CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208232Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	6/23/2020
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	208232
Applicant	Chiasma Inc.
Date of Submission	12/26/2019
PDUFA Goal Date	6/26/2020
Proprietary Name	Mycapssa
Established or Proper Name	Oral octreotide
Dosage Form(s)	Capsule/ 20 mg
Applicant Proposed Indication(s)/Population(s)	Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)
Applicant Proposed Dosing Regimen(s)	Starting dose of (b) (4) mg/day (b) (4) Doses 40, 60 or 80 mg/day, in two divided doses
Recommendation on Regulatory Action	Approval pending labeling negotiation
Recommended Indication(s)/Population(s) (if applicable)	Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)
Recommended Dosing Regimen(s) (if applicable)	Starting dose 40 mg/day (20 mg twice daily) Doses: 40, 60, 80 mg/day, in two divided doses

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer Review	Sonia Doi
Statistical Review	Anna Kettermann, Feng Li, Mark Rothmann
Pharmacology Toxicology Review	Federica Basso
OPQ Review	Muthukumar Ramaswamy, Joseph Leginus, Peter Krommenhoek, Rajesh Savkar, Leeza Rahimi
Clinical Pharmacology Review	Suryanarayana Sista, Jayabharathi Vaidyanathan
OPDP	Charuni Shah
OSE/DMEPA	Melina Fanari, Sevan Kolejian
DPMH	Christos Mastroyannis, Tamara Johnson

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPMH=Division of Pediatric and Maternal Health

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Acromegaly is a rare disease caused by growth hormone (GH)-secreting pituitary tumor, which results in excess GH and insulin-growth factor (IGF-1) secretion. 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., obesity, insulin resistance/diabetes). Patients with acromegaly have higher mortality rates than an age-matched control population due to metabolic complications[1].

To prevent morbidity and mortality in patients with acromegaly, the 2014 Endocrine Society Clinical practice guideline [2] recommend that subjects with acromegaly be treated with surgery (first-line therapy), radiation or medical therapies with a goal to normalize IGF-1 values, which signifies control of acromegaly and to decrease a random GH as it correlates with control of acromegaly. Biochemical control of disease occurs alongside rigorous treatment of other prevalent comorbidities (hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis and sleep apnea).

Approved therapies with an indication for the treatment of acromegaly include synthetic somatostatin analogs (SSA), a GH receptor antagonist and a dopamine agonist (bromocriptine). Four SSAs are currently available for medical treatment of acromegaly in USA (lanreotide, long-acting and short acting octreotide and pasireotide). Pegvisomant (Somavert) is an analog of GH that has been structurally altered to act as a GH receptor antagonist and has been approved for the treatment of patients with acromegaly.
The Agency has used normalization of IGF-1 and/or decrease in GH as a surrogate of benefit to support approval of several SSAs indicated to treat acromegaly. Registration trials have shown that all SSAs formulations normalize IGF-1 levels in 40-60% of patients or decreased GH levels to ≤ 2.5 mcg/l in 50-60% of patients, respectively, in treatment-naïve patients or in patients previously treated with SSAs. All approved SSAs are injectable formulations, thus, oral formulation of SSAs may be more convenient to the patients with acromegaly.

Benefits
The Applicant has demonstrated in a single pivotal, multi-center, randomized, double-blind, parallel-arm phase 3 trial (study OOC-ACM-303) that treatment with oral octreotide in patients with acromegaly previously been controlled on long-acting octreotide or lanreotide maintained the biochemical control of the disease at the end of 36-week treatment period. In this study, a greater proportion of individuals randomized to oral octreotide maintained biochemical control (based on the IGF-1 level ≤ 1 XUNL) of the disease at the end of the trial (i.e., 58% in active drug group vs. 19%, in placebo group, respectively). In addition, all but one subject treated with oral octreotide-maintained GH ≤ 2.5 ng/ml at the end of the trial. 75% of patients treated

[1] 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.
[2] 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.

with oral octreotide did not require rescue with injectable SSAs during the trial and continued on oral octreotide till the end of the trial. The overall data in this trial establish the benefit of oral octreotide. The response rate to oral octreotide treatment was also consistent with expectations and was comparable to the response rate to other SRLs (based on IGF-1 and/or GH levels) in patients with acromegaly.

Risks

The risks associated with the use of oral octreotide are generally consistent with risks expected for the SSAs class of drugs. Major toxicities associated with the use of SSAs include the risks of gastrointestinal disorders (nausea, vomiting, abdominal pain), disorders of gallbladder and bile duct, hyper and hypoglycemia, elevation in liver enzymes, bradycardia and QT prolongation.

The most common adverse events (AE) that occurred in patients treated with oral octreotide in the 9-month treatment phase of study 303 were diarrhea (28.6% of patients), nausea (21.4%), abdominal discomfort (14.3%), vomiting (14.3%). Hepatobiliary adverse reactions (cholecystitis and cholelithiasis) occurred in 2 patients, hyperglycemia-related AEs in 5 patients. The types and frequencies of these AEs seen in study 303 were expected based on the known safety profile of SSA drug class. Overall, no new safety signals were identified with use of oral octreotide in patients with acromegaly in clinical program. Product labeling will be used to mitigate the known risks associated with oral octreotide in the acromegaly population.

In conclusion, safety and efficacy data from the single pivotal, randomized, double-blind, phase 3 study conducted to support the approval of oral octreotide for the proposed indication have demonstrated that the benefits outweigh the potential risks in this population. Specifically, oral octreotide provides a benefit in maintaining normal IGF-1 and decreased GH levels in patients with acromegaly. Safety issues were consistent with expected class specific side effects (e.g., gallbladder abnormalities, hyperglycemia, GI adverse reactions); no new safety issues were identified. Safety issues will be mitigated through labeling. Thus, I recommend approval of oral octreotide.

However, I recommend to indicate the drug for patients who responded and tolerated previous treatment with octreotide and lanreotide only, since no patients on pasireotide were enrolled in the trial and the efficacy of the drug in maintenance of pasireotide-achieved control of acromegaly was not evaluated in the trial. Despite sharing many similarities to octreotide and lanreotide, pasireotide differs in its somatostatin receptor (SSTR) binding characteristics; octreotide and lanreotide bind primarily to SSTR2 vs. pasireotide binds to a broader range of receptors: SSTR 1, STTR2, STTR3 and SSTR5 and has particular affinity for SSTR5. Thus, some patients who controlled on pasireotide, might lose the control of the disease when switched to octreotide and actual response in these patients to oral octreotide remains unknown.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acromegaly is a rare disease caused by a GH-secreting pituitary tumor. • Chronic hyper-secretion of growth hormone (GH) stimulates production of insulin-like growth factor-1 (IGF-1) from effector organs that leads to disordered somatic growth, metabolic abnormalities, decreased quality of life and increased mortality, primarily due to metabolic complications. • The 2014 Endocrine Society Guideline on acromegaly recommends age-normalizing IGF-1 levels and random GH level ≤ 1 mcg/L in subjects with acromegaly as a means of preventing acromegaly-related complications (hypertension, hyperglycemia, obesity, osteoarthritis, sleep apnea, etc.), and thus improving morbidity and mortality in this population.	• Prolonged hypersecretion of GH and IGF-1 is associated with increased morbidity and mortality in patients with acromegaly, including decreased overall quality of life (QOL) and increased death due to metabolic complications. • Normalization of IGF-1 and GH is the goal of treatment and is associated with improvement in the signs and symptoms of the disease and amelioration of complications such as diabetes and obesity. • IGF-1 levels correlate with comorbidities better than GH levels**Error! Bookmark not defined.**
Current Treatment Options	• Transsphenoidal surgery is a first-line treatment for acromegaly. • Medical therapy is a second-line treatment option in patients not suitable for surgery and in patients with persistent or recurrent disease after surgery. • Approved therapies for the treatment of acromegaly include injectable formulations of somatostatin analogs and a GH receptor antagonist and an oral formulation of dopamine agonist (bromocriptine). • Somatostatin analogues (octreotide) are recommended by current guidelines from professional societies as the first-line medical therapy of acromegaly. • Dopamine agonists are less effective than alternatives and are not recommended as first-line medical therapy of acromegaly.	• Somatostatin analogs are the first line medical therapy of acromegaly. • Certain injectable SSAs analogs are approved for the treatment of acromegaly. • Therapeutic option with oral formulation of somatostatin analog would be valuable.
Benefit	• Oral octreotide maintained IGF-1 level ≤ 1XUNL in the 58% of patients with acromegaly who achieved disease control on long-acting SSAs compared to placebo (19%) in pivotal adequate and well controlled study. • All but one patient treated with oral octreotide also maintained GH ≤ 2.5 ng/ml till the end of the trial. • No patients who achieved the disease control at baseline with pasireotide were enrolled in the trials.	• Treatment with oral octreotide maintains biochemical control of acromegaly achieved on octreotide or lanreotide and should reduce morbidity (e.g., diabetes, hypertension) and mortality in patients with acromegaly. • The efficacy of the drug in patients who were treated previously with pasireotide formations is unknown.

