CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208232Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208232
Supporting document/s:	43
Applicant's letter date:	26 Dec 2019
CDER stamp date:	26 Dec 2019
Product:	Mycapssa (octreotide acetate) capsules
Indication:	Long-term maintenance in acromegaly patients (b) (4) (b) (4)
Applicant:	Chiasma, Inc
Review Division:	Division of General Endocrine
Reviewer:	
Supervisor/Team Leader:	Federica Basso, Ph.D.
Division Director:	Theresa Kehoe, M.D.
Project Manager:	Jennifer Johnson

Template Version: September 1, 2010

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Mycapssa (oral octreotide acetate) is an oral somatostatin analog indicated for long-term maintenance therapy in acromegaly patients [redacted] Mycapssa is an oral formulation of octreotide acetate containing excipients, referred to as Transient Permeability Enhancers (TPE), to increase intestinal absorbance and an enteric coating to allow intact passage through the stomach and disintegration in the small intestine. The sponsor is relying on previous nonclinical findings of safety for the reference listed drug (RLD), Sandostatin Injection (octreotide acetate for injection), which was approved under NDA #019667. The nonclinical studies conducted by Chiasma focused on the characterization and development of the TPE formulation to promote the oral bioavailability of octreotide.

The original NDA was submitted in June 2015 and was considered approvable from a PharmTox perspective (see Nonclinical review, Dr. Hawes 2-23-2016). However, the NDA received a Complete Response on 4/15/2016 due to CMC and clinical deficiencies. In the current NDA resubmission, no new nonclinical studies were submitted or required in support of approval. Therefore, a new nonclinical review was not conducted. Refer to Dr Hawes' original review from February 2016 for a comprehensive analysis of the nonclinical data originally submitted to support approval of Mycapssa.

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/s/

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA #208232
Supporting document/s:	Supporting Document Number (SDN 1), Applicant Serial number 0000
Applicant's letter date:	06/04/2015
CDER stamp date:	06/15/2015
Product:	Mycapssa (octreotide acetate) capsules
Indication:	Long-term maintenance in acromegaly patients (b) (4) (b) (4)
Applicant:	Chiasma, Inc.
Review Division:	CDER/ODEII/DMEP
Reviewer:	Jessica Hawes, Ph.D.
Supervisor/Team Leader:	Ronal Wange, Ph.D.
Division Director:	Jean-Marc Guettier, M.D.
Project Manager:	Jennifer Johnson

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1 Executive Summary

1.1 Introduction

Chiasma, Inc., is seeking market approval under the 505(b)2 regulatory pathway for Mycapssa (oral octreotide acetate), an oral somatostatin analog, for the indication of long-term maintenance treatment of acromegaly (b) (4) (b) (4) (b) (4) Mycapssa is a new oral formulation of octreotide acetate containing a combination of active drug, octreotide acetate, and excipients, referred to as Transient Permeability Enhancer (TPE), to increase intestinal absorbance along with an enteric coating to allow intact passage through the stomach and disintegration in the small intestine. The sponsor is relying on previous nonclinical findings of safety for the reference listed drug (LD), Sandostatin Injection (octreotide acetate for injection), which was approved under NDA #019667. The nonclinical studies that were conducted by Chiasma focused on the characterization and development of the TPE formulation to promote the oral bioavailability of octreotide in animals.

1.2 Brief Discussion of Nonclinical Findings

Chiasma is relying on previous nonclinical findings and comparability with the LD to support the safety profile of Mycapssa. The sponsor conducted oral nonclinical studies with Mycapssa capsule formulations in Cynomolgus monkeys, which did not reveal any new drug-related toxicity. Therefore, the toxicological profile of Mycapssa, consisting of oral octreotide acetate combined with the TPE formulation, was considered to be comparable to the LD. Furthermore, the nonclinical studies indicate that there are sufficient margins of safety and no significant safety concerns with any of the Mycapssa-related excipients or anticipated degradation products or stress-induced impurities. The sponsor's hazard assessments of the TPE formulation and Mycapssa-related impurities and degradation products are considered to be complete. Overall, the nonclinical data support long-term oral administration of the TPE formulation and the Mycapssa drug product. Therefore, the nonclinical data are sufficient to support approval of the proposed dose of Mycapssa in Acromegaly patients.

Recommended changes to the sponsor's proposed labeling primarily add clarification to the safety margins, which were are based on the comparability of octreotide exposures between oral Mycapssa and the LD. Other minor clarifications in molecular mechanism and animal toxicology sections are also recommended.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data support market approval of Mycapssa.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Reviewer recommended text additions are noted in black and deletions are noted with a strike through the sponsor's blue text. See section 11 Labeling Review for a full discussion.

Section: 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4) major birth defects occur in 2 to 4% (b) (4)

(b) (4) Miscarriage occurs in 15 to 20% of clinically recognized pregnancies (b) (4)

(b) (4)

Data

(b) (4)

Animal Data

(b) (4)

(b) (4)

8.3 Females and Males of Reproductive Potential

(b) (4)

Section: 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

Octreotide exerts pharmacologic actions similar to the natural hormone somatostatin, but is a more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin it also suppresses luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

Section: 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.1 Carcinogenesis & Mutagenesis & Impairment ~~O~~of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of (b) (4) octreotide acetate.

No carcinogenicity studies have been conducted with MYCAPSSA. No carcinogenic potential was demonstrated in mice treated with SC (b) (4)-injectable octreotide acetate for 85 to 99 weeks at doses up to 2000 µg/kg/day (8× the (b) (4) based on octreotide acetate injection body surface area). In a 116-week SC study in rats administered (b) (4) octreotide acetate, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 µg/kg/day (10× the (b) (4) based on octreotide (b) (4) injection body surface area) compared to an incidence of 8% to 10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated SC injections at the same site. (b) (4)

(b) (4)

There was also a 15% incidence of uterine adenocarcinomas in ~~the1250 µg/kg/day~~ female (b) (4) compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats, which does not occur in humans.

No fertility studies have been conducted with MYCAPSSA. (b) (4) injectable octreotide acetate did not impair fertility in rats at doses up to 1000 µg/kg/day, which represents 7× the (b) (4) based on injectable octreotide (b) (4) body surface area.

(b) (4)

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number
79517-01-4

Generic Name
USAN: Octreotide acetate
INN: Octreotide

Code Name
Oral octreotide acetate (OOA)
SMS 201-995
Octreolin

Proposed Trade Name
Mycapssa

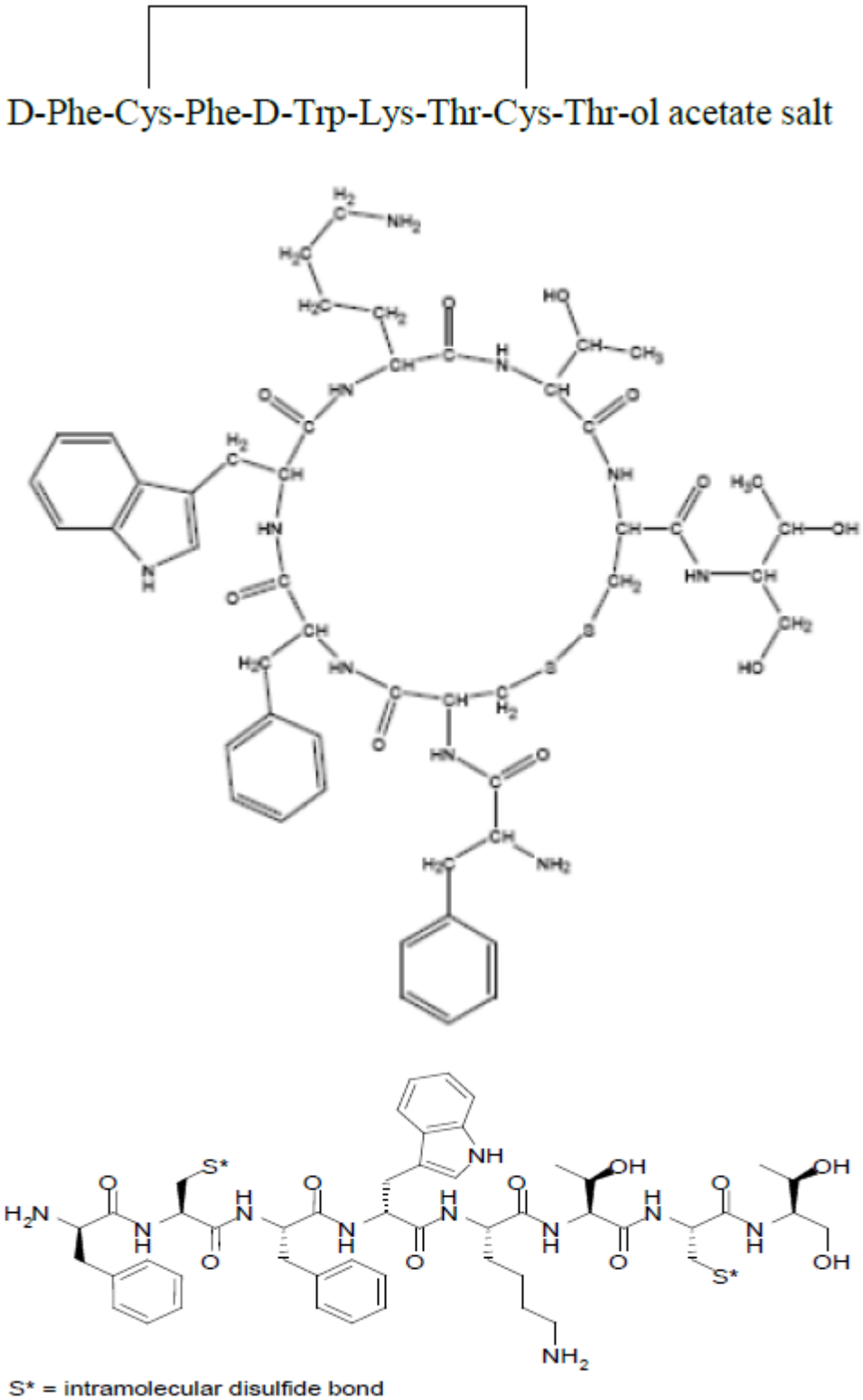
Chemical Name
L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2→7)-disulfide, [R-(R*, R*)]-acetate (salt)

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-threoninol, acetate salt
(Disulfide bond between Cys^2 and Cys^7)

Molecular Formula/Molecular Weight
$C_{49}H_{66}N_{10}O_{10}S_2$ / 1019.26 g/mol

Structure or Biochemical Description
Octreotide is the acetate salt of cyclic octapeptide, an analog of the tetradecapeptide somatostatin.

Sponsor's Figure 1: Octreotide Structures



(Figures excerpted from the Sponsor's package)

Pharmacologic Class
Somatostatin analog

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND #108163: Mycapssa (octreotide acetate) capsules, Chiasma

NDA #019667: Sandostatin (octreotide acetate) subcutaneous (SC) injection

2.3 Drug Formulation

Mycapssa is a novel formulation of octreotide with TPE components that increase intestinal absorption and allow for oral administration of octreotide. TPE is (b) (4)

(b) (4)

The Mycapssa formulation also includes an enteric-coated capsule (b) (4)

(b) (4)

All TPE components were evaluated in the pivotal 9-month monkey study, although Acryl-EZE was evaluated at a level (b) (4)% below the final product formulation. Nevertheless, the 4-week bridging study in monkeys evaluated the final formulation of all TPE components, including Acryl-EZE at or above clinically relevant exposure levels.

Sponsor's Table 1: Mycapssa Final Product Formulation

Table 1 Unit Dose Quantitative Composition, Function and Quality Standard

Component	Quality Standards	Function	Quantity per Unit Dose	
			mg/capsule	% w/w
Capsule Fill Mass				
Octreotide (free peptide)[b]	Manufacturer's	Active	20.0	(b) (4)
Polyvinylpyrrolidone K12 (PVP-12)	USP/Ph. Eur.		(b) (4)	
Sodium caprylate	NF/Ph. Eur.			
Polysorbate 80	NF/Ph. Eur.			
Glycerol monocaprylate (b) (4) (GMC)	Ph. Eur.			
Glycerol tricaprylate (GTC)	Manufacturer's			
Magnesium chloride	USP/Ph. Eur.			
(b) (4)				
Capsule Fill Weight				
Capsule Shell (Body & Cap)[c]				
Hard gelatin capsule, size 0	Manufacturer's	Capsule shell		(b) (4)
(b) (4)				
Gelatin	NF/Ph. Eur.		(b) (4)	
(b) (4)	NF/Ph. Eur.			
Acryl-EZE®[e]	Manufacturer's			
Print Ink				
Opacode® (b) (4) ink black[f]	Manufacturer's			
Theoretical Finished Unit Weight				
(b) (4)				

(Table excerpted from Sponsor's package)

2.4 Comments on Novel Excipients

In the Mycapssa drug product, there are 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 1 excipient (Acryl-EZE) that is above the current maximal approved levels for oral administration.

All other excipients are present at or below the maximum IIG limit for use in previously approved products, have a generally regarded as safe (GRAS) status, or are within appropriate safety limits defined by ICH guidance. The sponsor submitted excipient reviews for 10 of the Mycapssa components, which are fully reviewed below.

Excipient Review for PVP-12

Sponsor's report #75-65-09

Povidone (polyvinylpyrrolidone, PVP 12) is a (b) (4) (b) (4) (b) (4) Furthermore, the amount of PVP-12 in Mycapssa is below the IIG maximum level present in previously approved products. Therefore, there is not a safety concern for the amount of PVP-12 in Mycapssa.

