CHI-001^	I	Open-label, crossover, single dose escalation study to establish a "bridge" between Sandostatin and OOA	OOA: 3 mg, 10 mg, 20 mg Sandostatin s.c: 0.1 mg	12	Healthy males
CHI-002^	I	Open-label, crossover, randomized study to evaluate PK of single dose of OOA under fed and fasting conditions and to compare PK of OOA and Sandostatin	OOA: 20 mg Sandostatin s.c : 0.1 mg	24	Healthy volunteers
CHI-004^	I	Cross-over study to evaluate the duration of OOA-induced intestinal permeability	OOA: 20 mg	24	Healthy volunteers
CHI-005^	I	Open-label study to investigate the PK interaction between OOA and proton pump inhibitors (PPI)	OOA: 20 mg on Days 1 and 7 Nexium:40 mg QD x 6days	14	Healthy volunteers
CHI-006^	I	Single-dose, randomized, single blind, placebo-controlled crossover study	OOA: 40 mg HCTZ, warfarin, metformin, estradiol	20	Healthy volunteers.
OCT-01^	I	Single-center, pilot, randomized, open-label, 3-way crossover, adaptive study evaluated the effect of meal size and timing on OOA PK	OOA: 20 mg	24	Healthy volunteers

OCT-02^	I	Single-dose, crossover, randomized, single blind, placebo-controlled study evaluated the effect of OOA on the bioavailability of digoxin and lisinopril and the influence of ingested water volume on the PK profile of OOA	OOA: 40 mg	18	Healthy volunteers
OCT-03	I	Randomized, open-label, 3-sequence, crossover study to evaluate the interaction between OOA and drugs that affect GI motility and the effect of body posture on absorption of OOA	Oral octreotide acetate: 40 mg Metoclopramide 20 mg Loperamide 4 mg	18	Healthy volunteers
OCT-04	I	A randomized, single-blind, placebo-controlled, two-way crossover, single dose study to evaluate the interaction between OOA and cyclosporine	OOA: 40 mg Cyclosporine 300 mg Placebo	18	Healthy volunteers
CH-PHT-01^	II	Open label, dose-finding study evaluated the effects of OOA on hepatic venous pressure gradient	OOA: 10 mg or 20 mg	18	Subjects with cirrhosis and portal hypertension
CHI-007^^	I	Open-label, single dose study, to evaluate PK of OOA in subjects with severe renal impairment and end-stage renal disease (ESRD)	OOA: 40 mg	24	Subjects with severe renal impairment (6), ESRD (6) and healthy volunteers (12)
CH-ACM-01^^^	III	Open-label, comparative study to evaluate efficacy and safety of OOA in patients with acromegaly who are currently receiving somatostatin analogs.	OOA: 40 mg/day-80 mg/day based on IGF-1 levels	155	Patients with acromegaly

Source: Dr. Zemskova' s Octreolin pre-NDA summary, May 14, 2014

Appendix 2.