Risk and Risk Management	• The safety profile of oral octreotide has been generally well characterized and is generally consistent with the class • No new safety signals for oral octreotide in the acromegaly population were identified in clinical program • The most common AEs in study OOC-ACM-303 were diarrhea (28.6% of patients), nausea (21.4%), abdominal discomfort (14.3%), vomiting (14.3%). • Hepatobiliary adverse reactions (cholecystitis and cholelithiasis) occurred in 2 patients, hyperglycemia-related AEs in 5 patients. • Liver abnormalities (hepatitis acute, bilirubin increase, GGT increased, transaminase increased) occurred in 1 patient, each during the trial. • No QT interval changes were reported in patients treated with oral octreotide • Labeling will be sufficient to mitigate risks associated with use of oral octreotide in the acromegaly population	• Treatment with oral octreotide was associated with GI adverse events, hepatobiliary AEs, glucose abnormalities. All risks are monitorable risks. Monitoring and interventions will be recommended in labeling to address these risks. • Liver enzymes abnormalities, QT interval prolongation and bradycardia are the risks expected for the SSAs class of drugs and will be mitigated through the labeling • No risks identified require risk management beyond labeling to warrant consideration of a Risk Evaluation and Mitigation Strategy (REMS).

2. Background

On 6/12/2015 Chiasma submitted a New Drug Application (NDA) for octreotide, delayed release capsules for oral use (referred to as oral octreotide hereafter) 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 who responded to and tolerated treatment with* (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).

The proposed doses are a 20 mg twice daily- 40 mg twice daily.

The drug is octreotide 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) nd enables an intestinal absorption of the octreotide.

On 4/15/2016 Chiasma was issued a Complete Response Letter (CRL)[3] due to the following deficiencies:

- "Multiple deficiencies were identified at (b) (4) located at (b) (4) during the inspection (refer to CMC review from 4/12/2016) (Deficiency #1).
- The data obtained from a single pivotal Phase 3 open-label single arm study in patients with acromegaly (Study CH-ACM-01, refer to as Study 01 hereafter) did not provide substantial evidence "that the drug is effective as the effect captured in study CH-ACM-01 cannot be purported to represent the effect of Mycapssa" due to the multiple clinical and statistical deficiencies (Deficiency #2)."

To address the deficiencies the Applicant was asked to resolve deficiencies identified at (b) (4) (b) (4) facility and to establish efficacy of Mycapssa in a new prospective well-control trial.

In this resubmission, the Applicant submits the updated drug substance facility information and data on the efficacy and safety of the drug in the proposed indication from the new clinical trial (OOC-ACM-303, refer to as Study 303 hereafter).

Acromegaly is a chronic, rare disease with the annual incidence of approximately 3 per million[4]. The etiology of acromegaly is a GH (growth hormone)-secreting pituitary tumor in majority of the cases. The disease is characterized by disordered somatic growth and metabolic

[3] For full details refer to Complete Response Letter in DARRTS from 4/15/2016
[4] Melmed S. Acromegaly. N Engl J Med. 2006 Dec 14; 355(24):2558-73

abnormalities and arises due to chronic hyper-secretion of GH which acts to stimulate production of insulin-like growth factor-1 (IGF-1) from effector organs. 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., obesity, insulin resistance/diabetes). Patients with acromegaly have higher mortality rates than an age-matched control population due to metabolic complications[5].

To prevent morbidity and mortality in patients with acromegaly, the 2014 Endocrine Society Clinical practice guideline**Error! Bookmark not defined.** recommend that subjects with acromegaly be treated with surgery, radiation or medical therapies, or a combination of these with a goal 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. Biochemical control of disease occurs alongside rigorous treatment of other prevalent comorbidities (hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis and sleep apnea).
In general, surgery is the first-line therapy and the treatment of choice for acromegaly. The second-line therapy of acromegaly includes radiation and medical therapy. Medical therapy is employed in patients with persistence or recurrence of acromegaly despite having undergone surgery or radiation and in patients who are not surgical candidates.

Availability of medical therapies for the treatment of acromegaly

Several drugs are approved in US for the treatment of acromegaly including somatostatin analogs, a GH receptor antagonist and a dopamine agonist (bromocriptine)). Cabergoline, another dopamine agonist is currently used off-label for the treatment of acromegaly.

- Somatostatin analogs (SSAs) are the first-line medical therapy of acromegaly**Error! Bookmark not defined.**.

Somatostatin is an endogenous peptide produced in the hypothalamus; it inhibits synthesis and release of GH from the pituitary gland. Four injectable synthetic analogues of SSAs are currently available for medical treatment of acromegaly in US (lanreotide (Somatuline Depot), octreotide (Sandostatin LAR Depot and Sandostatin IR) and pasireotide (Signifor)). It should be noted that all but one SSAs are approved for the treatment of acromegaly; Sandostatin LAR is approved for a maintenance indication only, i.e. for those patients who have responded to and tolerated Sandostatin IR injections.

The response rate to the treatment with SSAs is variable and depends on multiple factors including the type of biomarkers and threshold used to evaluate the response (GH ≤ 5 mcg/l, GH ≤ 2.5 mcg/l, IGF-1 normalization alone, IGF-1 normalization and GH ≤ 2.5, etc.), the population studied (patients who are sensitive to the drug vs. treatment-naïve patients), definition of disease control at baseline (partial control, GH ≤ 5 mcg/L, ≤ 2.5 mcg/L, etc.) and assays used to evaluate biomarkers. In addition, SSAs are not expected to be effective in all patients. Overall, the registration trials have shown that decrease in GH levels to ≤ 2.5 mcg/l

[5] 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.

was observed in 35-55% of patients. When response rate was based only on IGF-1 normalization, 24-62% of patients had normalization of IGF-1 values at the end of treatment. It should be noted, that the response rate based on IGF-1 values is less affected by population preselection[6].

All SSAs are associated with adverse reactions including gallbladder abnormalities, hyperglycemia, diabetes, QT interval prolongation, and gastrointestinal AEs. The need of injections can affect compliance or acceptability of the treatment.

- Pegvisomant (Somavert) is an analog of GH that has been structurally altered to act as a GH receptor antagonist and has been approved for the treatment of patients with acromegaly. Pegvisomant is an injectable drug that reduces IGF-1 levels by 27-63% from baseline and normalizes IGF-1 in up to 82% of patients after 3-month of treatment. Treatment with pegvisomant is associated with such adverse events as hypoglycemia, liver toxicity, lipohypertrophy and injection site reactions.

- Dopamine agonists: The oral formulations of dopamine agonists cabergoline (off-label use) and bromocriptine (labeled use) are typically recommended for the treatment of patients with mild disease because dopamine agonists have been reported to be less effective than alternatives.

Regulatory background
The original application has a long regulatory history which has been reviewed previously[7]. This section summarizes only the major regulatory interactions with the Applicant related to the resubmission of this NDA and occurred after the CRL was issued (refer to Dr. Doi's review for further details).

- A Type A meeting between the Agency and the Applicant was held on 6/8/2016.

During this meeting the CRL deficiencies and information required to resolve these deficiencies and further clinical development plans were discussed. The Agency reiterated that in order to provide substantial evidence of effectiveness for Mycapssa, a new randomized and controlled clinical trial is needed. The trial should be designed to minimize bias and ensure the effect size captured is attributable to Mycapssa and not to confounders (e.g., inactive disease at baseline, carryover effect).

- Following a Type A meeting, the Applicant submitted a new proposal for an alternative path forward for Mycapssa, i.e. to reanalyze serum samples collected 2 weeks after the completion CH-ACM-01 study (refer to as study 01 here after) to address uncertainties that surrounded the efficacy of Mycapssa captured in Study 01 (inactive disease at baseline). However, the Agency reiterated that new clinical trial data is the path most likely to lead to successful resolution of clinical deficiencies. The Division emphasized that "*following a path other than the one laid out in CRL is a more risky proposition and any alternative plans*

[6] Pamela U Freda [1], Laurence Katznelson, Aart Jan van der Lely, Carlos M Reyes, Shouhao Zhao, Daniel Rabinowitz. Long-acting Somatostatin Analog Therapy of Acromegaly: A Meta-Analysis. J Clin Endocrinol Metab. 2005 Aug;90(8):4465-73.
[7] For full details refer to CDTL Memo in DARRTS dated 4/16/2016

should be discussed with the Agency prior to initiating and executing these plans" (refer to post-meeting comments in Type A Meeting Minutes Memo in DARRTS from 7/19/2016).

- A Type C Guidance teleconference was held between FDA and the Applicant on 10/31/2016. During this meeting, the Applicant's plan to provide the efficacy data from new Phase 3 study (OOC-ACM-302, refer to as Study 302 hereafter) to address a deficiency in CRL was discussed. Study OOC-ACM-302 is a phase 3, randomized, open label, active controlled study to evaluate maintenance of response and safety in acromegaly patients treated with octreotide capsules, and in patients treated with standard of care SRL who previously tolerated and demonstrated biochemical control on both treatments.