Excipient Review for Acryl-EZE

Sponsor's report #75-65-01

Acryl-EZE is the (b) (4) (b) (4) (b) (4)

(b) (4)

In the standard GLP 28-day, 3-month, and 9-month toxicology studies, all excipients were tested at higher levels of exposure than that achieved from the final drug product, except for the Acryl-EZE ((b) (4) mg in the clinical formulation vs. (b) (4) mg in monkey capsule). However, in the 28-day bridging study (#1300-015), the percentage of Acryl-EZE (b) (4) was identical to that of clinical formulations. The NOAEL for Acryl-EZE in the 28-day monkey study was (b) (4) mg/kg for one Mycapssa capsule, which is similar to a clinical dose of (b) (4) mg/kg Acryl-EZE contained in 4 Mycapssa (b) (4) ((b) (4) mg Acryl-EZE in a 60 kg adult) after correction for body surface area.

(b) (4)

(b) (4)

(b) (4) Acryl-EZE are not associated with safety concerns. Furthermore, the Acryl-EZE (b) (4) was not associated with new toxicities in the 1-month bridging study. Overall, the increased amount of (b) (4) used in the Mycapssa formulation is considered to be qualified in the 28-day non-clinical bridging study and is not associated with a significant safety concern.

Excipient Review for Gelatin Capsules

Sponsor's report #75-65-02

The gelatin capsules used in the Mycapssa drug product have GRAS status and the maximum proposed daily dose is below the maximum IIG limit. Thus, there is not a safety concern for the proposed gelatin capsule formulation.

(b) (4)

Excipient Review for Glyceryl Monocaprylate

Sponsor's report #75-65-04

Glyceryl monocaprylate (b) (4) is a (b) (4)

(b) (4)

Excipient Review for Glyceryl Tricaprylate

Sponsor's report #75-65-05

In Mycapssa, glyceryl tricaprylate (GTC) is being used as (b) (4) at a level of (b) (4) mg/capsule, resulting in a daily dose of (b) (4) g, which is equivalent to (b) (4) mg/kg for a 4 capsule dose in a 60 kg adult. GTC is also referred to (b) (4) which is present in previously approved products, but only at oral doses up to (b) (4) mg. Therefore, GTC is not considered to be a novel excipient, but the proposed level in each capsule is (b) (4) times higher than that of previously approved products.

(b) (4)

Published in vitro genotoxicity assays indicate that glyceryl tricaprylate is devoid of relevant mutagenic and clastogenic potential (Johnson, 2001). No signs of toxicity or target organs have been identified in 3 month subchronic safety studies with glyceryl tricaprylate. In a 47-week rat oral toxicology study, no toxicological effects or increases in tumors were observed at doses up to 7.4 mg/kg; however, this dose is significantly lower than those anticipated with Mycapssa. In a 2-year carcinogenicity study in rats, daily doses of 2.375, 4.75 and 9.5 g/kg administered 5 days a week resulted in increased incidences of pancreatic hyperplasia and adenoma at ≥4.75 g/kg with a NOAEL of 2.375 g/kg; however, these findings were similar to that of corn oil and safflower oil (NTP, 1994) and there is an approximately 15-fold margin of safety. Furthermore, chronic exposure of glyceryl tricaprylate was evaluated in the sponsor's GLP 9-month toxicology study with the octreotide-TPE formulation, which did not result in any significant toxicities (see section 6 General Toxicology). Based on these findings, there is not a significant concern for carcinogenicity with chronic administration of glyceryl tricaprylate at the proposed dose in Mycapssa.

Excipient Review for Magnesium Chloride

Sponsor's report #75-65-06

Magnesium chloride ($MgCl_2$) is a salt that dissociates into magnesium and chloride ions in the lumen of the gastrointestinal tract. Magnesium chloride is present in previously approved products with suspension, drops and injectable formulations, but not for oral administration. In the Mycapssa drug product, magnesium chloride is used as a (b) (4)

(b) (4)

Magnesium chloride is a compendial ingredient and has a GRAS status. The usual adult intake is about (b) (4) mg per day from all sources, which is nearly (b) (4)-fold higher than the (b) (4) mg present in each capsule of Mycapssa and (b) (4)-fold higher than the proposed daily dose of (b) (4) mg for four Mycapssa capsules. Thus, although magnesium chloride is considered to be novel since it is not currently listed on the IIG list for oral administration, there is no safety concern for the small amount present in Mycapssa.

Excipient Review for Opacode Black Ink

Sponsor's report #75-64-07

Opacode black ink is (b) (4) used for printing on tablets and capsules. The exact type of Opacode (b) (4) black ink obtained from (b) (4) for the use on Mycapssa capsules is not included in the IIG; however, various similar types of opacode black ink are included in the IIG with maximums up to (b) (4) mg. The sponsor reports that the total amount of opacode black ink is less than (b) (4) mg, which is less than (b) (4) % of the final Mycapssa drug product.

(b) (4)

(b) (4)

Excipient Review for Polysorbate 80

Sponsor's report #75-65-08

Polysorbate 80 is a (b) (4) that has a GRAS status and is present in Mycapssa below the maximum IIG limit. Thus, there is not a safety concern for the proposed use and level of polysorbate 80 in the Mycapssa formulation.

Excipient Review for Sodium Caprylate

Sponsor's report #75-65-10

Sodium caprylate (Ocatanoate) is being used in Mycapssa as a (b) (4) (b) (4), but is not included in the FDA IIG for oral administration. Thus, sodium caprylate is considered to be a novel excipient for oral administration.

Sodium caprylate is the sodium salt of caprylic acid, which is a naturally occurring fatty acid with GRAS status that was described above (Excipient Review for Glyceryl Tricaprylate). Sodium caprylate is marketed as a dietary supplement to promote intestinal health at oral doses up to 4554 mg/day (75.9 mg/kg/day for a 60 kg adult). In Mycapssa, (b) (4) mg of sodium caprylate is present in each capsule, resulting in (b) (4) mg per day and (b) (4) mg/kg/day for a 60 kg adult, which is nearly (b) (4)-fold lower than that of dietary supplements.

Sodium caprylate has been associated with cardiovascular changes in vivo and effects on sodium channels and action potential duration in vitro. Intravenous (IV) doses of approximately (b) (4) mg/kg sodium caprylate evoked ectopic ventricular beats when injected into anesthetized cats; however doses 10-fold lower (b) (4) did not have any effects (b) (4) resulting in a NOEL for IV administration that is approximately equivalent (b) (4), prior to adjustment for bioavailability differences, to the maximum clinical oral dose of 4 Mycapssa capsules per day. In an in vitro muscle contraction study, sodium octanoate shifted the relationship between potassium-induced tension and membrane potential which was attributed in part to an interaction with sodium channels in frog muscle fibers (Kossler and Nasledov, 1986). However, the relevance of the *in vitro* observations to sodium caprylate administered orally is not clear. In a Subchronic 16-week toxicology study, no treatment-related toxicity was reported in rats administered up 13,000 mg/kg/day caprylic acid (Bingham E, 2001), resulting in a safety margin of 350-fold. Furthermore, chronic exposure of sodium caprylate was evaluated in the sponsor's GLP 9-month toxicology study with the

octreotide-TPE formulation, which did not result in any significant toxicities (see section 6 General Toxicology). Overall, there is not a significant safety concern for the level of sodium caprylate used in the Mycapssa drug product.

2.5 Comments on Impurities/Degradants of Concern

In the initial IND #108163 submission, total impurities and degradation product specifications were limited to ≤(b) (4)%. However, the specification for total impurities/degradation products of the commercial drug product has been broadened to (b) (4)% for total degradation products in order to account for impurities that were identified after the Phase 3 clinical trial and initiation or completion of nonclinical toxicology studies. Thus, for a 20 mg capsule administered 4 times a day (80 mg/day Mycapssa), the total daily consumption of impurities and/or degradation products is limited to (b) (4)mg.

Specifications for microbial limits did not change. It is unclear if (b) (4) specifications changed or not.

Sponsor's Table 2: Mycapssa Drug Product Specifications

Table 1: Octreotide Capsules Finished Drug Product Specifications

Test	Encap Test Method	Commercial Specification (Encap Specification P542)
Appearance	Visual	White coated capsules, printed with "OT 20." The finished package matches the expected appearance with respect to capsule appearance and blister.
Identification A	EAM0186	The retention time (HPLC) is consistent with that of the standard.
Identification B	EAM0186	UV spectra is consistent with that of the standard.
Assay	EAM0186	(b) (4)% of label claim
Impurities /degradation products	EAM0238	(b) (4)
Uniformity of Dosage Units	EAM0186	Meets current USP <905> and Ph. Eur. 2.9.40
Dissolution	EAM018	Conforms to the current USP <711> and Ph. Eur. 2.9.3 A1/B1: Acid stage: At 2 h, ≤ (b) (4)% release (individual results). Buffer stage: At 45 min, ≥ (b) (4)% (Q = (b) (4)%) of labeled amount (individual results). A2/B2: Acid stage: The mean result must be ≤ (b) (4)% released with no individual result > (b) (4)% released. Buffer stage: The average result must be ≥ Q ((b) (4)%). No individual result can be < (Q - (b) (4)%).
Microbial Limits	USP < (b) (4) <62>, < (b) (4) > Ph. Eur. 2.6.12 Ph. Eur. 2.6.13	Total aerobic microbial count: ≤ (b) (4) cfu/g Total combined yeasts and molds count: ≤ (b) (4) cfu/g *E. coli*: absent
(b) (4)	EAM0217	(b) (4)

[a]In addition, an AQL test is applied using Appendix 1 of Encap specification P542 and using Encap SOP1079 for sampling.

AQL = ; cfu/g = colony forming units/gram; HPLC = high-performance liquid chromatography NA = not applicable; NMT = not more than; Ph. Eur. = European Pharmacopoeia; RRT = relative retention time; USP = United States Pharmacopoeia; UV = ultraviolet

Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage.

(Table excerpted from Sponsor's package)

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Sponsor's Table 4: Degradant Human Equivalent Doses and Qualification

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The proposed patient population is acromegaly patients (b) (4)

(b) (4)

The maximum recommended high dose (MRHD) is four 20 mg Mycapssa capsules daily, administered as 40 mg twice a day (BID, 40 mg morning + 40 mg evening) with a daily total of 80 mg/day, which is equivalent to 1.33 mg/kg in a 60 kg adult. The expected exposures for a repeated 80 mg/day dose are AUC_{0-12} =19.5 h·ng/mL and C_{max} = 5.30 ng/mL.

2.7 Regulatory Background

- Chiasma submitted a Pre-IND #108163 meeting request and package to the Agency on 4/1/2010. The Division denied the Pre-IND meeting request, but responded to the sponsor's questions on 8/30/2010.
- On 6/17/2010, Octreolin was granted an orphan drug status for the oral treatment of acromegaly.

- A new IND package was submitted on 11/10/2010 under the code name oral octreotide acetate.
- Chiasma submitted a letter of authorization from (b) (4) for using all or part of octreotide acetate (DMF No. (b) (4)
- On 12/17/2010, a partial clinical hold letter was issued by the FDA in response to IND application #108163 based on incomplete histopathology evaluation of all treatment groups in the 28-day repeat dose study in monkeys.
- The partial clinical hold was removed on 3/30/2011 after receiving a complete response to the partial clinical hold letter which included the histopathology evaluation of all treatment groups.
- On 6/29/2011, Chiasma requested the End-of-Phase 2 (EOP2) meeting to discuss the development plans for treatment of acromegaly. In the EOP2 package, a draft of the Phase 3 protocol (CH-ACM-01) and a complete report for the 3-month repeat dose toxicity study in monkeys were submitted.
- In the EOP2 meeting on 7/25/2011, the Agency stated that a chronic toxicology study would be required to support dosing for more than 3 months. In this meeting, the Agency noted concerns with the long-term toxicity and potential carcinogenicity of the two excipients sodium caprylate and glyceryl tricaprylate. The Agency also requested additional safety information for TPE.
- On 8/9/2011, a meeting between the sponsor's representatives and the FDA was held to discuss the development plans.
- On 8/30/2011, additional nonclinical safety data from the 3-month monkey toxicology study was submitted with histopathological evaluation of all lung tissues and the nonclinical contract research organization's historical data.
- On 9/15/2011, Chiasma communicated their plans to conduct a 9-month chronic toxicology study in monkeys to address FDA's request for chronic toxicity data and provided a written assessment of the chronic toxicity and carcinogenicity of the two excipients sodium caprylate and glyceryl tricaprylate. In addition, the Sponsor requested FDA's concurrence that, pending the results of the 9-month toxicity study, the nonclinical package with Octreolin would be sufficient to support marketing approval.
- On 11/3/2011, the Agency stated that since the drug product will be used as a chronic indication, a carcinogenicity study might be required depending on the results of a 9-month monkey toxicity study.
- In April of 2013, a waiver for the conduct carcinogenicity studies was discussed with ECAC by email and was considered to be acceptable (review #3).
- On 4/11/2014, the sponsor submitted their pre-meeting package for a Type B Meeting (Face to Face) containing 2 nonclinical questions. The purpose of this meeting was to discuss the proposed content and format of an NDA application for oral octreotide acetate via the 505(b)(2) pathway. According to previously addressed Type C meeting questions received 11/1/2013, the specification for impurities/degradation products of the commercial drug product was broadened to account for impurities that were identified after the Phase 3 clinical trial and nonclinical toxicology studies were already initiated or completed.
- On 5/19/2014, the following nonclinical responses were sent to the sponsor:
    - Response to nonclinical question #9:

        - "The scope of the nonclinical studies is sufficient to support filing of the NDA application. Whether or not the nonclinical studies are sufficient to support approval of OOA is a matter of review of the NDA application package."
    - Response to nonclinical question #10:
        - "The proposed 4-week monkey bridging toxicology study is of duration sufficient to satisfy ICH guideline Q3B(R2) recommendations; however, qualification of the current drug product in the 4-week monkey study is a matter of review. Please clearly indicate the differences in drug product formulation and specifications used in the bridging and original toxicology studies."
- On 5/21/2014, the agency met with sponsor representatives, but did not discuss the nonclinical questions.
- On 10/3/2014, a request for a Pre-NDA meeting was received; however, a type C guidance meeting via teleconference was granted for 12/8/2014 instead. No nonclinical issues were discussed at this meeting.
- Chiasma submitted the NDA #208232 package to the Agency on 6/15/2015.