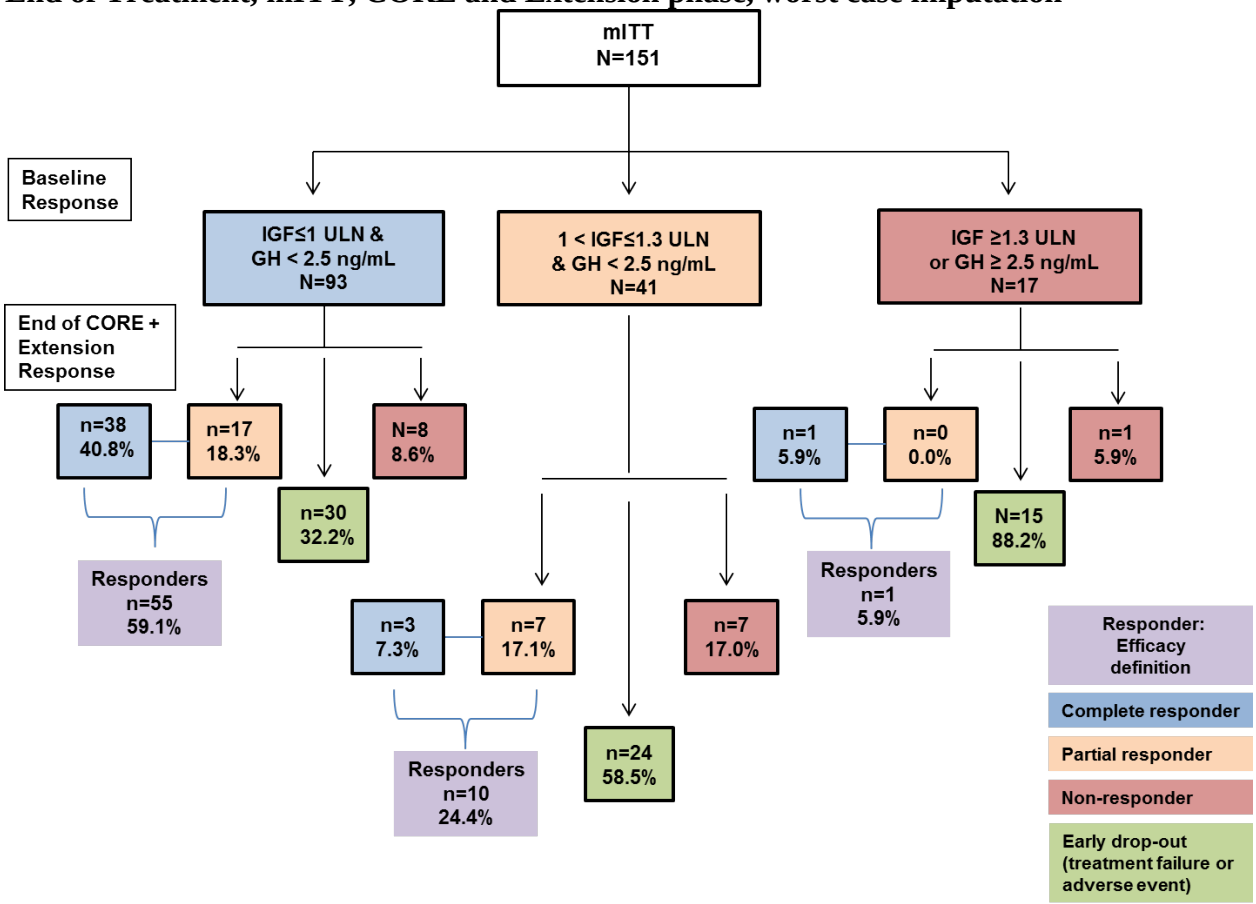
Table 42. Schedule of Assessments

Study Procedures	Screening	Baseline	Core Treatment Period (at Least 7 Months)			Extension Treatment Period (6 Months)	Follow-up
			Dose Escalation Phase		Fixed Dose Phase	Fixed Dose Phase	
Visit	S	BL	TA1 – TA15		TB1 – TB6/EOT	TE1 – TE3/EOT-Ext	FU
Week	≤ 4 Weeks	≤ 4 Weeks	Day 0	Every 2 Weeks (2-5 Months)	Monthly (2-5 Months)	Every Second Month (6 Months)	EOT or EOT-Ext + 2 Weeks
Obtain signed informed consent	X				X[1]	X[1]	
Screening number assignment	X						
Parenteral somatostatin analog therapy	X	X					
Inclusion/exclusion criteria	X				X[1]	X[1]	
Medical history/demographics	X						
Complete physical examination	X	X					
Patient training (food, diary, drug)			X	X	X	X	
Symptom-directed physical examination			X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
ECG[2]	X	X	X	X[2]	X[2]	X[2]	X
Pituitary MRI	X				X[3]		
Gall bladder ultrasound	X				X[4]	X[4]	X
Hematology[5]	X	X	X	X[5]	X[5]	X[5]	X
Chemistry[6]	X	X	X	X[6]	X[6]	X[6]	X
Insulin and HbA_{1c}		X			X[7]	X[7]	
TSH, free T4, and vitamin B12		X			X[7]	X[7]	
Lipid profile[8]		X			X[8]	X[8]	
Acute phase reactants (CRP and TNF-α)		X		X[9]	X[9]	X[9]	X
Octreotide antibodies assessment			X[10]	X[10]	X[10]	X[10]	
Urinalysis	X						
Serum pregnancy test (WOCBP only)[11]	X	X	X	X	X	X	X
GH[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	
IGF-1	X	X	X	X	X	X	
PK sub-study[13]					X		
Concomitant medications recording	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Study drug accountability and diary review				X	X	X	
Study drug administration			X	X[14]	X	X	
Assess need for early rescue				X	X	X	
Treatment satisfaction		X		X[15]	X[15]	X[15]	X
Food and dosing assessment				X[16]	X[16]	X[16]	

Source: CSR, Table 3
Footnotes in table are not presented here

Appendix 3.

Figure 10. Shift in IGF-1 and mean Growth Hormone response categories from Baseline to End of Treatment, mITT, CORE and Extension phase, worst case imputation



Source: Data from response to Information request received by FDA February 24, 2016, Table 20

For text reference, please see section 6.1.4, "Primary Efficacy Endpoint – Extension population"

Appendix 4.

Table 43. List of Treatment failure Subject IDs

Number of patients	Patient ID	Treatment Failure	Treatment Period
1	(b) (6)	Treatment Failure	Dose Escalation
2		Treatment failure	Fixed Dose
3		Treatment failure	Dose Escalation
4		Treatment failure	Dose Escalation
5		Treatment failure	Dose Escalation
6		Treatment failure	Dose Escalation
7		Treatment failure	Dose Escalation
8		Treatment failure	Dose Escalation
9		Treatment failure	Fixed Dose
10		Treatment failure	Dose Escalation
11		Treatment failure	Dose Escalation
12		Treatment failure	Dose Escalation
13		Treatment failure	Dose Escalation
14		Treatment failure	Dose Escalation
15		Treatment failure	Dose Escalation
16		Treatment failure	Dose Escalation
17		Treatment failure	Dose Escalation
18		Treatment failure	Dose Escalation
19		Treatment failure	Fixed Dose
20		Treatment failure	Dose Escalation
21		Treatment failure	Dose Escalation
22		Treatment failure	Dose Escalation
23		Treatment failure	Dose Escalation
24		Treatment failure	Dose Escalation
-		Lost to follow up	Dose Escalation
-		Lost to follow up	Dose Escalation

*Source: Table 14.1.4, CSR
Note: this does not include the 14 patients who elected not to continue into the extension treatment period or those who terminated early from the extension.
Highlights are to show differences

9.1 Literature Review/References

References have been cited as footnotes throughout the document.

9.2 Labeling Recommendations

Not applicable.

9.3 Advisory Committee Meeting

There is no advisory committee planned for MYCAPSSA at this time.

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/s/

SMITA B ABRAHAM
04/12/2016

MARINA ZEMSKOVA
04/12/2016