The Agency disagreed with the Applicant that the design of the proposed 302 study would address deficiencies stated in the CRL. The Agency expressed multiple concerns with the study design including enrolling patients without confirmation of active disease at baseline, use of run-in-phase which pre-selects responders, definition of the disease control (i.e. IGF-1 ≤ 1.3 X upper limit of normal reference range (ULN)), etc. The Agency recommended again to conduct randomized, double-blind and controlled study to address CRL deficiencies.

- To address the Agency's recommendations, the Sponsor proposed to evaluate the efficacy and safety of the drug in the intended population in a new randomized, double blind, placebo-controlled trial and submitted a request for a Special Protocol Assessment (SPA) of this study protocol (Study 303) on 12/16/2016. The Division issued a SPA agreement letter on 8/4/2017. The Division and the Sponsor reached overall agreement on the proposed study design including the statistical analysis plan (SAP). Some of the trial design attributes required for the agreement were:

- the study will be a double-blind, randomized, placebo control study
- the duration of double-blind placebo controlled period of the study will be 36 weeks
- the proposed primary endpoint will be the proportion of patients who maintain an IGF-1 level ≤ 1XULN at the time period between weeks 34 through 36 at the end of the controlled period.
- maintenance of the response will be evaluated based on determining the average IGF-1 level available for the last 2 IGF-1 assessments obtained between weeks 34 and 36. Patients with average IGF-1 ≤ 1 X ULN will be classified as responders. Patients with average IGF-1 level > 1 X ULN at the end of the study and those who discontinue study medication during the study will be classified as non-responders.
- the primary analysis will be conducted on Full Analysis Set (FAS) population defined as all randomized patients regardless of whether the study drug was received. Sensitivity analyses will be conducted to examine the impact of missing data using multiple imputation.
- the sample size estimate for acromegaly (50 patients) is satisfactory considering that the amount of missing data will be kept at minimum.
- selected patient population will be patients with acromegaly in whom prior treatment with SSAs has been shown to be effective and tolerated and with average IGF-1 ≤ X ULN (based on 2 values) at baseline
- the timing of IGF-1 assessments at baseline. Eligibility will be determined based on average IGF-1 of Screening 1 and Screening 2 visits. Baseline IGF-1 levels, for analysis purposes, will be determined based on average of Screening 2 and Baseline visits.

Screening 2 visit will occur within 2 weeks prior to Baseline/randomization visit. Baseline visit will be scheduled within ± 3 days of the intended routine dosing interval following the last injection.
- predefined withdrawal criteria that includes IGF-1 levels > 1.3 XULN AND exacerbation of acromegaly clinical signs and symptoms as defined in the protocol

- The original SPA was further amended (requested on 1/26/2018, approved on 5/11/2018)

This Amendment revised the secondary and exploratory endpoints within the clinical protocol and SAP. The following secondary endpoints, (b) (4) were changed to "descriptive endpoints" (which are without adjustment for multiplicity). In addition, the (b) (4), proportion of patients who begin rescue treatment prior to and including week 36, was changed to secondary endpoint status. The proposed changes were found to be acceptable by the biostatistician and clinical reviewer (refer to reviews in DARRTS from 5/2/2018 and 5/3/208, respectively).

- Type C meeting (10/8/2019)

The Applicant and the Agency discussed the overall plan for NDA resubmission, content and format of the different NDA modules and the information needed to be included in NDA to address deficiencies outlined in CRL.

The Agency requested to that the safety data for Study 01 and Study 303 be presented separately in integrated summary of safety due to the differences in the study designs and populations enrolled in the studies. The Agency also asked the Applicant to include summaries of safety findings from study OOC-AACM-302 including narratives for all death, SAEs and AEs leading to discontinuation. This study is being conducted by the Applicant to support the marketing of the drug in the European Union; the study is currently ongoing.

The Applicant asked the Agency to confirm that the deficiencies conveyed to (b) (4) (b) (4) (deficiency #1 in CRL) have been resolved and is no longer a deficiency for NDA resubmission. The Agency indicated that the resolution of the above deficiency cannot be confirmed at this time since FDA's evaluation of GMP status of facilities listed in NDA will be conducted upon receipt of NDA.

The Agency also indicated that whether the results from the study 303 will be sufficient for resolution of deficiency #2 in CRL will be a review issue. Lastly, the Division agreed that no additional clinical pharmacology studies needed to be included in NDA resubmission.

- Type B pre-NDA meeting was held between the Applicant and the Agency on 10/8/2019.

The Division agreed that completed Study 303 may address CRL deficiency #2 and is adequate to support resubmission of NDA. However, the Division indicated that adequacy of the data derived from this study for approval of NDA will be a review issue.

The Division disagreed with the Sponsor that Study CH-ACM-01 is necessary to support the submission since the results of this study were already reviewed and it was determined that these results do not provide substantial evidence of efficacy and safety of the drug in the intended population for the reasons outlined in CRL. The Agency also noticed that the data from this study is not interpretable and therefore not acceptable for (b) (4).

The Division also asked to include in NDA a sub-group analysis per dose level of prior SSAs injection.

Lastly, the Division also asked for multiple clarifications regarding the results of the analyses of primary and secondary endpoints to be included in NDA (e.g., the response definitions for primary and secondary endpoints, definition of "failure" in the analysis of secondary endpoint, median time to loss of response, etc.)

- The drug received orphan designation status for "the oral treatment of acromegaly" on 5/11/ 2010 by the Office of Orphan Products Development.

3. Product Quality

Office of Pharmaceutical Quality (OPQ) recommends approval of this NDA.

The original NDA received CR, and one of two deficiencies listed in CRL for the original NDA was an issue associated with drug substance manufacturing facility, (b) (4) (b) (4) The facility did not have an acceptable compliance status and a Withhold was issued and the CR letter contained the deficiency outlined below (Deficiency #1):

> *"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."*

In this resubmission, a review of the compliance history of the (b) (4) was conducted. The facility had undergone three surveillance inspections since (b) (4) and all were with voluntary action indication (VAI) outcomes. Therefore, the overall recommendation for the facilities with the application in Panorama is adequate (refer to Dr. Krommenohoek's review in Panorama dated 5/18/2020).

There were no approvability issues with drug substance, drug product, process, and biopharmaceutics sections during the review of the original NDA and no new chemistry, manufacturing and control (CMC) information was included in this resubmission. CMC and biopharmaceutics reviewers continue to recommend approval (Refer to the reviews in DARTTS from 5/7/2020 and 6/1/20).

The active ingredient in Mycapssa, octreotide, has a molecular weight of 1019.3.
Mycapssa is manufactured as delayed-release capsules and formulated to contain 20 mg of octreotide. An enteric coated capsule contains (b) (4) (b) (4) (b) (4) applicant to enhance peptide absorption at the intestinal wall. Excipients are polyvinylpyrrolidone (PVP-12), sodium caprylate, magnesium chloride, polysorbate 80, glyceryl monocaprylate, glyceryl tricaprylate, gelatin, gelatin capsules and Acryl-EZE®

(methacrylate). (b) (4) are included in the NDA.

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

The nonclinical pharmacology/toxicology
Review team recommends approval of the application. No new nonclinical pharmacology/toxicology data were submitted.

5. Clinical Pharmacology

The clinical pharmacology review team recommends approval of the application. The drug's clinical pharmacology has been previously reviewed and no new information was included in the current submission.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Drs. Doi (Clinical) and Kettermann (Biostatistical) have reviewed the efficacy data and recommend approval (refer to Clinical Review in DARRTS from 6/9/2020) and Statistical Review in DARRTS from 6/1/2020). I agree that the applicant has provided the substantial evidence of effectiveness necessary to support approval. The evidence was provided from data derived from a new pivotal trial 303 submitted with the re-submission.

Although the Applicant included efficacy data from Study 01 to support the efficacy of the drug in the intended population, these results were previously reviewed by the Agency and it was determined that these results do not provide substantial evidence of efficacy of the drug in the intended population for the reasons outlined in CRL. Thus, these results will not be discussed in this memo; refer to CDTL review from 4/16/2016 for details. However, the study provided additional supportive safety data obtained in patients with acromegaly during the treatment with oral octreotide. These data captured additional class specific AEs not observed in study 303 most likely because of the small size of the study. Refer to the Safety section below.

The design of Study 303 is briefly summarized below.

Study 303 was a randomized, double blind, placebo-controlled, multicenter (19 sites in US), study evaluating efficacy and safety of oral octreotide in patients with acromegaly who previously tolerated and demonstrated biochemical control on long-acting injectable SSAs (Sandostatin LAR Depot or lanreotide).

As stated above, the design (exclusion and inclusion criteria, endpoints, size of the study and analysis plan for this pivotal study were agreed under SPA agreement issued on 8/4/2017.

The primary objective of the study was to evaluate the efficacy of oral octreotide versus placebo in maintenance of biochemical control in patients with acromegaly who previously demonstrated biochemical control on SSAs.

The secondary objectives of the study were to evaluate the efficacy of oral octreotide versus placebo in maintenance of biochemical control based on GH ≤ 2.5 ng/ml in intended patient population and to evaluate safety of oral octreotide for the proposed indication.