3 Studies Submitted

3.1 Studies Reviewed

Studies Not Reviewed in This or Previous Reviews	
Study #	**Brief Title**
Excipient Reports	
756509	Excipient Review for PVP-12
756501	Excipient Review for Acryl-EZE
756502	Excipient Review for Gelatin Capsules
756503	Excipient Review for Gelatin (b) (4)
756504	Excipient Review for Glyceryl Monocaprylate
756505	Excipient Review for Glyceryl Tricaprylate
756506	Excipient Review for Magnesium Chloride
756507	Excipient Review for Opacode Black Ink
756508	Excipient Review for Polysorbate 80
756510	Excipient Review for Sodium Caprylate
Pharmacokinetics	
LCMSC 296.1	Quantitation of Octreotide in Monkey Plasma via HPLC with MS/MS Detection
75-30-17	Pharmacokinetic Analysis of Octreotide after intrajejunal Administration to Rats (15-66 mg/g)
1300-003	Amendment to the Final Report – A Pharmacokinetic Study of Octreotide in Cynomolgus Monkeys after a Single or Subcutaneous Dose
1300-005	Amendment to the Final Report – A Pharmacokinetic Study of Octreotide in Cynomolgus Monkeys after Single or Multiple Oral Doses
Toxicology	
1300-015	Octreotide Capsules: A 28-Day Oral (capsule) Toxicity Study in Cynomolgus Monkeys
Special Toxicology Review	

756903	DEREK & Leadscope Evaluation of the Five Octreotide Degradants Structures
756904	DEREK & Leadscope Evaluation of the Two Octreotide Degradants Structures

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Referenced works include Pharmacology and Toxicology review #1 (12/4/2010), review #2 (7/8/2011), review #3 (4/20/2013), memo #1 (3/16/2011), and memo #2 (10/20/2011) written by Dr. Parvaneh Espandiari under IND #108163.

The Pharmacology review (10/9/1998) under NDA #21008 for Sandostatin LAR written by Dr. David Hertig was also referenced for comparison to Sandostatin data.

4 Pharmacology

4.1 Primary Pharmacology

Octreotide is an octapeptide that acts as an analog of the natural hormone somatostatin by interacting with G protein-coupled somatostatin receptors. There are 5 distinct human somatostatin receptor subtypes, SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5, which have distinct chromosomal localizations and tissue-specific expressions that indicate differential function in different organ systems (Hofland and Lamberts, 1996, Barbieri et al., 2013). Octreotide binds with highest affinity to the SSTR2 subtype (IC_{50} = 0.4-2.1 nM), see Table 3: Octreotide Affinity for Somatostatin Receptor Subtypes, which is expressed in the brain and kidney, leading to stimulation of phosphotyrosine phosphatase activity and inhibition of adenylyl cyclase and calcium influx. Octreotide binds with a lower affinity to the SSTR5 subtype (IC_{50} = 5.6-32 nM), which is expressed in the brain, heart, adrenal, placenta, pituitary, small intestine, and skeletal muscle, leading to inhibition of adenylyl cyclase. Octreotide also binds with a similar affinity to the SSTR3 subtype (IC_{50} = 4.4-34.5 nM), which is expressed in the brain and pancreas, also leading to inhibition of adenylyl cyclase. Relatively very low to no affinity (IC_{50} >1 μM) has been reported for SSTR1 (brain, lung, stomach, jejunum, kidney, liver, and pancreas) and SSTR4 (brain and lung) subtypes. Somatostatin receptor-mediated inhibition of adenylyl cyclase activity leads to downstream decreases in intracellular cyclic adenosine monophosphate (cAMP) levels and decreased hormone secretion (Figure 1: Somatostatin Receptor Signaling). SSTR2 activation inhibits calcium influx via either a direct interaction with voltage-activated calcium channels or an indirect interaction with ion-channels, such as stimulation of potassium channels (Patel et al., 1990). SSTR2 activation also stimulates phosphotyrosine phosphatases, such as SHP-1, SHP-2 and PTPη, leading to induction of downstream proapoptotic signals and caspase activation. Somatostatin receptors have also been linked to stimulation of phospholipase C and mobilization of intracellular calcium with the following order of potency: SSTR5 > SSTR 2 > SSTR3 > SSTR4 > SSTR1 (Hofland and Lamberts, 1996).

Table 3: Octreotide Affinity for Somatostatin Receptor Subtypes

Ligands		Binding affinity (IC_{50} nM)				
		sst1	sst2	sst3	sst4	sst5
Endogenous	SST-14	**0.1–2.26**	**0.2–1.3**	**0.3–1.6**	**0.3–1.8**	**0.2–0.9**
	SST-28	**0.1–2.2**	**0.2–4.1**	**0.3–6.1**	**0.3–7.2**	**0.05–0.4**
	CST-14	**2.1**	**0.5**	**3.8**	**18.2**	**0.9**
	CST-17	**0.25–7.0**	**0.6–0.9**	**0.4–0.6**	**0.5–0.6**	**0.3–0.4**
Synthetic peptides in clinical use	Octreotide	>1000	**0.4–2.1**	4.4–34.5	>1000	**5.6–32**
	Lanreotide	>1000	**0.5–1.8**	43–107	>1000	**0.6–14**
	Pasireotide	**9.3**	**1**	**1.5**	>100	**0.16**

High affinity for individual SST receptors is reported in bold.

(Table excerpted and highlighted from Barbieri et al., 2013)

Figure 1: Somatostatin Receptor Signaling

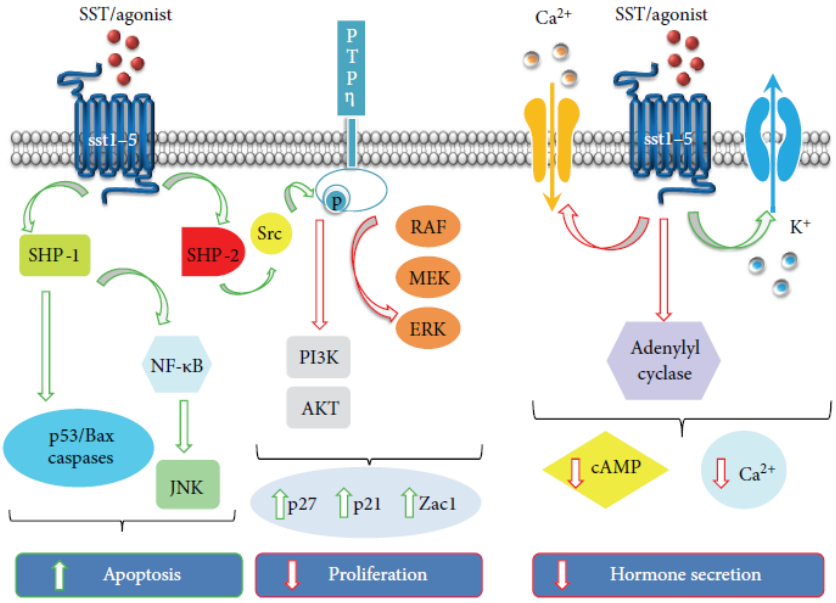

FIGURE 1: Schematic representation of the intracellular signaling pathways modulated by somatostatin receptors. Antiproliferative effects of somatostatin (SST) and its analogs; SST and analogs binding to SST receptors activate different phosphotyrosine phosphatases (PTPs) SHP-1 and SHP-2 and PTPη. Activated SHP-1 triggers intracellular proapoptoptic signals involving the induction of caspase activation and p53/Bax. SHP-1 also cause apoptosis by activation of the transcription factor NF-κB leading to the inhibition of the MAP kinase JNK anti-apoptotic effects. SHP-2 activates Src that directly interacts with PTPη inducing its phosphorylation in tyrosine and activation. PTPη dephosphorylates intracellular effectors involved in the control of cell cycle progression, such as the ERK and the PI3K/Akt pathways, causing the upregulation of the cyclin kinase inhibitors $p21^{cip1/waf1}$ and $p27^{kip1}$ and the tumor suppressor gene Zac1. As a result, cells accumulate in G1 phase without entering S-phase and cell proliferation is blocked. Antisecretory effects of SST and its analogs; SST inhibits the secretion/synthesis of many hormones through the inhibition of voltage-dependent Ca^{2+} channels and activation of K^+ channels, decreasing intracellular Ca^{2+} concentration, and inhibition of adenylyl cyclase, lowering intracellular cAMP levels. Activated pathway: green arrows; inhibited pathway: red arrows.

(Figure excerpted from Barbieri et al., 2013)

In the anterior pituitary, activation of somatostatin receptors inhibits release of growth hormone (GH), thyroid-stimulating hormone (TSH) and prolactin (PRL). In patients with acromegaly, octreotide substantially reduces GH and/or IGF-I (somatomedin C) levels. Like somatostatin, octreotide suppresses the luteinizing hormone (LH) response to gonadotropin releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits the release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and

pancreatic polypeptide. In the pancreas, somatostatin receptors also suppress exocrine secretion and release of insulin and glucagon. Octreotide has also been shown to inhibit secretion of GH, insulin and glucagon in animals.

The TPE elements in the Mycapssa formulation enable administration of octreotide acetate via the oral route, eliminating the need for SC injection. TPE is an (b) (4) (b) (4) (b) (4) he function of the TPE formulation is two-fold; (b) (4) (b) (4)

The sponsor references the LD for nonclinical pharmacology data characterizing octreotide activity. However, the sponsor conducted mechanism of action pharmacology studies characterizing the mechanism, magnitude, duration and reproducibility of TPE-induced permeability in the GI. The sponsor demonstrated that TPE alters the localization of the tight junction proteins ZO-1 and calaudin (Cla-3), allowing passage of biotin-labelled octreotide between intestinal epithelial cells (enterocytes). Data from in vivo rat pharmacology studies indicate that the TPE-induced permeability is reversible with a window of 60 to 90 minutes of increased permeability and is restricted to molecular sizes ≤ (b) (4) kDa. The systemic exposure of the repeated administration (3 doses) of the TPE system was similar to a single dose administration which was equivalent to the sum of the 3 sequential doses. Furthermore, intestinal permeability increases were not altered after daily administration for 14 consecutive days.

4.2 Secondary Pharmacology

Nonclinical secondary pharmacology studies were not conducted for Mycapssa. However, the secondary pharmacology and drug-drug interactions for the active component octreotide have been characterized for the LD, and there is significant clinical experience with octreotide exposure, and several clinical studies evaluating drug-drug interactions were conducted with Mycapssa.

Octreotide has been associated with alterations in nutrient absorption and orally administered drugs. The increased GI permeability of the TPE system is also likely to alter nutrient absorption and increase absorption of concomitant therapies with molecular sizes ≤ (b) (4) kDa. Thus, between the pharmacological effects of octreotide and the TPE-enhanced permeability, altered intestinal absorption of concomitant drugs and/or altered nutrient absorption are anticipated with Mycapssa.

Several drug-drug interactions with Mycapssa were investigated in clinical trials. In a drug interaction trial with lisinopril, concomitant administration of Mycapssa resulted in an increase in absorption and exposure to lisinopril. Concomitant administration of

Mycapssa with levonorgestrel showed a reduction in the bioavailability of levonorgestrel. There were no drug-drug interactions with co-administration of Mycapssa and either ethinyl estradiol or warfarin. Co-treatment with proton pump inhibitors may decrease Mycapssa absorption and systemic bioavailability. Octreotide acetate may increase availability of bromocriptine, but decrease bioavailability of cyclosporine. Similarly, Mycapssa decreases the rate of absorption of digoxin.

Somatostatin analogs are known to inhibit the secretion of insulin and glucagon. Thus, patients on insulin or hypoglycemic agents may be at an increased risk for hypoglycemia.

Nonclinical studies evaluating interactions with Mycapssa and CYP 450 enzymes have not been evaluated. However, limited published data indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of GH. Thus, increased exposure of concomitant drugs metabolized by CYP3A4 may be possible.

4.3 Safety Pharmacology

The sponsor conducted 5 pharmacology studies examining the effects of the TPE system on gastrointestinal permeability. Although the sponsor labeled these as safety pharmacology studies, they are considered to be molecular mechanism and absorption studies; thus, they are discussed under primary pharmacology and PK/ADME sections of this review.

Dedicated respiratory, cardiovascular and neurological safety pharmacology studies were not conducted for Mycapssa. However, the safety pharmacology of the active component, octreotide, has been fully characterized. Furthermore, there is extensive clinical experience with octreotide. As described in the LD label, incidences of bradycardia, conduction abnormalities, and arrhythmias have occurred in acromegaly patients treated with octreotide. Other ECG changes observed include QT prolongation, axis shifts, early repolarization, low voltage, R/S transition and early wave progression.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics (PK) of octreotide is linear and increases dose-proportionally in non-clinical species and in humans. With the (b) (4)% Acryl-EZE (b) (4) (b) (4) used in Mycapssa, T_{max} was achieved in monkeys approximately 3 hours after oral administration. The half-life of orally administered enteric-coated Mycapssa capsules is approximately 45 minutes in monkeys, which is 15 times longer than the 2 to 3 minute half-life of somatostatin, but less than the 1.7 to 1.9 hour half-life of the SC injectable octreotide formulation.

Nonclinical PK studies were conducted by the sponsor following different routes of administration in rats, pig and monkeys.

In rats, 12-day repeat administration of the octreotide-TPE formulation did not result in any changes in the octreotide PK profile; however, plasma levels were >50-fold higher after direct intestinal administration compared to oral administration. Systemic exposures to octreotide increased linearly with intrajejunal doses of the TPE formulation, but reached maximal absorption at 50 mg/g (50,000 mg/kg), of which an equivalent dose is not likely to be achieved clinically. Octreotide absorption along the gastrointestinal (GI) tract was highest when the formulation contained TPE. Octreotide absorption occurred throughout the small intestine with the greatest amount of absorption in the duodenum-jejunum and the least amount in the ileum-colon. Overall absorption in rats ranged from 3.5% to 10.3% after jejunal administration of the (b) (4) TPE formulation. Studies in rats also demonstrated that levels of liver exposure to octreotide were similar for both oral and SC administration, suggesting that increased liver toxicity from active drug exposure is not anticipated with the oral octreotide-TPE formulation.

In pigs, lower systemic levels of octreotide were observed after oral administration of gelatin capsules compared to SC administration. Nevertheless, bioavailability of up to 5.8% was achieved with jejunal intubation of (b) (4) TPE formulations.

Administration of enteric-coated octreotide-TPE capsules in monkeys resulted in octreotide exposures that increased linearly with increasing doses and oral bioavailability ranging from ~1.5% to 2.4%. The greatest bioavailability was reported with use of a (b) (4)% Acryl-EZE (b) (4) which is also used in the final Mycapssa drug product. C_{max}, T_{max} and half-life PK parameters were unaffected by (b) (4) formulations.

Although the comparison of octreotide absorption under fed and fasted conditions were not determined in animals, clinical studies indicate that administration of Mycapssa (Lot #OT-3-120710-1) with a high-fat/high-calorie meal leads to an approximately 90% decrease in absorption.

The distribution of systemically absorbed octreotide is likely to be similar to the LD. Relatively quick elimination from most organs is anticipated with exposures declining to less than 20% of maximal within 4 hours of absorption. Slower elimination rates are expected for the pituitary, pancreas and thyroid target organs. The highest levels of systemic octreotide exposures are expected in the kidney and liver. Octreotide protein binding is 65%, in which octreotide is primarily bound to lipoprotein and, to a lesser extent, albumin.

The formulation used in Mycapssa does not result in a chemical or physical change in the active component octreotide. Thus, the metabolism and excretion of octreotide is considered to be identical to that of the LD, which has been previously characterized. Hence, the active moiety in Mycapssa is expected to be predominantly excreted via the urine, with 32% being eliminated as unchanged octreotide. Thus, prolonged exposure

is anticipated in subjects with renal impairment, the elderly, and with hepatic function impairment.

Study title: Quantitation of Octreotide in Monkey Plasma via HPLC with MS/MS Detection

Sponsor's study #LCMSC 296.1

Key Study Findings

- A high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) method was validated for quantitation of octreotide in 200 μl of monkey plasma between concentrations of 0.084 and 25.0 ng/mL
- Octreotide plasma samples were stable up to 25 hours at room temperature or up to 218 days at -70 °C
- Octreotide binds to container walls in the absence of matrix-related components

Methods

For validation of bioanalytical method "LCMSC 296.1", reproducibility, precision, accuracy, stability, carryover, and recovery of the octreotide analyte were assessed using monkey plasma samples.

Monkey plasma aliquots of 200 μl were diluted with phosphate buffer containing internal standard and octreotide concentrations, and were quantified by HPLC-MS/MS. Eight calibration standards from 0.100 to 25.0 ng/mL were used to evaluate linearity. Precision and accuracy were determined using quality control pools at the lower limit of quantitation, 2.5 times the lower limit, the approximate midpoint of the calibration range, and 80% of the upper limit of quantitation. Intra-assay and inter-assay precision and accuracy were evaluated for each pool by analyzing 6 replicates during 3 validation runs, 1LYP2-A, 2LYP2-A, and 3LYP2-A. General extraction recovery was evaluated in one of the validated runs (2LYP2-A) by comparing analyte responses of pre-extraction spiked samples to those of post-extraction spiked samples. Two follow-up runs, 1LYP4-A and 2LYP4-A, assessed extraction recovery in which spiking solutions were either not dried in matrix-related samples or non-matrix samples, or where all extracts were collected in deactivated glass vials prior to drying. Stability was evaluated after 5 freeze/thaw cycles thawed at room temperature of low- and high-level octreotide quality controls. Stability in thawed matrix was assessed after remaining at room temperature for 25 hours prior to extraction and analysis. Long-term analyte stability was assessed by storing in frozen matrix up to 218 days at -70 °C. To evaluate specificity, monkey plasma (n=6) samples containing 5% aprotinin, +/- spiking with 0.250 ng/mL octreotide, were extracted and analyzed for the octreotide internal standard during validation run 3LYP2-A. Matrix blanks were analyzed directly following high-concentration analyte samples to assess carryover between samples.

Results

The lower limit of quantitation for octreotide was 0.084 ng/mL. In monkey plasma specificity samples, no significant chromatographic peaks were detected at mass

transitions or expected retention times of the analyte or its internal standard that would interfere with quantitation. There were no significant matrix suppression effects that could compromise sensitivity or accuracy of the assay. There were no indications of carryover from high-concentration samples into the next run.

Extraction recovery analyses indicated that octreotide adsorbs to container walls in the absence of matrix-related components, most likely because it is a very hydrophobic peptide.

Octreotide was stable when stored at room temperature up to 25 hours and at -70 °C for up to 218 days.

Overall, quantitation of octreotide using bioanalytical method "LCMSC 296.1" was validated in 200 μL Cynomolgus monkey plasma samples in the concentration range of 0.084 to 25.0 ng/mL, containing tripotassium EDTA in the absence or presence of 5 % aprotinin.
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Study title: Pharmacokinetic Analysis of Octreotide after Intrajejunal Administration to Rats (15-66 mg/g)

Sponsor's study #75-30-17

Key Study Findings

- Linear increases in exposure with intrajejunal doses of the octreotide-TPE formulation up to 50 mg/g
- Maximal absorption at 50 mg/g (50,000 mg/kg)

Methods

Cannulated rats were used to determine the effect of high levels of octreotide (15 to 66 mg/g) on TPE-mediated absorption kinetics. Cannulated SD rats (10/group) were administered 15, 33, 50, and 66 mg (b) (4) CH-906-4 via cannula at their proximal jejunum. Blood samples were collected at 3, 6, 10, 25, 60, and 90 minutes post-dose. Octreotide plasma concentrations were measured using a validated HPLC-MS/MS method.

Sponsor's Table 5: Octreotide TPE formulation for Rat Intrajejunal Administration

Table 2 Formulation Composition

(b) (4)

(Table excerpted from Sponsor's package)

Results

Systemic octreotide in plasma was observed at 3 minutes post-dose, with C_{max} being achieved between 3 and 6 minutes post-dose. Increases in exposures were dose-proportional up to 50 mg/g; however, there was not an increase in AUC or C_{max} exposures at 66 mg/g. These data indicate that octreotide exposures increase linearly with the TPE formulation up to 50 mg/g. These data further indicate that maximal absorption is achieved at doses ≥50 mg/g

Sponsor's Figure 2: Octreotide TPE Formulation PK – Intrajejunal Rat

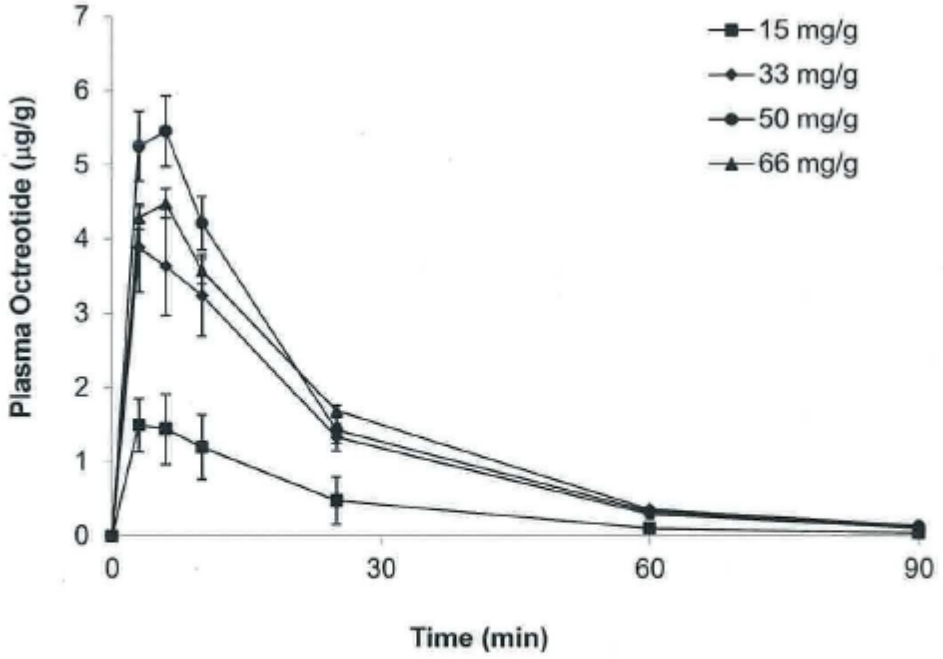


Figure 1 **Linear presentation of mean plasma octreotide concentrations after intrajejunal administration of Octreotide-TPE to rats.** Octreotide (15-66 mg/g) formulated in TPE was IJ administered to cannulated, nonanesthetized rats through the intestinal

Sponsor's Table 6: Octreotide TPE Formulation PK – Intrajejunal Rat

Table 4 **Pharmacokinetic parameters for octreotide after intrajejunal administration of OOA to rats, as determined by LC/MS/MS method**

Group		1	2	3	4
Octreotide dose	mg/g	15	33	50	66
Octreotide Dose	µg/kg	10,817±803	24,227±32234	38,529±2973	51,316±3802
C_{max}	ng/mL	1632±608	4056±1398	6047±1904	4704±1519
$AUC_{[0-90]}$	min×ng/mL	36459±14846	99371±31716	122965±47652	118061±51929
T_{max}	min	3 (3-6)	3 (3-6)	4.5 (3-6)	3 (3-6)

Arithmetic mean (± Standard Deviation) is presented with the exception of T_{max} (range), for which the median is reported.

(Table & Figure excerpted from Sponsor's package)

Study title: Amendment to the Final Report – A Pharmacokinetic Study of Octreotide in Cynomolgus Monkeys after a Single Oral or Subcutaneous Dose

Sponsor's study #1300-003

Key Study Findings

- The CH-906-1 formulation, which is similar to the Mycapssa formulation, is likely to improve absorption efficiency
  - CH-906-1 bioavailability = 1.5%
  - The bioavailability of the CH-811-1 formulation could not be determined

Method

Five male Cynomolgus monkeys were administered octreotide acetate (80 μg/kg) via SC injection or oral Octreolin (0.5, 0.5, 5, or 8 mg) capsules in a cross-over design (Sponsor's Table 7). Oral dose groups 1, 3 and 4 were of the same "(b) (4) formulation, CH-811-1, and were prepared the same. Oral dose group 5 was prepared with a different (b) (4) formulation, CH-906-1, containing (b) (4) (b) (4) (Sponsor's Table 8). After SC injection and administration of oral dose groups 1, 3 and 4, blood samples were collected prior to dosing and at 15, 30, 45, 60, 80, 100, 140, 180, and 240 post-dose. After the oral dosing of group 5, blood samples were collected prior to dosing and at 45, 90, 135, 180, 225, 270, 315, 360, 405, 465, 525, and 585 minutes post-dose. Octreotide plasma concentrations were measured using HPLC-MS/MS.

Sponsor's Table 7: Study #1300-003 Design

Group	Test Article	Number of Males	Dose Route	Dose Level	Matrix Collected
1	Octreotide	5	Oral Capsule	8 mg	Blood [A]
2	Octreotide	5	Subcutaneous, Bolus	0.08 mg/kg	Blood [B]
3	Octreotide	5	Oral Capsule	0.5 mg (Lot C26A)	Blood [A]
4	Octreotide	5	Oral Capsule	0.5 mg (Lot C26B)	Blood [A]
5	Octreotide	5	Oral Capsule	5 mg	Blood [C]

[A] Blood samples will be collected predose and at approximately 30, 45, 60, 75, 90, 105, 120, 135, 150, 180, and 240 minutes postdose.
[B] Blood samples will be collected predose and at approximately 15, 30, 45, 60, 80, 100, 140, 180, and 240 minutes postdose.
[C] Blood samples will be collected predose and at approximately 45, 90, 135, 180, 225, 270, 315, 360, 405, 465, 525, and 585 minutes postdose.