Patient population
Patients > 18 years old with acromegaly (defined as documented evidence of GH-secreting tumor based on MRI/pathology report and documented evidence of IGF-1 levels > 1.3X ULN) and who achieved biochemical control on previous SSAs (long-acting octreotide or lanreotide, but not pasireotide) therapy were eligible to participate in the study. The reason for not allowing patients on pasireotide to be enrolled in the study was not specified in the protocol. The required duration of previous SSAs therapy was at least 6 months with being on stable dose for at least 3 months prior to study enrollment. The biochemical control on SSAs at baseline was defined as average IGF-1 (calculated from 2 samples obtained during screening period) ≤ 1XULN. As discussed during T-con meeting with the Applicant on 10/31/206 and agreed in SPA, the washout of subjects on injectable SSAs and re-confirmation of the disease activity prior to initiating treatment is not required in a placebo-controlled trial.

The Applicant appropriately excluded patients who had surgery within the last 6 months prior to the enrollment and patients who underwent pituitary radiation in past, since the effect of surgery and radiation treatment on acromegaly control may be delayed and confound overall efficacy of the drug. The Applicant also excluded patients with unstable cardiac disease, uncontrolled diabetes or symptomatic cholelithiasis due to the known adverse reactions of hyperglycemia, QT-prolongation and cholelithiasis associated with SSAs.

Study design
The study was comprised of screening period, a 36-week double blind placebo-controlled treatment period (Core Phase) and open-label extension period (OLE).

Screening period (up to 8 weeks)
During the screening period the maintenance of the biochemical control achieved with previous SLRs treatment was confirmed and was based on average IGF-1 value ≤ 1 X UNL. The average value was calculated from two IGF-1 values obtained at two screening visits, each. Screening visit 2 had to occur within 2 weeks of randomization.

Core Phase (36 weeks)
All eligible patients were randomized at Baseline to receive oral octreotide or placebo in a 1:1 ratio, and randomization was stratified by previous SSAs dose (low (octreotide 10 mg/month or lanreotide 60 mg/month or 120 mg/8 weeks) vs. high dose). Baseline visit was scheduled within ±3 days of the intended routine dosing interval following the last SSA injection.
Patients visited clinic every 4 weeks during the controlled period. During each visit, IGF-1 levels

were collected, and patients were assessed for the presence of symptoms of acromegaly and drug tolerability.

Open-Label Extension Period (OLE)
Following completion of the controlled period (either on study drug or upon meeting predefined withdrawal criteria (refer to these criteria below) and being followed per protocol through week 36), patients were offered entry into OLE to receive octreotide capsules.

Follow-up Period
Patients who discontinued study medications during the OLE for any reason, or who completed the 36-week controlled period but did not enter OLE were continued with or were reverted to their prior injectable SSAs treatment and were followed-up for 12 weeks after their last treatment visit.

Dosing regimen
The starting dose was 1 capsule (20 mg) twice daily (total daily dose 40 mg/day). Study medication was administered twice daily with a glass of water, at least 1 hour prior to meal or 2 hours after meal.

The dose could be increased to 60 mg/day, and subsequently to 80 mg/day at any time during the study if any of the following criteria had been met: increase in IGF-1 levels (defined as > 30% increase in IGF-1 level compared to baseline level), IGF-1 level > 1 X ULN on two consecutive visits, new or worsening of acromegaly symptoms (headache, fatigue, perspiration, swelling, arthralgia, dysglycemia, hypertension, or other signs in that investigator considered to be related to acromegaly).

At any time during controlled period, those patients who were treated with maximum dose of study medication (80 mg/day of drug or placebo) and met predefined withdrawal criteria (as agreed under SPA) defined as IGF-1 > 1.3 UNL and exacerbations of signs/symptoms of acromegaly for 2 consecutive visits while treated with 80 mg/day were allowed to discontinue study medication and be rescued with injectable SSAs. Patients could also discontinue study medications during controlled period and start injectable therapy for reasons other than the predefined withdrawal criteria (e.g., adverse events, patient's decision). All patients who discounted treatment with study drug preliminary were required to be followed up until Week 36.

Retrospectively, the dose titration based solely on acromegaly symptoms is unclear. The primary objective of the study was to evaluate the biochemical control of the disease based on normalization of IGF-1 levels; improvement in symptoms was not included in primary objective of the study. Overall, the study was not designed to evaluate the improvement in signs and symptoms (presence of specific symptoms was not required at baseline, change in symptoms was not a primary or secondary endpoint, no prespecified analysis was conducted to assess the improvement in symptoms on the drug vs. placebo at the end of the study, etc.). As per Endocrine Society guideline (2014), the treatment goal is a maintenance of a biochemical control that signifies the control of acromegaly. Thus, it remains unclear why patient with controlled IGF-1 remains symptomatic, since normalization of biochemical markers correlates with control of

acromegaly[8]. In addition, acromegaly symptoms used to guide patient withdrawal from the study were not specific and may be related to other concomitant medical conditions (hypertension, diabetes, infections, etc.) and/or medications.
It should be also noted, that many of these symptoms (e.g., headache, fatigue, sweating) are subjective and there are no validated patient-reported outcome assessing the significance of these symptoms to the patients available to date.

Primary efficacy outcome
The primary efficacy endpoint was a responder analysis examining the number of subjects in FAS population who maintained biochemical response at the end of the controlled period. FAS was defined as all randomized patients regardless of whether the study drug was received. Maintenance of biochemical response at the end of the study was defined as average IGF-1 ≤ 1XUNL calculated from two IGF-1 values obtained between week 34 and 36. If patient had a single IGF-1 collection between Week 34 and 36, the determination of the response was based on this single value. Patients with average IGF-1 values ≤ 1XUNL or with a single IGF-1 value ≤ 1XUNL were classified as responders. Patients who discontinued the study drug at any time during controlled period were classified as non-responders regardless of their IGF-1 values.

The agreement between the Applicant and the Agency on the selection of normalization of IGF-1 as the efficacy endpoint and on the primary efficacy analysis as a responder analysis looking at the percentage of subjects having maintained IGF-1 ≤ X1 UNL at the end of the trial was finalized under the SPA. The Agency accepts the normalization of IGF-1 levels as a surrogate endpoint to establish clinical benefit in acromegaly for the reasons briefly summarized below:

- All currently marketed SSAs for the treatment of acromegaly were approved based on the biochemical control of the disease, i.e. normalization of IGF-1 and/or improvement in GH levels (to ≤ 5 ng/ml or to ≤ 2.5 ng/ml).
- The current treatment guidelines for acromegaly management recommend normalization of IGF-1 values, which signifies control of acromegaly and to decrease a random GH ≤ 1 mcg/L as it correlates with control of acromegaly[9]. Biochemical control of disease occurs alongside rigorous treatment of other prevalent comorbidities (hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis and sleep apnea).
- The Applicant and the Agency agreed under SPA that maintenance of the biochemical control at baseline and at the end of the trial (primary efficacy outcome) will rely solely on IGF-1 normalization, since the IGF-1 levels are less pulsatile (compared to GH levels) and are relatively stable therefore have more clinical utility in monitoring of disease control in clinical practice. Natural secretion of GH is pulsatile, and thus, there are wide variations in plasma GH levels during the day. As such, a single GH value is not reliable in defining disease control and collection of multiple samples during the day is time-consuming and inconvenient for patients. In addition, as per current Endocrine Society Guidelines for

[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] 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.

acromegaly (2014), IGF-1 is a marker of integrated GH secretion and correlates better with symptoms and comorbidities, including hyperglycemia than GH levels. Lastly, metabolic abnormalities (obesity, diabetes, cardiovascular disease, lipid abnormalities) are primarily driven by elevated IGF-1 levels in response to GH oversecretion. Thus, the improvement in IGF-1 may translate into improved signs and symptoms of the disease and ultimately lead to decrease morbidity and mortality associated with acromegaly.

However, decrease in GH levels to ≤ 2.5 ng/ml were used as a supportive secondary efficacy endpoint. It should be noted, that the GH threshold recommended by scientific societies for the definition of the disease control has changed over the years (from ≤ 10 ng/ml in earliest studies to ≤ 5 ng/ml, to ≤ 2.5 ng/ml, and to ≤ 1 ng/ml due to the development of more sensitive assays to detect the lower levels of GH. However, although the latest recommended cutoff of GH is ≤ 1 ng/ml; many health care practitioners continue to use the cutoff of ≤ 2.5 since the detection of lower cutoff requires ultrasensitive assay, this cutoff is accepted as a "safe" cutoff (in terms of development of GH deficiency or other side effects) by the majority of physicians and there are epidemiologic data from published literature that GH cutoff of ≤ 2.5 ng/ml is associated with decreased mortality in acromegalic patients[10] [11]. The Agency accepted GH ≤ 2.5 ng/ml as a surrogate to determine the efficacy of all approved SSAs to date and the safety of SSAs in lowering GH further to ≤ 1 ng/ml has not been evaluated to date. Lastly, the definition of the control of the disease on previous treatment with octreotide and lanreotide was based on the labeling recommendations for these drugs, i.e. GH ≤ 2.5 ng/ml. Thus, the Agency agreed under SPA to accept GH ≤ 2.5 ng/ml at the end of the study as a supportive evidence of maintenance of the disease control in the intended population.