(Table excerpted from Sponsor's package)

Sponsor's Table 8: Study #1300-003 Dose Group Formulations

Table 2 Octreolin Formulation Composition (Test Items 1-4)

(b) (4)

(Table excerpted from Sponsor's package)

Results

Both formulations examined capsules (b) (4) However, the CH-906-1 formulation is more similar to the final Mycapssa drug product formulation in that it (b) (4) On the other hand, the CH-811-1 formulation was significantly different from the final product in that it contained (b) (4)

For CH-811-1 dose groups 1, 3 and 4, AUC exposure could only be calculated for 0-240 hours post-dose for oral administration even though exposures had not returned to

baseline by 240 hours (Sponsor's Table 10); therefore, the bioavailability of octreotide could not be accurately calculated. However, since exposures were determined up to 585 minutes post-dose for dose group 5, the bioavailability of Octreotide could be assessed and was determined to be 1.5% after oral administration. The C_{max} exposure of the 5 mg CH-906-1 (group 5) formulation was 50% higher than that of the 8 mg CH-811-1 (group 1) oral dose, indicating that the CH-906-1 formulation was likely to be more efficiently absorbed. Nevertheless, the bioavailability between the different formulations could not be compared.

Sponsor's Table 9: SC Dose Group 2 PK

Table 5 Octreotide pharmacokinetic parameters after its subcutaneous administration (80 µg/kg) to monkeys *

Parameter	Subcutaneous dose
C_{max} (ng/mL)	153 ± 26
T_{max} (min)	15 (15-30)
$AUC_{(0-t)}$, (minxng/mL)	15415 ± 3132
$AUC_{(0-inf)}$, (minxng/mL)	17556 ± 4618
t½ (min)	63 ± 19

*Results are presented as Mean ± standard deviation (n=5) with the exception of T_{max} (range) for which the median is reported.

(Table excerpted from Sponsor's package)

Sponsor's Figure 3: SC Dose Group 2 PK

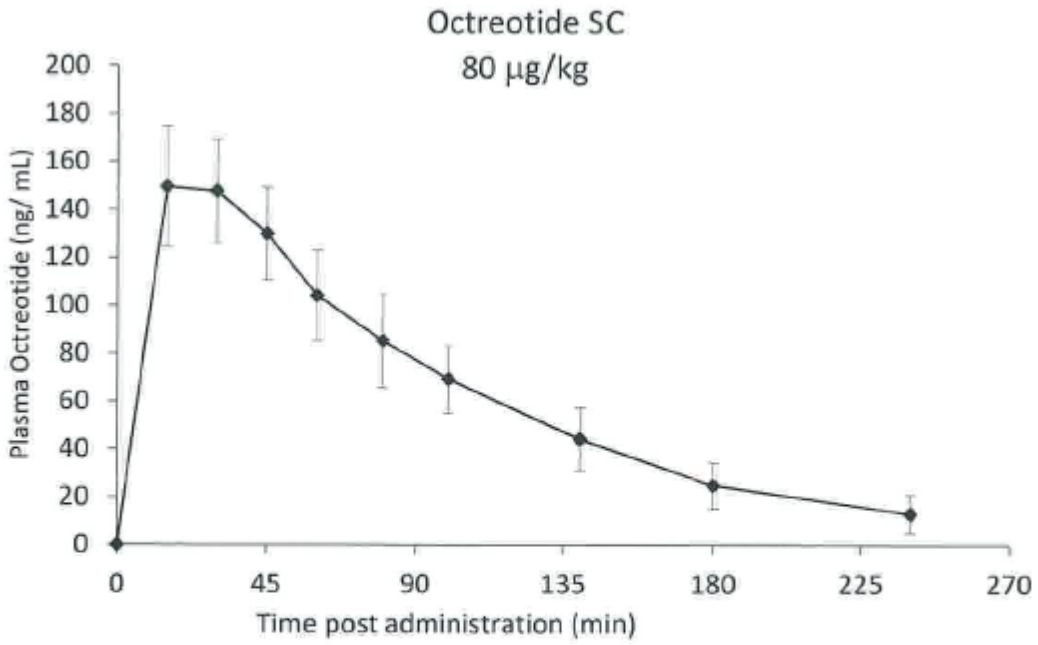


Figure 1 **Linear representation of octreotide plasma levels after sc injection.** Mean plasma concentration of octreotide after sc administration of a single 80 µg/kg dose to monkeys. Data presented as Mean ± standard deviation, n=5.

(Figure excerpted from Sponsor's package)

Sponsor's Table 10: Oral Dose Groups 1, 3, 4 & 5 PK

Table 3- Pharmacokinetic parameters after oral administration of encapsulated Octreotide formulation CH-811-1 to monkeys

Parameter	Dose, mg[% (b) (4) enteric coating]		
	Dose 1	Dose 3	Dose 4
	8.12 [7.1]	**0.49** [4.6]	**0.49** [6.0]
Cmax (ng/ mL)*	12.05 ± 3.2	0.91 ± 0.5	0.65 ± 0.3
Tmax (min)*	240	240	240
AUC (0-t), (ng x min/mL)	1410 ± 940 (66.6)	92 ± 63 (68.8)	59 ± 37 (63.4)

The results are Mean ± standard deviation except for Tmax for which the median is reported. The numbers in brackets are %CV. n=5

* Maximal levels were probably not reached in all monkeys because of the short sampling time.

Table 4- Pharmacokinetic parameters after oral administration of encapsulated Octreotide formulation CH-906-1 to monkeys

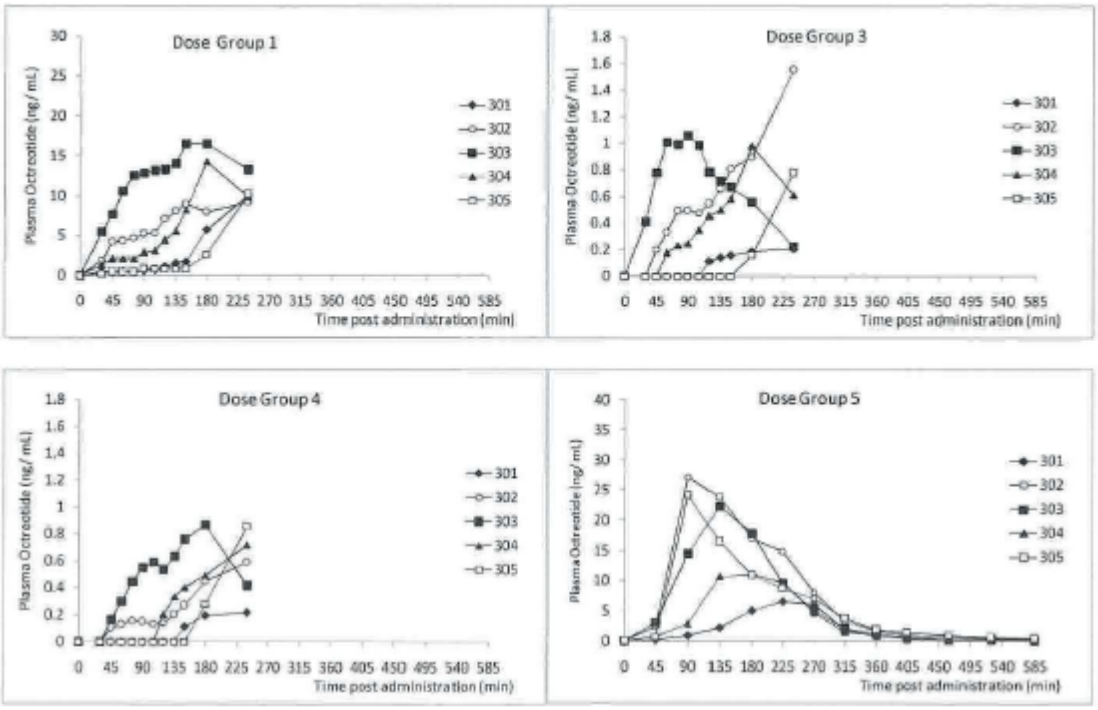
Parameter	Dose, mg [% (b) (4) enteric coating]
	5 [6.7]
Cmax (ng/ mL)	18.2 ± 8.9
Tmax (min)	135
AUC (0-t), (ng x min/mL)	2908±1363 (47)
AUC (0-inf), (ng x min/mL)	2936±1380 (47)
%rBA	1.5

The results are Mean ± standard deviation except for Tmax for which the median is reported. The numbers in brackets are %CV. n=5.

(Tables excerpted from Sponsor's package)

Sponsor's Figure 4: Oral Dose Groups 1, 3, 4 & 5 PK

Figure 2- Plasma concentration of Octreotide in individual monkeys (#301-305) after oral administration of single target doses (linear axes)



(Figures excerpted from Sponsor's package)

Study title: Amendment to the Final Report – A Pharmacokinetic Study of Octreotide in Cynomolgus Monkeys after Single or Multiple Oral Doses

Sponsor's study #1300-005

Key Study Findings

- Octreotide capsule exposures and bioavailability were higher with the (b) (4)% (b) (4)-(b) (4) enteric coating compared to (b) (4)% (b) (4)
- PK profiles of (b) (4)% (b) (4) and (b) (4)% (b) (4) enteric coatings were comparable
- PK profiles of (b) (4)% and (b) (4)% (b) (4) enteric coatings were comparable
- (b) (4) enteric coatings with (b) (4) and (b) (4) did not significantly alter octreotide PK parameters
- Pentagastrin administration did not alter octreotide PK parameters
- Enteric coatings did not alter C_{max}, T_{max} or half-life PK parameters of octreotide

Methods

Eight non-naïve cynomolgus monkeys (2 males and 2 females per group, 2 groups per treatment) were administered 1 or 2 capsules of 9.75 mg octreotide acetate with 6 different coatings via oral gavage. Prior to dosing in the morning, animals were fasted for 10 hours. Animals in group 3 received 2 capsules with coating 1 at the same time in

the morning. Animals in group 8 received 2 doses with coating 1 administered 6 hours apart and were fasted 4 hours prior to the 2nd dose. At approximately 30 minutes prior to dosing, animals in group 4, 9 and 10 were pretreated with a single SC injection of 0.15 mg/mL pentagastrin (15 μg/kg) prior to being dosed with 1 capsule with coating 1. Blood samples were collected according to the table below. Detailed clinical examinations were performed at pretest and 1 hour post-dosing.

Sponsor's Table 11: Study #1300-005 Design

Group	Test Article [A]	Number of Males/Females	Dose Route	Target Dose Level (mg/animal)	Dose Volume (capsules/animal)	Matrix Collected
1	Coating 6	2/2	Oral, capsule	9.75	1 AM	Blood[B]
2	Coating 2	2/2	Oral, capsule	9.75	1 AM	Blood[B]
3	Coating 1	2/2	Oral, capsule	19.5	2 AM	Blood[B]
4	Coating 1	2/2	Oral, capsule	9.75	1 AM + pentagastrin[C]	Blood[B]
5	Coating 3	2/2	Oral, capsule	9.75	1 AM	Blood[B]
6	Coating 4	2/2	Oral, capsule	9.75	1 AM	Blood[B]
7	Coating 5	2/2	Oral, capsule	9.75	1 AM	Blood[B]
8	Coating 1	2/2	Oral, capsule	19.5	1 AM & 1 PM	Blood[D]
9	Coating 6	2/2	Oral, capsule	9.75	1 AM	Blood[B]
10	Coating 1	2/2	Oral, capsule	9.75	1 AM	Blood[B]

[A] All capsule formulations will be provided preformulated and will be used as received
[B] Blood samples will be collected predose and at approximately 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, and 7 hours postdose
[C] Pentagastrin (15 ug/kg, 0.1 mL/kg) will be given subcutaneously approximately 1/2 hour prior to dosing.
[D] Blood samples will be collected predose and at approximately 0.75, 1.5, 2.25, 3, 3.75, 4.5, 6 (immediately prior to second dose), 6.75, 7.5, 8.25, 9, and 11 hours after the first (morning) dose.

(Table excerpted from the Sponsor's package)

Results

White, frothy vomitus was observed in 1 animal at 1 hour post-dose on Day 1. There were no other drug-related clinical signs or reoccurrences of vomitus.

Given the small number of animals and the large inter-animal and inter-group variability, it is difficult to come to concrete conclusions. Nevertheless, there was an apparent, yet not statistically significant, increase in octreotide absorption with capsules (b) (4) (b) (4) with an approximate 2-fold increase in bioavailability.

Sponsor's Figure 5: Octreotide PK Comparison of Enteric Coatings

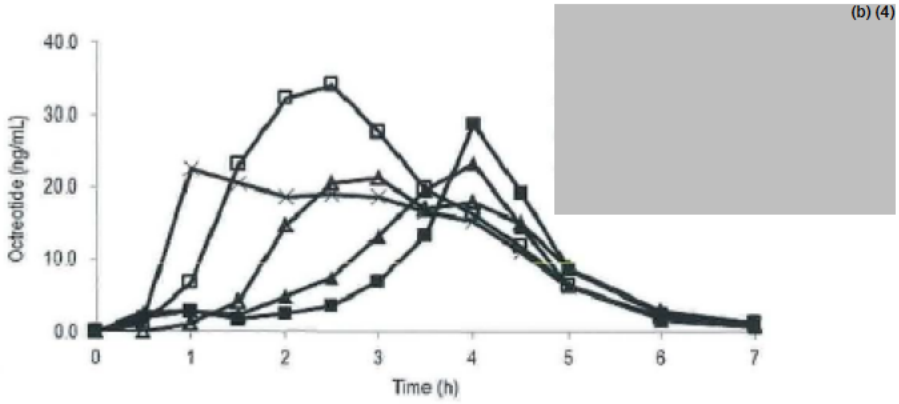


Figure 1: Mean plasma concentrations of octreotide after oral administration of OOAcapsules with different coatings.

Note: Group number 3, OOA capsules coated with (b) (4) are not presented in this graph due to different dosing (2 capsules of 9.75 octreotide vs. single capsule of 9.75 octreotide)

(Figure excerpted from Sponsor's package)

Mean AUC exposure levels per capsule and bioavailability (1.13 to 1.28%) were similar between (b) (4) coatings of (b) (4) However, mean AUC per dose and bioavailability were both approximately 2-fold lower for the (b) (4) (b) (4) Mean exposures and bioavailability of (b) (4) were comparable, although (b) (4) was the highest. Mean T_{max} ranged between 2.5 and 4 hours.

Sponsor's Table 12: Octreotide PK Comparison of Enteric Coatings

Table 6: Summary of PK parameters for octreotide after oral administration of 9.75 mg capsules with different enteric-coatings to cynomolgus monkeys.

	Enteric Coating (b) (4)					
Group No.	1	2	3	5	6	7
No. of Capsules	1	1	2	1	1	1
No. of Animals	4	4	4	4	4	4
PK Parameter						
Dose (mg/kg)	2.2 ± 0.4	2.4 ± 0.2	4.3 ± 0.7	2.1 ± 0.4	2.5 ± 0.2	2.2 ± 0.4
C_{max} (ng/mL)	39±27	29±25	56±33	23±28	25±21	35±37
T_{max} (min)	195 (120-270)	240 (240-270)	165 (150-240)	210 (150-240)	240 (30-240)	225 (60-270)
$AUC_{(0-T)}$ (minxng/mL)	5639±3626	2994±2264	9392±5715	3960±5113	3142±2706	4748±4744
$AUC_{(0-inf)}$ (minxng/mL)	5709±3622	3051±2299	9577±5895	4035±5208	3182±2724	4809±4747
AUC/dose	2495±1297	1281±934	2373±1763	2140±2972	1335±1236	2133±1759
$T_{1/2}$ (min)	44±2	37±3	45±6	44±4	39±8	44±5
F_{rel} (%)	1.35±0.70	0.69±0.51	1.28±0.95	1.13±1.60	0.73±0.67	1.15±0.95

Data presented as Arithmetic mean ± standard deviation except for Tmax presented as the Median (Range).

(Table excerpted from Sponsor's package)

There were no significant differences in PK parameters in animals treated with or without pentagastrin.

Sponsor's Table 13:Octreotide PK +/- Pentagastrin

Table 7: Summary of PK parameters for octreotide after oral administration of OOA capsules with or without pentagastrin.

	(b) (4)	(b) (4) pentagastrin	(b) (4)	(b) (4) pentagastrin
Group No.	1	9	3	4+10
No. of animals	4	4	4	8
PK Parameter				
Dose (mg/kg)	2.2 ± 0.4	2.4 ± 0.4	4.3 ± 0.7	2.4 ± 0.3
C_{max} (ng/mL)	39±27	62±47	56±33	52±33
T_{max} (min)	195 (120-270)	210 (90-240)	165 (150-240)	240 (150-240)
$AUC_{(0-t)}$ (minxng/mL)	5639±3626	8645±8646	9392±5715	8015±4787
$AUC_{(0-inf)}$ (hxng/mL)	5709±3622	9510±9511	9577±5895	9699±5268
AUC/dose	2495±1297	5237±1447	2373±1763	3632±2266
$T_{1/2}$ (min)	44±2	41.5±2.6	45±6	38.1±3.4
F_{rel} (%)	1.35±0.70	2. 18±1.75	1.28±0.95	1.86±1.13

Data presented as Arithmetic mean ± standard deviation except for T_{max} presented as the Median (Range)

(Table excerpted from Sponsor's package)

There were no significant differences in PK parameters between administrations of 2 capsules simultaneously or 2 capsules 6 hours apart.

Sponsor's Table 14: Two Capsule Dosing Administration PK Comparison

Table 8: Summary of PK parameters for octreotide after oral administration of 2 capsules (19.5 mg/day) to cynomolgus monkeys.

	(b) (4) (1 AM and 1 PM Capsules)	(b) (4) (2 AM capsules)
Group No.	3	8
Dose (mg/ day)	19.5	19.5
No. of animals	4	4
PK Parameter		
Dose (mg/kg)	4.3 ± 0.7	5.0 ± 0.3
C_{max} (ng/mL)	56±33	34±26
T_{max} (min)	165 (150-240)	293 (90-450)
$AUC_{(0-t)}$ (hxng/mL)	9392±5715	8645±6056
$AUC_{(0-inf)}$ (hxng/mL)	9577±5895	8660±6054
AUC/dose	2373±1763	1709±1103
$T_{1/2}$ (min)	45±6	95±36
F_{rel} (%)	1.28±0.95	0.89±0.61

Data presented as Arithmetic mean ± standard deviation except for Tmax presented as the Median (range)

(Table excerpted from Sponsor's package)

Overall, these data indicate that (b) (4) enteric coatings have similar PK profiles. Also, that (b) (4) enteric-coated capsules with (b) (4) did not significantly alter octreotide PK. Furthermore, PK parameters of C_{max}, T_{max}, and half-life were not affected by the type of enteric coatings used in this study.

5.2 Toxicokinetics

The toxicokinetics (TK) of enteric coated octreotide-TPE capsules were evaluated in monkeys and humans, but could not be evaluated in rats and pigs.

After repeat administration, steady-state AUC and C_{max} exposures were similar between monkeys and humans that were administered daily doses of Mycapssa capsules consisting of the octreotide-TPE formulation with an (b) (4) enteric coating. However, it is noted that T_{max} increased from 1 hour to 3-4 hours in monkeys after repeat dosing. The increase in T_{max} in monkeys is indicative of slower absorption after repeat dosing.

Table 4: Steady State TK & PK Parameters of the Final Mycapssa Formulation in Monkeys and Humans

Species	Dose			$AUC_{(0-t)}$ (h·ng/mL)	C_{max} (ng/mL)	T_{max} (hours)	$T_{1/2}$ (hours)
	mg	Dose (mg/kg)	HED				
Monkey	20 mg (Study 1300-015)	3 - 5	1.6 - 1.8	15.5 - 18.6	3 - 4.14	3 - 4*	ND
Human (Study CH-ACM-01)	40 mg (20 mg BID)	0.7	0.7	8.41	2.51	1.5	3.5
	60 mg (40 mg + 20 mg)	1	1	14.7	3.83	1.4	3.2
	80 mg (40 mg BID)	1.3	1.3	19.6	5.30	1.0	4.5

* Day 1 T_{max} = 1 hour

Sponsor's Table 15: TK & PK Parameters in Monkeys – Study 1300-015

Table 1: Summary of toxicokinetic parameters for octreotide on Days 1 and 28 after oral administration of Octreotide Capsules, 20 mg, QD × 28 days to male and female Cynolmogus monkeys.

Group	Sex	Parameter*	Study Day 1	Study Day 28
Octreolin 20 mg QD	Male	Cmax (ng/mL)	85.3 ± 89.0 (3)	6.11 ± 7.33 (4)
		Tmax (hr)	1.09 (3)	3.09 (4)
		AUC(0-t) (hr×ng/mL)	170 ± 166 (3)	18.6 ± 19.0 (4)
	Female	Cmax (ng/mL)	31.3 ± 25.8 (4)	4.28 ± 3.29 (4)
		Tmax (hr)	1.08 (4)	4.14 (4)
		AUC(0-t) (hr×ng/mL)	60.2 ± 47.0 (4)	15.5 ± 9.25 (4)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) is reported.

(Table excerpted from Sponsor's package)

Sponsor's Table 16: TK & PK Parameters in Humans - Study CH-ACM-01

Table 2: Summary of steady-state pharmacokinetic parameters for octreotide after chronic OOC administration of 40 mg as 20 mg BID, 60 mg as 40 mg AM & 20 mg PM, or 80 mg as 40 mg BID to patients with acromegaly.

Parameter*	Dosing Regimen		
	40 mg (20 mg BID)	60 mg (40 mg AM & 20 mg PM)	80 mg (40 mg BID)
C(0) (ng/mL)	0.40 ± 0.41 (21)	0.55 ± 0.43 (11)	1.62 ± 2.59 (14)
Cmax (ng/mL)	2.51 ± 2.03 (21)	3.83 ± 3.18 (11)	5.30 ± 4.06 (14)
Tmax (h)	1.50 (21) [0.48 – 3.00]	1.42 (11) [0.50 – 3.00]	1.00 (14) [0.00 – 2.00]
AUC(2-4) (h×ng/mL)	2.79 ± 2.68 (21)	4.37 ± 3.81 (11)	5.39 ± 4.21 (14)
AUC(0-4) (h×ng/mL)	5.71 ± 5.04 (21)	9.22 ± 7.33 (11)	12.6 ± 9.40 (14)
AUC(0-t) (h×ng/mL)	8.41 ± 7.75 (21)	14.7 ± 12.6 (11)	19.6 ± 15.8 (14)
AUC(0-12) (h×ng/mL)	8.17 ± 8.49 (13)	20.3 ± 12.5 (7)	19.5 ± 16.3 (12)
λz (1/h)	0.2294 ± 0.1041 (20)	0.2371 ± 0.0708 (11)	0.1784 ± 0.0649 (12)
t½ (h)	3.47 ± 1.18 (20)	3.19 ± 1.07 (11)	4.47 ± 2.02 (12)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

(Table excerpted from Sponsor's package)

6 General Toxicology

To evaluate the potential toxicity and TK of Mycapssa, the sponsor conducted 4 GLP-compliant toxicology studies in cynomolgus monkeys with oral octreotide capsules including a 28-day study, a 13-week study, a chronic 9-month study, and a 28-day bridging study.

In the 28-day repeat-dose toxicity study (#1300-002), monkeys received daily administration of 9.75 or 19.5 mg octreotide-TPE, the TPE system alone, or olive oil vehicle control. Histopathology evaluations were originally limited to high dose animals, but were subsequently conducted on all treatment groups, except for TPE alone. Infiltration of lymphocytes in the kidney and minimal inflammation in the liver was observed in the 19.5 mg treatment group; however, since there were no indications of kidney or liver dysfunction, these findings are considered to be non-adverse. Therefore, the NOAEL for this study was established at 19.5 mg/day (4.9 mg/kg/day), which is relatively similar to the MRHD of 80mg with a safety margin of 1.2x $MRHD_{BSA}$ (based on body surface area). Overall, there were no significant signs of drug-related toxicity, including the GI tract, liver and kidney which are expected to be exposed to the highest concentrations of octreotide and the TPE components. In the TPE system alone group, all excipients were tested at higher levels than Mycapssa except for the Acryl-EZE which only contained (b) (4) mg per capsule compared to the clinical formulation of (b) (4) mg/capsule. Although histopathology was not evaluated for the TPE system alone group, there were no significant clinical signs of toxicity. Thus, the higher level of excipients alone was not fully characterized in this study. Nevertheless, the higher level of Acryl-EZE is not likely to significantly increase toxicity and was evaluated in the 28-day bridging study.

In the 3-month study (#1300-007), monkeys were dosed once a day for 13 weeks with 20 mg/day of Octreolin (enteric-coated oral octreotide-TPE capsule), 0.1 mg/day of the LD (SC Sandostatin injection, positive control) and olive oil (oral capsule, vehicle negative control). Increases in uterus with cervix organ weights in females and decreases in mandibular salivary gland organ weights in both sexes were reported with test article administration; however, the organ weights remained within the normal biological ranges for this species and there were no corresponding microscopic-related findings. In addition, statistically significant increases were reported in the absolute brain weight of males treated with Octreolin compared to the negative control males; however, statistical significance was not achieved in brain weights relative to body weight and there were no histopathology-related findings in the brain of any animals across all groups. Thus, the organ weight changes are not considered to be significant or adverse drug-related findings. C_{max} and AUC exposures were 2.5 to 3-fold higher in LD-treated animals on Days 1 and 28, but were comparable to animals treated with the test article by Day 91. Given the small number of animals and individual variability, there was not a significant difference in steady-state exposures. Overall, there were no adverse test article-related toxicities and the safety profile of the test-article was considered to be comparable to the LD after daily administration for 3 months.