Baseline average IGF-1 levels for the primary analysis purposes were calculated from two IGF-1 values obtained at Screening visit 2 and at Baseline visit. If patient was missing a baseline visit IGF-1, the single IGF-1 level from screening 2 could be used to determine baseline IGF-1 level for the analysis purposes.

Secondary efficacy outcomes:

- Proportion of patients who had GH ≤ 2.5 ng/ml at baseline and maintained GH ≤ 2.5 ng/ml (calculated from 5 samples obtained 30 minutes apart) at week 36. Patients who discounted drug during controlled considered as non-responders.
- Time to loss of response defined as earliest time when average IGF-1 (based on 2 consecutive values) was > 1 x ULN in patients who were treated with maximum dose of study medication (80 mg/day).
- Time to loss of response defined as earliest time when average IGF-1 (based on 2 consecutive values) was ≥ 1.3 x ULN in patients who were treated with maximum dose of study medication (80 mg/day).
- Proportion of patients who began rescue treatment prior to and including week 36.

[10] Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S, Acromegaly Consensus Group (2010) A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 95(7):3141–3148

[11] Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK, AACE Acromegaly Task Force (2011) American association of clinical endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly–2011 update: executive summary. Endocr Pract 17(4):636–646

Baseline Demographics and patient disposition

A total of 56 patients with acromegaly who were controlled on SSAs (long-acting octreotide or lanreotide) for at least 3 months were enrolled in the study and received oral octreotide (28 patients) or placebo (28 patients). All patients completed controlled period. Of 56 patients enrolled in the study, 30 patients were on the study drug at the end of controlled period (21/28 patients (75%) on oral octreotide and 9/28 patients (32%) on placebo. All patients who discontinued study drug treatment continued their participation in the study up to the end of the controlled period, however, 26/56 patients discontinued the drug prematurely during controlled period (Table 1).

Table 1. Patient Disposition for the Controlled Period (Full Analysis Set)

	Placebo n (%)	**Mycapssa** n (%)
Randomized	28	28
Completed Controlled Period	28 (100)	28 (100)
Completed Controlled Period on study drug	9 (32)	21 (75)
Completed Controlled Period, discontinued study drug	19 (68)	7 (25)
Adverse Event	1 (4)	2 (7)
Treatment failure	18 (64)	5 (18)
met withdrawal criteria	18 (64)	3 (11)
did not meet withdrawal criteria	0	2 (7)
Eligible for Open Label Extension	9 (32)	21 (75)
Entered OLE	9 (32)	19 (68)

Source: CSR OOC-ACM-303, Table 5, page 70

The two randomized groups were relatively well balanced at baseline with respect to main demographic and disease characteristics.
The patients' demographic characteristics at enrollment in the study were generally consistent with those of patients with acromegaly seen routinely in clinical practice. The mean age at baseline was 55 years (range 30 to 79 years) in active drug group patients and 54 years (range 38 to 73 years) in patients on placebo; 50% of all patients were female.
With respect to the underlying diagnosis of acromegaly, 10 patients (36%) in active drug group and 9 patients (32%) in placebo group had pituitary macroadenoma (> 10 mm), respectively. Majority of patients enrolled in the study underwent pituitary surgery in the past: 25 (89%) patients in active drug group and 24 (86%) of patients in placebo group, respectively. Overall, 19 patients in the active drug group (68%) and 17 patients in placebo group (61%) were treated with long-acting octreotide; the remainder of the patients received lanreotide.
As per the Applicant's analysis, acromegaly was controlled on previous SSAs treatment in all patients as defined by average IGF-1 levels calculated from two values collected at Screening visit 1 and 2: mean average IGF-1 value was 0.79 x UNL (range 0.3-1 XUNL). However, when Dr. Kettermann reanalyzed the baseline data she discovered use of rounding of IGF-1 values used for the determination of baseline control of the disease and subject eligibility (refer to the discussion below). An example of the rounding discrepancy is subject # (b) (6) who had an average IGF-1 value of 1.0495. Based on her analysis, 2 subjects randomized to Mycapssa and 5 subjects randomized to placebo were not controlled during the screening, and thus only 49 subjects were eligible to participate in the study.

During labeling negotiations, the applicant disagreed with the removal of these 7 subjects. After review of the statistical analysis plan and the applicant's argument, the review team agreed that there was lack of clarity on what was acceptable for rounding of baseline values for eligibility and results from all subjects were included in labeling. The efficacy results below include both analyses.

Efficacy results

The statistical review for efficacy was performed by Dr. Anna Kettermann. Efficacy findings were also discussed in Dr. Sonia Doi's review. The efficacy findings are briefly summarized below. For a more detailed discussion of the efficacy findings, see Drs'. Kettermann and Doi reviews.

The results of the Applicant's primary analysis (exact logistics regression model) demonstrated that 58.2% of patients on oral octreotide were responders at the end of controlled period vs. 19.4% patients on placebo (p=0.008). Dr. Kettermann verified the Applicant's results for the primary analysis and confirmed that the study demonstrated superiority of Octreotide capsule versus placebo in terms of maintenance IGF-1 levels ≤ 1 x UNL compared to baseline. However, Dr. Kettermann also detected use of rounding of screening and baseline IGF-1 values and IGF-1 values at the end of the study included in primary analysis (e.g., IGF-1 level of 1.0495 X ULN were reported as IGF-1 $\leq$ 1X ULN). As per Dr. Kettermann, use of rounding may affect recruitment and primary outcome. Thus, she reanalyzed the data obtained from the subject whose eligibility was defined based on IGF-1 levels without rounding (refer to the discussion in the Baseline Demographics section above) and excluding 3 patients who were non-responders at the end of the study based on the IGF-1 values without rounding using Applicant's predefined exact logistics regression model but without preliminary rounding of IGF-1 data. The results of her analysis did not affect overall conclusion that oral octreotide is superior to placebo and is overall effective in the intended population and recommendations for the approval of this NDA. The results of the Applicant's and FDA's analyses are summarized in table 2.

Table 2. SSAs dose-adjusted response rates under different eligibility assumptions.

Cohort		Adjusted proportions			Odds ratio Octreaotide/placebo
		Placebo	Mycapssa	Difference 95%CI	estimate 95%CI
The Applicant's analysis					
The Applicant's cohort^	Responder	19.42	58.16		
	Non-responder	80.58	41.84		
				38.74 (10.68, 59.90)	5.7674 (1.4440, 28,.2115)
FDA's Analysis					
All subjects selected by applicant (Cohort 1)*	Responder	10.93	54.39		
	Non-responder	89.07	45.61		
				43.46 (16.48, 64.43)	9.717 (1.802, 86.926)
Average of 2 screening measurements (Cohort 2) **	Responder	10.74	51.34		
	Non-responder	89.26	48.66		
				40.61 (13.91, 60.96)	8.774 (1.495, 89.221)
Baseline measurement alone (Cohort 3) **	Responder	9.36	48.39		
	Non-responder	90.64	51.61		
				39.03 (12.81, 59.47)	9.08 (1.372, 118.702)

^ The Applicant's Cohort (56 patients)- study eligibility is based on average IGF-1 values calculated from 2 screening values prespecified in the protocol using the Applicant's rounding of IGF-1 values approach. Maintenance of biochemical response at baseline for the analysis purposes was based on baseline IGF-1 values (the average of 2 IGF-1 values measured within 2 weeks of randomization (at Screening visit #2 and at Baseline visit)).
* Cohort 1 (all 56 patients) – study eligibility is based on average IGF-1 values calculated from 2 screening values prespecified in the protocol using the Applicant's rounding of IGF-1 values approach;
** Cohort 2 (49 patients)- study eligibility is based on average IGF-1 values calculated from 2 screening values prespecified in the protocol without rounding of IGF-1 values;
***Cohort 3 (48 patients)- eligibility is based on baseline IGF-1 values used for the primary analysis purposes (average of 2 values obtained at Screening visit 2 and at Baseline visit) without rounding of IGF-1 values.
Source: Statistical review from 6/1/2020, Table 6, modified.

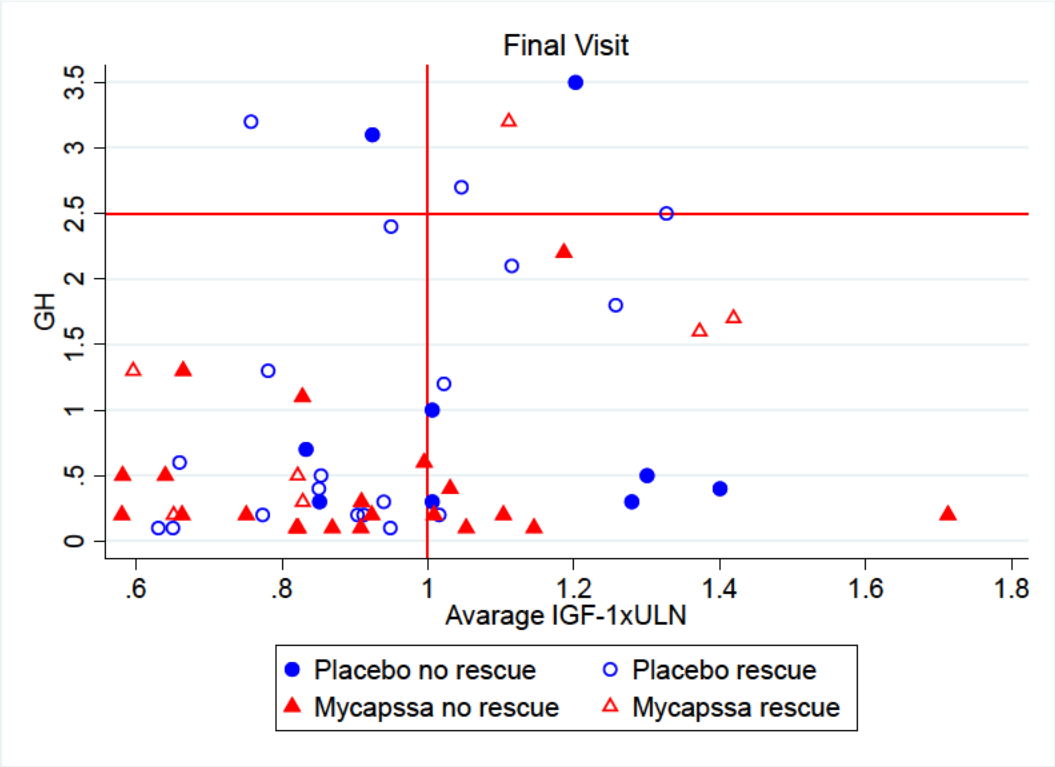
In conclusion, I agree with Dr. Kettermann's conclusion that the Applicant demonstrated that the drug is effective in the proposed application. Although the Applicant's analysis was not optimal, it is overall acceptable, and the conclusions on efficacy based on Applicant's analysis and on Dr. Kettermann's analysis are the same. Lastly, I do not agree with the results of the analysis in Cohort 3, since it is based on determination of eligibility using single IGF-1 level at baseline. Use of single IGF-1 value to define the control of the disease is less reliable due to the multiple factors (including assay inter- and intra-variability).

Drs. Kettermann and Doi also concluded that the response rate was not affected by the dose of previous SSAs treatment (low vs. high).

Secondary endpoints

- Dr. Kettermann verified the results of the secondary analysis evaluating proportion of patients with GH ≤ 2.5 ng/ml and confirmed that only one subject treated with Mycapssa and 5 subjects treated with placebo had GH > 2.5 ng/ml at the end of the trial (Figure 1). These results are supportive for the conclusion drawn from the trials' primary endpoint and are consistent with the response rate based on the evaluation of GH levels for the approved SSRs.

Figure 1. Scatter plot IGF-1 vs GH (final result)



Source: Biostatistician's review, figure 7.

- To evaluate the durability of the response, the Applicant evaluated mean time to loss of the response (defined as mean IGF value > 1.3XUNL and >1XUNL, respectively while patients being treated with maximum dose of study drug 80 mg/day). The Applicant also evaluated the proportion of patients in each group requiring rescue treatment prior to the end of the controlled period. In general, it is expected that patients who withdrawn from active treatment and/or treated with placebo should loss the control of the disease earlier as compared to patients who is treated with active drug and more patients on placebo will require rescue treatment because of the loss of the control. Indeed, the Applicant's secondary analyses demonstrated that:

- mean time to loss of the response based on average IGF-1 > 1 x UNL was 27.3 in oral octreotide group vs. 15.5 weeks in placebo
- mean time to loss of the response based on average IGF-1 > 1.3 x UNL was 29 weeks in oral octreotide group vs. 18.9 weeks in placebo

- more patients on placebo begun rescue treatment prior to the end of controlled period: 19 patients on placebo (67.9%) vs. 7 patients on active drug (25%)

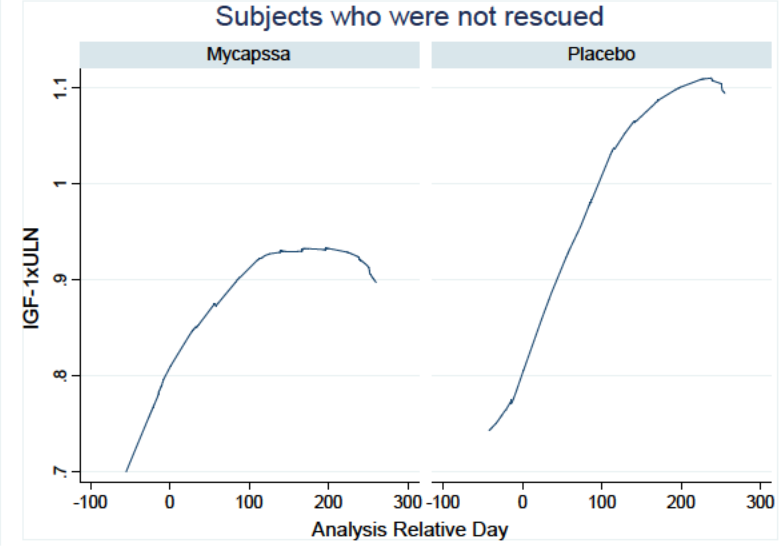
Dr. Kettermann conducted secondary analyses of these endpoints and concluded that the results are inconclusive due to the multiple factors, including the fact that several subjects, were rescued prior reaching the prespecified threshold of IGF-1 > X 1.3 UNL (leaving only random subgroup for the evaluation and making it look like that the overall time to loss of response in the treatment group was longer), rounding of IGF-1 values discussed above. Refer to statistical review for further details.
However, the data on the proportion of patients who were able to continue on the study drug vs. those who discounted the drug prematurely provides useful information to the health care providers on the expected durability of the response, thus, I recommend to include it in the label in descriptive manner without providing p values due to the above uncertainties.

Additional analyses:

- Change from baseline to end of the controlled period in IGF-1 (exploratory endpoint)

Dr. Kettermann examined the trend in IGF-1 levels (x-axis) over time (y-axis) for the patients who were not rescued in the trial (see figure 2 reproduced below). This is an exploratory analysis. She concluded that, although the majority of subjects treated with Mycapssa had IGF-1 levels ≤ 1XUNL at the end of the trial, the IGF-1 levels continued to rise during the 303 trial. She also noted that the trend in IGF-1 levels over the time observed in 303 study was comparable to the trend observed in study 01. Based on these observations, she concluded that some subjects may lose IGF-1 control over time and therefore, patients should undergo regular monitoring of their IGF-1 levels to make sure that their acromegaly is under control.

Figure 2. Overall IGF-1 patterns for subjects who were not rescued



Legend: Lowest plots for subjects who were not rescued (21 subjects on Mycapssa and 9 on placebo). Analysis day of zero indicates the baseline measurement.
Source: Stats review, figure 6.

I agree with her conclusions. Although the results of this analysis provide some insight regarding how patients with controlled acromegaly respond to the treatment with oral octreotide, the results should be interpreted with caution (b) (4) (b) (4) (b) (4) 1 levels to periodically evaluate the control of the disease.

- Evaluation of titration schedule

Dr. Doi concluded that the proposed maximum dose of 80 mg/day is acceptable but recommended that that starting dose should be 40 mg/day based on the analysis of the response rate in each dose subgroup and according to the titration schedule implemented in core phase of the study. As evident by the Applicant's and Dr. Doi's analysis, one third of the responders (5/16 patients) were on 40 mg/day at the end of the trial. One of two patients who were on 60 mg/day responded to this dose and the rest (10/16), required an increase in the dose to 80 mg/day to respond. Thus, I agree with Dr. Doi that starting dose should be 40 mg/day; the efficacy and safety of it as starting dose was evaluated in well controlled study and there were considerable number of the responders remained on this dose by the end of the trial.

Since the titration schedule was complicated in the trial and affected by the Investigator's decision, Dr. Doi evaluated the pattern in dose escalations observed in patients treated with oral octreotide to better understand the titration schedule and to recommend the adequate dose titration schedule in the label. As per her analysis (refer to figure 5 and table 11 in her review), 7 patients did not require further dose escalation beyond starting dose. Of 21 patients who required dose escalation, 2 patients were on 60 mg dose at the end of the trial and 19 patients were advanced to 60 mg/day and subsequently to 80 mg/day.