The 9-month monkey study (#1300-009) was conducted to provide chronic exposure data for the octreotide-TPE formulation and for the excipients sodium caprylate and glyceryl tricaprylate. Animals received daily oral administration of 20 mg octreotide-TPE enteric coated capsules, wherein all excipients, except for Acryl-EZE, were tested at higher levels compared to the levels of excipients in the final drug product. Acryl-EZE was evaluated at a (b) (4) % lower level than the final drug product formulation. Gelatin encapsulated olive oil was orally administered as a negative control and 0.1 mg/day of the LD Sandostatin was administered subcutaneously as a positive control. An increased incidence of sparse hair and red discolored skin was observed in both sexes treated with the test article and the LD, which is consistent with known octreotide-related effects in humans. A higher incidence of watery feces was also observed in animals treated with the test article. Although potentially drug-related, these clinical findings are not considered to be adverse. There were no significant drug-related effects on ECG, clinical pathology parameters, organ weights or microscopic examinations. Exposures were reasonably comparable between test-article and the LD on Days 1, 180, and 270, with the exception of the interim Day 90 where test article exposures were comparatively low. Overall, the data suggest that the chronic systemic exposure and tolerance of the test article was comparable to the LD. Furthermore, there were no new drug-related toxicities observed in animals treated with the octreotide-TPE enteric coated capsules compared to the LD. Based on these findings and available data for human use of sodium caprylate and glyceryl tricaprylate, a waiver for the conduct of carcinogenicity studies was granted for the test article. The NOAEL for chronic exposure of the test article was set at 20 mg/day with safety margins of 1-2x $MRHD_{BSA}$, 1.5-5x $MRHD_{AUC}$ (based on AUC exposure), and 2.4-8x $MRHD_{Cmax}$ (based on C_{max} exposure).

A 28-day GLP-compliant bridging study (#1300-015) was conducted in monkeys with the final Mycapssa drug product formulation containing stress-induced elevated levels of octreotide-related impurities and degradation products. The intention of this study was to qualify the stress-induced impurities. The bridging study is reviewed below.

Study title: Octreotide Capsules: A 28-Day Oral (Capsule) Toxicity Study in Cynomolgus Monkeys

Sponsor's study #1300-015

Study no.:	1300-015
Study report location:	eDr, SDN #1, 6/15/2015
Conducting laboratory and location:	(b) (4)
Date of study initiation:	9/24/2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Oral Octreotide Acetate (Octreolin) 20 mg, Batch #3165K12A, 95.4% purity, stored under stress conditions (7 months at 25°C/60%RH followed by 12 months at 2 to 8°C)

Key Study Findings

- NOAEL = 20 mg/animal/day
  - Safety margins of 1x $MRHD_{BSA}$, 1x $MRHD_{AUC}$ and 1x $MRHD_{Cmax}$
- Potentially drug-related, yet non-adverse, decreased heart rate in 50% of males
  - Consistent with clinical experience with octreotide acetate
- No new drug-related toxicities were identified
- Despite significant variability, overall PK and TK are comparable to data from the previous formulation used in the pivotal 9-month monkey toxicology study
- The drug formulation used in this study is an acceptable representation of anticipated impurities and degradation products in the proposed marketed formulation
- This study sufficiently bridges the new formulation to the pivotal 9-month monkey toxicology study

Sponsor's Table 17: Study Design

Group Assignments			
Group Number	Dose Level (mg/animal/day)	Number of Animals	
		Male	Female
1	0	4	4
2	20	4	4

(Tables excerpted from sponsor's package)

Methods

Doses:	20 mg/day
Frequency of dosing:	Once daily for 28 consecutive days
Route of administration:	Oral
Dose volume:	1 capsule
Formulation:	20 mg octreotide acetate enteric-coated capsules containing TPE
Vehicle:	Olive oil in enteric-coated capsules
Species/Strain:	Cynomolgus monkey / *Macaca fascicularis*
Number/Sex/Group:	4/sex/group
Age:	4 years and 8 months to 7 years of age
Weight:	Males ranged in weight from 4.77 to 7.19 kg. Females ranged in weight from 3.89 to 5.02 kg.
Satellite groups:	None
Unique study design:	• Animals were fasted 8-10 hours prior to dosing and fed 2 hours (±1 hour) after dosing • Mycapssa capsules were treated under stress conditions (7 months at 25°C/60% RH followed by 12 month at 2 to 8°C) to enrich for octreotide-related impurities.
Deviation from study protocol:	Animals were fasted approximately 12 hours prior to dosing on Day 1. Deviations from the study protocol did not affect the integrity of the study data.
Clinical Findings:	Cageside observations for morbidity, mortality, and injury were conducted twice daily. Detailed examinations were conducted once weekly and included evaluation of skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, salivation, tremors, convulsions, reactivity to handling, and unusual behavior.
Body weights:	Animals were weighed the day before dosing and once weekly thereafter.
Food consumption:	Qualitative observations of food consumption were conducted twice daily.
Ophthalmoscopy:	Animals were examined once prior to dosing and again prior to scheduled necropsy.
Electrocardiogram:	QRS duration and RR, PR, and QT intervals were measured prior to the dosing phase and predose and 1-2 hours postdose on Day1 and during the last week of dosing.
Hematology:	Overnight fasted blood samples were collected from all animals prior to the dosing phase and terminal necropsy. Parameters evaluated included leukocyte counts, erythrocyte counts, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, calculated mean corpuscular hemoglobin concentration, absolute reticulocytes, and platelet counts. Evaluated coagulation parameters included prothrombin time,

	activated partial thromboplastin time, and fibrinogen. Blood smears were also prepared and stained for potential evaluation.
Clinical chemistry:	Overnight fasted blood samples were collected from all animals prior to the dosing phase and terminal necropsy. Parameters evaluated included cardiac troponin, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, urea nitrogen, creatinine, total protein, albumin, globulin and A/G (albumin/globulin) ratio, glucose, total cholesterol, triglycerides, electrolytes (sodium, potassium, and chloride), calcium, and phosphorus.
Urinalysis:	Urine was collected from all animals using steel pans under the cages for at least 16 hours. Parameters evaluated included volume, color, appearance, specific gravity, pH, protein, glucose, bilirubin, ketones, blood, urobilinogen, and microscopy of centrifuged sediment.
Gross pathology:	At necropsy on Day 29, all animals were examined for external and body cavity (abdominal, thoracic, and cranial) abnormalities, as well as palpable masses.
Organ weights:	Absolute organ weights and weight ratios relative to body and brain weights were determined for all animals at necropsy on Day 29. Organs evaluated included adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, pituitary gland, prostate gland, spleen, testes, thymus, thyroid and parathyroid gland, and the uterus with the cervix. Paired organs were weighed together. Thyroid and parathyroid glands were weighed together.
Histopathology:	Tissues were harvested at necropsy on Day 29. Eyes, optic nerves, and testes were fixed using a modified Davidson's fixative, followed by formalin. All other tissues were fixed in neutral buffered formalin. Fixed tissues from all animals were embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic evaluation.
	Adequate Battery: yes (X), no ( )

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination Groups 1 and 2
Adrenal glands	X	X	X
Aorta		X	X
Bone with bone marrow, femur (proximal end)		X	
Bone with bone marrow, femur (distal end with tibiofemoral joint)		X	X
Bone with bone marrow, sternum		X	X
Bone marrow smear		X	
Brain (cerebrum, midbrain, cerebellum, medulla/pons)	X	X	X
Epididymides	X	X	X
Esophagus		X	X
Eyes (with optic nerve)		X	X
Gallbladder		X	X
GALT (Gut-Associated Lymphoid Tissue)		X	X
Gross lesions		X	X
Heart	X	X	X
Kidneys	X	X	X
Large intestine, cecum		X	X
Large intestine, colon		X	X
Large intestine, rectum		X	X
Larynx		X	X
Liver	X	X	X
Lung with bronchi		X	X
Lymph node, mandibular		X	X

	Lymph node, mesenteric: X X X Mammary gland (process females only): X X Nerve, sciatic: X X Ovaries: X X X Oviducts: X X Pancreas: X X Pituitary gland: X X X Prostate gland: X X X Salivary gland, mandibular: X X Salivary gland, parotid: X X Salivary gland, sublingual: X X Seminal vesicles: X X Skeletal muscle, rectus femoris: X X Skin: X X Small intestine, duodenum: X X Small intestine, ileum: X X Small intestine, jejunum: X X Spinal cord, cervical: X X Spinal cord, lumbar: X X Spinal cord, thoracic: X X Spleen: X X X Stomach, cardia: X X Stomach, fundus: X X Stomach, pylorus: X X Testes: X X X Thymus: X X X Thyroid gland (with parathyroid): X X X Tissue masses with regional lymph node: X X Tongue: X X Trachea: X X Ureters: X X Urinary bladder: X X Uterus with cervix: X X X Vagina: X X (Table excerpted from sponsor's protocol) Peer review: yes ( ), no (X)
Toxicokinetics:	Non-fasted blood samples were collected from all animals on Day 1 and Day 28 at 0 (predose), 1, 2, 4, and 8 hours postdose. Octreotide concentrations were determined in all drug-treated samples and 1 hour post-dosing of control samples using a validated HPLC-MS/MS method.

Observations and Results

Clinical Signs

There were no abnormal treatment-related clinical signs.

Mortality

There were no mortalities.

Body Weights

There were no treatment-related effects.

Male body weights were equally matched in both groups prior to dosing (±0.2%); however, the replacement of one male in the 20 mg group on Day 1 that was 23% larger than all the other 7 males in both groups skewed the drug-treated group towards a larger body weight. Thus, although the drug-treated male body weights were 9.7% higher than controls, there was no statistical significance.

Drug-treated female body weights were 8.8% lower than controls at the end of the study. However, given that they were 9.3% lower than controls at the beginning of the study, there was not a drug-related change in relative body weights.

Table 5: 28-Day Bridging Study #1300-015 Body Weights

MALES: Body Weight			
Study Time	Dose (mg/day)	BW gain (g) over study	BW % control
Week 4 (End of Treatment)	0	+0.043	-
	20	+0.283	109.7%
FEMALES: Body Weight			
Study Time	Dose (mg/day)	BW gain (g) over study	BW % control
Week 4 (End of Treatment)	0	+0.067	-
	20	-0.012	91.2% (↓8.8%)

Feed Consumption

No treatment-related effects on qualitative food consumption observations were reported.

Ophthalmoscopy

There were no treatment-related effects.

ECG

The sponsor reported that there were no treatment-related effects on ECG parameters. However, decreases in mean heart rates were observed in males prior to dosing (↓7%) and after dosing (↓11%) on Day 28 of drug treatment, with corresponding increases in mean RR intervals both prior to (↑8%) and after dosing (↑14%). These data include

individual heart rate decreases of 12-13% prior to dosing and 20-21% after dosing in 50% of the males on Day 28. In contrast, fluctuations in heart rates of control animals varied by less than 10% throughout the course of the study. Furthermore, the decreases in heart rates of drug-treated animals are consistent with sinus bradycardia (decrease <50 bpm) observed clinically in 19-25% of patients treated with octreotide acetate. Therefore, the reductions in male heart rates are considered possibly drug-related, but are not likely to be adverse and do not represent a new concern for octreotide administration.

Sponsor's Table 18: Mean Heart Rate & RR Interval - Males

Summary of Heart Rate, beats/minute - MALE

	0 mg/animal/day			20 mg/animal/day		
Study Interval	Mean	SD	N	Mean	SD	N
Pretest	245.40	12.860	4	238.44	15.200	4
Day 1 predose	247.45	11.139	4	246.75	13.022	4
Day 1 Postdose	254.92	9.967	4	230.97	26.394	4
Terminal predose	251.85	8.299	4	221.65[a]	19.078	4
Terminal Postdose	235.95	24.390	4	211.62	30.412	4

Summary of RR Interval, msec - MALE

	0 mg/animal/day			20 mg/animal/day		
Study Interval	Mean	SD	N	Mean	SD	N
Pretest	245.02	12.696	4	252.37	15.213	4
Day 1 predose	242.84	10.731	4	243.70	13.404	4
Day 1 Postdose	235.65	9.163	4	262.43	30.985	4
Terminal predose	238.43	7.798	4	272.22[a]	23.569	4
Terminal Postdose	256.28	25.613	4	287.82	39.894	4

a = p value < 0.05

(Tables excerpted from Sponsor's package)

Table 6: 28-Day Bridging Study #1300-015 Individual Male Heart Rates

Individual Heart Rate (bpm)							
20 mg/day Male #	Pre-dose (naïve)	Day 1		Day 28			
		Post-Dose	Change*	Pre-Dose	Change*	Post-dose	Change*
509	244	246	+2	214	-30 (↓12.3%)	192	-37 (↓21.3%)
510	242	221	-21 (↓8.7%)	231	-11 (↓4.5%)	221	-21 (↓8.7%)
511	256	258	+2	243	-13 (↓5.1%)	250	-6 (↓2.3%)
512	229	199	-30 (↓13.1%)	200	-29 (↓12.7%)	183	-46 (↓20.1%)

* Change compared to pre-dose values in drug naïve animals prior to receiving drug treatment

Hematology

There were no biologically significant or treatment-related effects.

A statistically significant decrease in lymphocytes (↓35%) was observed in females treated with Mycapssa capsules compared to concurrent controls. However, a similar 28% decrease was present prior to dosing and values are within the normal biological range. Thus, despite the statistical significance, the reported decrease in lymphocytes is not considered to be drug-related.

Clinical Chemistry

There were no biologically significant or treatment-related effects.

A small, but statistically significant, decrease in male albumin/globulin (A/G) ratio (↓14%) was reported in males after drug treatment compared to concurrent control mean values. However, the A/G ratio values were similar to values prior to dosing and were within the normal biological range. Thus, the difference in A/G ratio was not considered to be biologically significant or treatment-related.

Compared to concurrent control mean values, statistically significant increases in female alkaline phosphatase (↑35-41%), gamma glutamyl transferase (↑56-62%) and aspartate aminotransferase (↑76%) values were present prior to dosing and were not treatment-related. Similarly, statistically significant decreases in female triglyceride levels (↓30-38%) compared to concurrent control mean values were also present prior to dosing and were not treatment-related.