Several patients (14/21 patients who required dose increase to 60 mg/day and 11/19 patients who required further dose increase to 80 mg/day) had dose increased based solely on symptoms (with IGF-1 $\leq$ 1 XUNL at time of the dose increase). As discussed above, it is unclear why patient with controlled IGF-1 remains symptomatic, since normalization of biochemical markers correlates with control of acromegaly, the symptoms are not specific and the overall goal of treatment to achieve biochemical control of the disease.
No clear pattern in frequency of dose escalation were overall noted, the dose was escalated to 60 mg in 1-24 weeks after the initiation of the treatment, and subsequently, to 80 mg/day in 4-15 weeks after the last dose titration. However, 7/21 patients had dose increase to 60 mg in $\leq$ 4 weeks, and 8 patients had dose increase to 80 mg in $\leq$ 4 weeks after the last dose titration. Thus, based on this pattern and the predefined IGF-1 monitoring during the trial (monthly), I recommend monitoring IGF-1 levels every 2-4 weeks during the dose titration.

To conclude, I am in agreement with both the statistical and clinical recommendations for the approval of the drug for the proposed indication. The results of the trial provided substantial evidence of efficacy of oral octreotide in the intended population (i.e. in patients who are well-controlled on SSAs) and demonstrated that 58% of patients treated with oral octreotide compared to 19% of patients in placebo group maintained the control of the disease at the end of the study. The results of primary analysis are supported by the results of secondary analysis demonstrating that the majority of patients treated with oral octreotide maintained the control of the disease based on GH levels ($\leq$ 2.5 ng/ml). The response rates based on IGF-1 levels and/or

GH levels during the treatment with oral octreotide are also consistent with the response rates observed during the treatment for injectable SSRs. The results of the secondary analysis, i.e. proportion of patients on the oral octreotide who did not require rescue with injectable SSAs during 9 months of treatment should be included in the label to provide health care providers with useful information on the durability of the response.

However, I recommend approval of the drug for those patients who were previously treated with octreotide or lanreotide only, since this was a patient population enrolled and evaluated in the pivotal study. The efficacy of the drug in maintenance of pasireotide-achieved control of acromegaly was not evaluated in the trial. Despite sharing many similarities to octreotide and lanreotide, pasireotide differs in its somatostatin receptor (SSTR) binding characteristics. Whereas octreotide and lanreotide bind primarily to SSTR2, pasireotide binds to a broader range of receptors: SSTR 1, STTR2, STTR3 and SSTR5, and has particular affinity for SSTR5, and thus some patients who controlled on pasireotide, might lose the control of the disease when switched to octreotide.

Lastly, I disagree with the Applicant's intent to include the description of the improvement in clinical signs and symptoms in the label. The study was not designed to evaluate the improvement in these symptoms (e.g., symptoms were not predefined in inclusion criteria, were not primary or secondary endpoints) and interpretability of these results is complicated due to the subjective nature of the assessment (patient-reported outcomes are not validated to date).

I recommend starting dose of 40 mg/day, since the evidence of efficacy and safety of this dose was sufficiently evaluated in core period of the study and approximately third of the responders were on this dose at the end of the trial. I recommend that the dose should be titrated based on IGF-1 levels and control of symptoms of acromegaly (see discussion above); the IGF-1 levels should be monitored every 2-4 weeks during dose titration. Lastly, I also agree with reviewers' recommendations that the control of the disease should be monitored during the treatment with oral octreotide, since there was a trend in increase of IGF-1 levels over the time.

8. Safety

Dr. Doi has summarized all the safety findings derived from the clinical program of oral octreotide, refer to her review for details.
Primary safety data for oral octreotide for the treatment of acromegaly include data from the pivotal study 303. Additional supportive safety data in patients with acromegaly comes from two Phase 3 study in acromegalic patients (Study 01 and Study OOC-ACM-302) and from 11 Phase 1 studies in healthy volunteers and patients with renal and hepatic impairments. Study OOC-ACM-302 (Run-in-Phase, Randomized Controlled Treatment phase and Extension Phase in patients with acromegaly) is still ongoing (cut-off date 1/07/2019) and blinded, thus provides only limited data on the safety of the product in patients with acromegaly. Data from Phase 3 Study 01 (core and extension) and Phase 1 studies were reviewed by Dr. Abraham during the review of original NDA (refer to Dr. Abraham's review in DARRTS). Thus, the results from Studies 01, OOC-ACM-302 and Phase 1 and 2 studies will not be discussed in this memo, unless otherwise specified.

Overall, 552 subjects received at least 1 dose of oral octreotide; of these, 338 acromegaly

patients were exposed to oral octreotide in three Phase 3 studies. Based on data obtained to date (cutoff date 7/11/2019) from two Phase 3 studies (Study 01 and 303) in 203/338 patients with acromegaly, 23 patients received drug for < 3 months, 38 patients - for 3-6 months, 34 patients -for > 6 months, 16 patients for > 9 months and 92 patients for > 12 months. This level of exposure is acceptable for the orphan drug to support chronic dosing.

This CDTL review will further summarize the primary safety data from the controlled period of study 303. This period provides the most informative data on common product related safety issues because the study allows side by side comparison of oral octreotide to placebo, were obtained in randomized groups in blinded fashion with frequent assessment and had a 9-month duration of controlled observation. Additional safety data will be referenced as needed.

In study 303, the mean duration of exposure (SD) was 33.7 (5.09) weeks in controlled period.
In the controlled period of Study 303, 23 patients were treated with oral octreotide for 6 to <9 months, and 5 patients were treated with oral octreotide for < 6 months. Of these patients, majority of patients (67%; 19/28 patients) received 80 mg/day of oral octreotide at time of the last assessment; 7 patients were on 40 mg/day dose and 2 patients were on 60 mg daily dose.

Death
No death occurred during the study 303.

There were two deaths in study 01(sepsis due to the bile duct obstruction (assessed as drug-related by Dr. Abraham, during the original review of NDA) and due to pancreatic tumor (not drug-related).

AEs that led to the study discontinuation
Three subjects discontinued 303 study prematurely due to non-serious AEs: two in oral octreotide group and one in placebo group. The AEs that led to discontinuation of oral octreotide were headache (1 patient) and 4 gastrointestinal AEs in the other patient (nausea, vomiting, heartburn, and abdominal discomfort).

There were more patients (21/150 patients) withdrawn from the study 01 due to the AEs, however, it is most likely due to the fact that study 01 was a larger study and more patients were exposed to oral octreotide.

Serious Adverse Events (SAEs)
A total of 6 SAEs were reported in study 303 up to cutoff date. All case narratives were reviewed by Dr. Doi. Four SAEs occurred during controlled period of the study: 3 SAEs occurred in 2 patients in oral octreotide group and 1 SAE -in patient randomized to placebo. SAEs in oral octreotide group were: 2 events of acute cholecystitis in 1 patient and worsening of left hip pain in 1 patient with history of arthritis. Dr. Doi concluded that events of acute cholecystitis could be related to the study drug due to the known propensity of somatostatin analogs to reduce gallbladder motility.

In addition, 2 patients in OLE period developed 2 SAEs: complete atrioventricular block (AV block) and amaurosis fugax. Patient with AV block was completely asymptomatic and received a pacemaker for the treatment of the event; the drug was continued. Both events were assessed

as nonrelated to the study drug by the Applicant. I agree that amaurosis fugax is not related to the study drug. However, a causal relationship between the event of AV block and the drug cannot be excluded completely even though some confounding factors were presented (underlying conductive abnormalities). The drug has propensity to prolong QT interval and the event occurred soon (2 weeks) after the treatment with oral octreotide at dose 60 mg.
Dr. Doi concluded that the SAE profile of the drug in study 303 was comparable to the profile observed in study 01 and also consistent with known class effect of octreotide. SAEs of cholecystitis and AV block are known AEs associated with SLRs use and are appropriately labeled to mitigate risks. I agree with Dr. Doi's conclusion.

Common Adverse Reactions
All oral octreotide-treated subjects had at least one adverse event in the controlled period of the trial. The table below summarizes the common treatment emergent adverse reactions noted in the controlled period of the study that occurred in more than 5% of octreotide-treated subjects and more than in placebo-treated subjects.

Table 3. Common TEAEs (incidence ≥5% by PT) in the controlled period (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: Clinical Review, table 19.

Overall, the AE profile observed in study 303 was consistent with the known AE profile of SSAs in patients with acromegaly. By SOC, gastrointestinal (GI) disorders were the most frequently

reported AEs in patients treated with oral octreotide (67.9%) followed by infections (13%) and hepatobiliary disorders (10.7%).

GI-related AEs
Among GI- related events that occurred in patients treated with oral octreotide the most frequent AEs were diarrhea (28.6%) followed by nausea (21.4%), abdominal discomfort (14.3%), vomiting (14.3%), abdominal pain and abdominal pain upper (10.7 %), constipation (10.7%), and dyspepsia (10.7%). GI AES are known (and labeled) AEs associated with use of all SLRs.

Two patients treated with oral octreotide vs. 0 patients treated with placebo were diagnosed with intestinal polyp. The narratives were reviewed by Dr. Doi who concluded that these events were most likely not related to the drug. I agree with her conclusion. It should be also noted that acromegaly itself is associated with an increased risk of developing colonic polyps and GI polyps are also more frequently occur in older population. Lastly, absence of colonoscopy at baseline and at the end of the study in all patients complicates further casualty assessment of the event.

Gallbladder and bile duct disorders
Dr. Doi reviewed results of gallbladder ultrasound (obtained at baseline and at the end of the treatment) and all narratives of cases with hepatobiliary-related AEs 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. Hepatobiliary disorders occurred in 3 patients treated with oral octreotide and include acute cholecystitis (1 patient) and cholelithiasis (2 patients). All events resolved with appropriate treatment. In addition, 2 patients in oral octreotide group shifted from “normal” at baseline to “abnormal” ultrasound results at the end of the study.

Hepatobiliary AEs are labeled AEs for all SSAs; octreotide is known to inhibit gallbladder contractility and to induce bile stasis.

The proposed labeling for oral octreotide appropriately includes these AEs in Warning and Precaution section of the label.

Cardiac safety/QT prolongation
The SSA drug class is recognized to induce bradycardia and QT prolongation in humans.
In study 303, ECG was evaluated at baseline and at the end of the controlled period. No patients had new QTcF > 450 msec during the trial and no patients experienced an increase in QTcF >30 msec above baseline. One patient with preexisting conductive abnormalities developed asymptomatic SAE of third-degree AV block (described above) and one patient had non-serious AEs of heart rate irregular. The Applicant appropriately proposed to include cardiac abnormalities in Warning and Precaution section of the label.

Glucose abnormalities
Dr. Doi reviewed glucose parameters that occurred during the study. Of 28 patients treated with oral octreotide, 5 patients with normal glucose levels at baseline had elevated glucose levels above normal range at the end of the controlled period and one patient with hyperglycemia at baseline had worsen of glucose parameters. In 1 patient, HbA1 C increased above normal range

at the end of the study. AEs of glucose abnormalities were reported in 4 patients treated with oral octreotide: 3 patients had glucose increased, 1 patient had hypoglycemia. All AEs were non-serious AEs, patients were asymptomatic, and no hyperglycemic emergencies were reported. Hyper- and hypoglycemia are known adverse reactions associated with this class of the drugs. The proposed labeling for oral octreotide includes glucose abnormalities as a *Warning and Precaution*. Frequent monitoring of glucose and HbA1C levels, especially for patients with pre-existing diabetes or pre-diabetes, is recommended in the label for this drug and should mitigate the risk of worsening of hyperglycemia.

Liver Transaminases
Transient elevations in liver transaminases are known (and labeled) risk associated with use of SSAs. Liver related AEs that occurred during the treatment with oral octreotide were hepatitis acute, bilirubin increase, GGT increased, transaminase increased and were reported in 1 patient, each. No Hy's law was reported. Dr. Doi noted that causality assessment was complicated in the majority of cases due to the presence of confounding factors (e.g., use of hepatotoxic concomitant medications, occurrence of the event after the drug was discontinued). Overall in study 303, no new safety signals regarding oral octreotide's effect on liver transaminases were identified.

Analyses of other laboratory values and vital signs summarized in the clinical review do not identify any new safety signals.

Lastly, the safety profile of the drug observed in study 303 (e.g., GI related AEs, hepatobiliary AEs, cardiac abnormalities) was overall consistent with the safety profile of the drug observed in study 01. Few class specific AEs (e.g., TSH abnormalities) were not reported in study 303, but were observed in study 01, most likely because less patients were exposed to oral octreotide in study 303 compared to study 01 (28 patients vs. 150 patients, respectively). Thus, I recommend including the safety results of both Phase 3 studies (01 and 303) in the label to capture all class specific AEs that occurred in clinical program of oral octreotide. I also agree with Dr. Doi's conclusion that the Applicant's "adverse events of special interest" (headache, sweating, etc.) were symptoms of acromegaly and not adverse reactions associated with drug use. Thus, these symptoms should be removed from Section 6, since they do not characterize the safety profile of the drug.

Immunogenicity
The immunogenicity data obtained from the oral octreotide clinical program was reviewed by Dr. Sista (refer to Clinical Pharmacology review from 6/1/2020).
As per his review, no anti-drug antibodies were found in study 01; no antibodies were tested in study 303. Reviewers also reviewed published literature on immunogenicity of octreotide and did not find any significant reports on immunogenicity of octreotide. Dr. Sista concluded, that the risk of immunogenicity with oral octreotide is very low. In general, immunogenicity is associated with injectable products, since the orally administered drugs are degraded in GI fluids and oral octreotide, in particular, has low bioavailability (0.5%).

In conclusion, I agree with Dr. Doi's assessment that no new safety signals were identified during the 9-month trial. The safety observations made during the oral octreotide clinical program in patients with acromegaly are consistent with the known SSAs class specific side

effects (e.g., gallbladder abnormalities, GI adverse reactions). Safety issues will be mitigated through labeling.

9. Advisory Committee Meeting

An advisory Committee meeting was not convened for this application.

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. In addition, the proposed indication, i.e. treatment of acromegaly, is a solely adult indication. GH-secreting pituitary adenomas are extremely rare in children and constitute a separate clinical entity of pituitary gigantism.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) inspection
No clinical sites were selected for inspection to support the re-submission of NDA 208232. The decision for not selecting clinical sites for inspection in Study OOC-ACM-303 was supported by the reasons outlined below and in concurrence with OSI:

- There were no significant issues with sponsor trial implementation and oversight with the original application.
- There were no relevant deviations in the new pivotal study (OOC-ACM-303) that would require a clinical site inspection.
- 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.

Dr. Doi also indicated that in the original NDA submission, three foreign clinical sites involved in the pivotal Study CH-ACM-01 and the Applicant 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.

Financial Disclosure and compliance with Good Clinical Practice standards.
Financial disclosure documentation was reviewed by Dr. Doi. She did not identify any issues that could influence the outcome of the trial. She also confirms that the study was conducted in accordance with the principles of Good Clinical Practice governing clinical study conduct.

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 3/2/2020.

Division of Pediatric and Maternal Health (DPMH) Consult

Division of General Endocrinology (DGE) had consulted DPMH to provide an input on the proper format and content of the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of oral octreotide labeling to follow the Pregnancy and Lactation Labeling Rule (PLLR).

DPMH revised relevant sections of labeling for compliance with the PLLR and for compliance with the PLLR and provided labeling recommendations (refer to DPMH review from 5/28/2020 in DARRTS). I agree with all DPMH recommendations.

Lastly, DPMH recommended issuing a postmarketing requirement for a single-arm pregnancy safety study (SPSS) to monitor the outcomes of women and infants exposed to oral octreotide during pregnancy. Following the discussion between DPMH and DGE on feasibility of such study in the intended population, DPMH agreed that such study is not feasible, since oral octreotide is indicated in an orphan population and as such there may not be enough patients who become pregnant to conduct a meaningful study. In addition, 2014 Endocrine Society Clinical practice guideline**Error! Bookmark not defined.** recommends to stop medical acromegaly treatment for the duration of pregnancy and treat only symptomatic patients for headache/tumor growth.

12. Labeling

Prescribing Information

Agreement on the final labeling language has not been reached at the time that this review was completed. Refer to the complete labeling in the approval letter. The following sections should be addressed in the label:

- INDICATIONS AND USAGE:
  - The indication should be restricted to patients who previously maintained the control of the disease on long-acting octreotide or lanreotide, since the oral octreotide clinical program did not evaluate safety and efficacy of the drug in the patients who previously maintained control of the disease on pasireotide.

- DOSAGE AND ADMINISTRATION:
  - The starting dose should be 40 mg/day. The efficacy and safety of this dose is provided from well-controlled trial in patients with acromegaly. In addition, 5 patients maintained control on the lowest dose.
  - The dose titration should be based on IGF-1 levels and patient's signs and symptoms, and not on acromegaly symptoms alone.
  - IGF-1 levels should be monitored every 2 (b) (4) weeks during the titration of the drug, and monthly thereafter. Although there was no prespecified intervals for the escalation to next dose in the study, the IGF-1 values were collected monthly to assess the control of the disease and the majority of dose escalations, if required, occurred at monthly intervals (refer to the discussion on the doses in Efficacy section above).
  - The drug should be withdrawn periodically to assess disease activity.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - WARNINGS AND PRECAUTIONS section appropriately describes class specific adverse reactions associated with octreotide use including cholelithiasis and complications of cholelithiasis, glucose and thyroid function abnormalities, cardiac function abnormalities.
- CLINICAL STUDIES section:
  - I recommend including the efficacy results from study 303 only in this section. These results from this study provided substantial evidence of effectiveness of the drug for the proposed indication. (b) (4)

(b) (4)

I recommend removing

(b) (4)

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A Risk Evaluation and Management Strategy (REMS) is not needed for oral octreotide for the proposed indication. All risks are appropriately labeled in the label to inform patients and prescribers and mitigate risks associated with use of this drug.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No safety findings prompt the need for Postmarketing Requirements and Commitments.

14. Recommended Comments to the Applicant

None.

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

/s/

MARINA ZEMSKOVA
06/23/2020 05:04:54 PM

THERESA E KEHOE
06/23/2020 06:26:57 PM
I concur with Dr. Zemskova and the regulatory decision outlined in this memo