Urinalysis

There were no treatment-related effects.

Gross Pathology

There were no treatment-related effects.

Organ Weights

There were no statistically significant changes in organ weights of drug-treated animals.

Histopathology

There were no biologically significant or treatment-related effects.

An increase in the incidence rate of minimal mononuclear cell infiltration of the kidneys was reported in 50% of males (2/4) and 100% of females (4/4) with drug treatment compared to no findings in concurrent control males and an incidence rate of 50% (2/4) in concurrent control females. However, (b) (4) historical control data demonstrate that lymphocytic infiltrates are frequently and incidentally observed in up to 75% of cynomolgus monkeys. Furthermore, published studies have demonstrated that background renal lymphocytic infiltration rates can be as high as 100% in Cynomolgus monkeys (Chamanza et al., 2010). Thus, the reported renal lymphocytic infiltration

incidence rates in drug-treated animals are considered to be within the range of normal background findings and are not likely to be treatment-related.

Urinary bladder findings in males and females are considered to be incidental findings within the normal biological range.

Sponsor's Table 19: Microscopic Urinary Tract Findings

Summary of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/animal/day	20 mg/animal/day
kidneys		(4)	(4)
infiltration, mononuclear cell	- minimal	0	2
within normal limits		4	2
urinary bladder		(4)	(4)
infiltration, mononuclear cell	- minimal	0	1
within normal limits		4	3

Summary of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/animal/day	20 mg/animal/day
kidneys		(4)	(4)
fibrosis	- minimal	0	1
infiltration, mononuclear cell	- minimal	2	4
within normal limits		2	0
urinary bladder		(4)	(4)
hemorrhage	- moderate	1	0
inflammation, subacute/chronic	- moderate	1	0
within normal limits		3	4

(Tables excerpted from sponsor's package)

Toxicokinetics

AUC and C_{max} exposures were 4 to 10-fold lower on Day 28 compared to Day 1; however, the exposures were also associated with significant variability. Despite the high variability and reduction in exposures on Day 28, overall drug exposures are comparable to those achieved in the pivotal 9-month monkey toxicology study #1300-009. An apparent trend for a gender effect with increased exposures in males was reflected in the mean data on both Day 1 and Day 28, but is considered to be confounded by the large variability, particularly in males. T_{max} was achieved by 1 hour after dosing on Day 1, but was delayed to 3-4 hours post-dose on Day 28. In previous toxicology studies with administration of Mycapssa capsules, T_{max} ranged from 0.5 to 3 hours. Thus, overall pharmacokinetics is considered to be similar to the previous capsule formulation used in the previous toxicology studies, including the pivotal 9-month monkey study.

Sponsor's Table 20: Toxicokinetics

Table 1: Summary of toxicokinetic parameters for octreotide on Days 1 and 28 after oral administration of Octreotide Capsules, 20 mg, QD × 28 days to male and female Cynolmogus monkeys.

Group	Sex	Parameter*	Study Day	
			1	28
Octreolin 20 mg QD	Male	Cmax (ng/mL)	85.3 ± 89.0 (3)	6.11 ± 7.33 (4)
		Tmax (hr)	1.09 (3)	3.09 (4)
		AUC(0-t) (hr×ng/mL)	170 ± 166 (3)	18.6 ± 19.0 (4)
	Female	Cmax (ng/mL)	31.3 ± 25.8 (4)	4.28 ± 3.29 (4)
		Tmax (hr)	1.08 (4)	4.14 (4)
		AUC(0-t) (hr×ng/mL)	60.2 ± 47.0 (4)	15.5 ± 9.25 (4)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) is reported.

(Table excerpted from sponsor's package)

Dosing Formulation Analysis

The uniformity of lot #3165K12A used in this study was orignially (b) (4)% of label claim, but decreased to (b) (4)% after to exposure to the extreme storage conditions of 6 months at 25 °C/ 60% RH, followed by 12 months at 5 °C. Thus, approximately (b) (4)% of the drug product degraded over the (b) (4) months of extreme storage. The formulation of the lot used in this study was identical to the final Mycapssa formulation. Total degradation products and related impurities were quantified using the new, more sensitive analytical HPLC method using fluorescence detection, EAM0238 (Sponsor's Table 21). The total amount of degradation products and related impurities was (b) (4)% (w/w), which is within (b) (4)% of the new specification limit of (b) (4)% and which is nearly (b) (4)-fold higher than the previous limit of (b) (4)% applied to the drug product used in the pivotal 9-month monkey toxicology study.

Sponsor's Table 21: Batch #3165K12A Degradants & Impurities

	(b) (4)
Related impurities/ degradation products (Test method: EAM0238 v 01)	

(Table excerpted from Sponsor's package)

Lot #3165K12A was also one of 4 lots assessed in primary registration stability studies (Sponsor's Table 22), in which lot #3165K12A contained the most impurities/degradants (according to the original less-sensitive analytical HPLC method using UV detection, EAM0186) among the 4 drug lots, but was comparable on all other aspects (Sponsor's Table 23). Furthermore, lot #3164K12A was also comparable to the commercial scale batches (Sponsor's Table 24). Thus, lot #3165K12A is considered to be a reasonable representation of the Mycapssa drug product intended for commercial distribution.

Sponsor's Table 22: Drug Product Lots Used in Batch Analyses

Table 1 Batch Listing

Batch Number	Manufacturer	Manufacture date (MM/DD/YY)	Batch Size	Purpose
3163K12A	LSNE/Encap/ Almac	05/24/12	(b) (4) apsules	Primary Registration stability Clinical studies
3164K12A	LSNE/Encap/ Almac	07/26/12	apsules	Primary Registration stability Clinical studies
3165K12A	LSNE/Encap/ Almac	07/26/12	apsules	Primary Registration stability Clinical studies
3166K12A	LSNE/Encap/ Almac	07/30/12	apsules	Primary Registration stability Clinical studies
3193A13A	LSNE/Encap/ Almac	10/26/12	apsules	Supportive Registration stability Clinical studies
3194A13A	LSNE/Encap/ Almac	10/26/12	apsules	Supportive Registration stability Clinical studies
3475K14	LSNE/Encap/ Almac	01/27/14	capsules	Commercial Scale-up
3535B15A	LSNE/Encap/ Almac	05/05/14	capsules	Commercial Scale batch Stability

LSNE = Lyophilization Services of New England
Encap = Encap Drug Delivery
Almac = Almac Clinical Services Ltd

(Table excerpted from Sponsor's package and highlighted)

Sponsor's Table 23: Batch Analysis of Lots Used in Stability Studies

Table 2 Batch Analysis Release Test Results – Drug Product Batches Used as Primary Stability Studies

Test	Method	Specification P542 (Current at Time of Release of PSBs)	Current Commercial Specifications	Batch Number			
				3163K12A	3164K12A	3165K12A	3166K12A
Appearance[1]	Visual	White coated capsules printed with "OT 20"	White coated capsules printed with "OT 20"	Complies	Complies	Complies	Complies
Octreotide identification	EAM0186	Retention Time and UV spectra consistent with standard	Retention time and UV spectra consistent with standard	Complies	Complies	Complies	Complies
Octreotide assay	EAM0186	(b) (4) % of label claim	(b) (4) % of label claim	Complies	Complies	Complies	Complies
Impurities/ degradation products	EAM0186	Any individual impurity/degradation product: ≤ (b) (4) % Total impurity/degradation products: ≤ (b) (4) %		Complies	Complies	Complies	Complies
	EAM0238		(b) (4)	NA	NA	NA	NA
Uniformity of dosage units	EAM0186	Meets current USP <905> and Ph. Eur. 2.9.40	Meets current USP <905> and Ph. Eur. 2.9.40	Complies	Complies	Complies	Complies

(b) (4)

(Table excerpted from Sponsor's package and highlighted)

Sponsor's Table 24: Batch Analysis of Commercial Scale Lots

Table 4 Batch Analysis Results – Commercial Scale Drug Product Batches

Test	Method	Specification P542 (Current at time of Release of 3475K14)	Commercial Specification P542 as Applied for 3535B15A	Batch Number	
				3475K14	3535B15A
Appearance[1]	Visual	White coated capsules printed with "OT 20"	White coated capsules printed with "OT 20"	Complies	Complies
Octreotide identification	EAM0186	Retention Time and UV spectra consistent with standard	Retention Time and UV spectra consistent with standard	Complies	Complies
Octreotide assay	EAM0186	(b) (4) % of label claim	(b) (4) % of label claim	(b) (4)	
Impurities /degradation products	EAM0186	Any individual impurity/degradation product: ≤ (b) (4) % Total impurity/degradation products: ≤ (b) (4) %		(b) (4)	NA
	EAM0238		(b) (4)	NA	(b) (4)
Uniformity of dosage unit	EAM0186	Meets current USP <905> and Ph. Eur. 2.9.40	USP <905> and Ph. Eur. 2.9.40	Complies (b) (4) % of label claim	Complies (b) (4) % of label claim

(Table excerpted from Sponsor's package)

7 Genetic Toxicology

Genetic toxicology studies were not conducted for Mycapssa. However, the genetic toxicology profile for the active component octreotide has been fully characterized under the LD. Studies in laboratory animals with octreotide acetate have demonstrated no mutagenic potential of octreotide acetate.

8 Carcinogenicity

The sponsor did not conduct any carcinogenicity studies. However, nonclinical carcinogenicity studies were conducted in mice and rats with the LD, as described in the Sandostatin label, which demonstrated that there is no mutagenic potential for octreotide acetate. Based on the lack of relevant carcinogenic potential for the LD,

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 carcinogenicity studies was granted for Mycapssa.

No carcinogenic potential was demonstrated in mice treated subcutaneously with octreotide for 85 to 99 weeks at doses up to 2000 μg/kg/day, which was equivalent to 8x $MRHD_{BSA}$ for the LD, but which is roughly 10-fold lower than the Mycapssa oral dose based strictly on body surface area (0.12x $MRHD_{BSA}$ for Mycapssa).

In a 116-week subcutaneous study in rats administered octreotide, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 μg/kg/day (10x $MRHD_{BSA}$ for LD, 0.15x $MRHD_{BSA}$ for Mycapssa) compared to an incidence of 8%-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. However, there have been no reports of injection site tumors in patients treated with Sandostatin Injection for at least 5 years. There was also a 15% incidence of uterine adenocarcinomas 1250 μg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

9 Reproductive and Developmental Toxicology

The sponsor did not conduct any reproductive and developmental toxicology studies. Nevertheless, nonclinical reproductive and developmental toxicology studies conducted in vitro and in vivo with octreotide acetate have been described in the label for the LD Sandostatin.

As described in the LD label, octreotide did not impair fertility in rats at doses up to 1000 μg/kg/day, which represents 7x the human exposure based on body surface area of subcutaneously injected octreotide acetate (7x $MRHD_{BSA}$ for LD), but which is roughly 10-fold lower than the Mycapssa oral dose of 80 mg/day based on body surface area alone (0.12x $MRHD_{BSA}$ for Mycapssa). Since animal studies with octreotide have failed to reveal evidence of fetotoxicity or teratogenicity, octreotide has been listed as a pregnancy category B compound.

According to the LD label, reproduction studies have been performed in rats and rabbits at doses up to 16x $MRHD_{BSA}$ for the LD and revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there is no controlled data for exposure to octreotide during human pregnancy, postmarketing data indicate that a limited number of exposed pregnancies have been

reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-300 μg/day of Sandostatin S.C. or 20-30 mg/month of Sandostatin LAR, however some women elected to continue octreotide therapy throughout pregnancy. In cases with a known outcome, no congenital malformations were reported.

Lactation studies with octreotide have not been conducted. There is no data on the excretion of octreotide in human milk. Furthermore, safety and efficacy experience in children is limited.

10 Special Toxicology Studies

The sponsor evaluated the potential of 7 degradation products in Mycapssa using two Q(SAR) prediction methodologies, DEREK and Leadscope 2013.

Study title: DEREK & Leadscope Evaluation of the Five Octreotide Degradants Structures

Sponsor's study #75-69-03

Key Study Findings

- The following octreotide degradants do not pose a significant genotoxic risk (b) (4)

Methods

The 5 octreotide degradants, (b) (4) (b) (4) were evaluated using 2 (Q)SAR prediction methodologies, rule-based DEREK 3.0.1 Nexus 1.5 and statistical-based Leadscope Model Applier version 1.5.0-4.

Results

Derek predictions were negative for all genotoxicity and carcinogenicity endpoints for all 5 degradants.

A low incidence of positive predictions resulted from the Leadscope Modeler genotoxicity suite. (b) (4) resulted in a (b) (4) (b) (4) but not in (b) (4) cells or for (b) (4). All other degradants only had a (b) (4) for the in vivo mammalian mutation assay, but not for the 2 in vitro mammalian mutation assays or the typically more sensitive microbial gene mutation assays in *E. coli* and *Salmonella*. Furthermore, the large majority of the predictions were negative.

The overall weight of evidence indicates that there is not a significant genotoxic risk for carcinogenicity, genotoxicity or mutagenicity with any of the 5 degradants examined. The results of both prediction methodologies complement each other and do not indicate a significant genotoxic risk.

Study title: DEREK & Leadscope Evaluation of the Two Octreotide Degradants Structures

Sponsor's study #75-69-04

Key Study Findings

- The following octreotide degradant (b) (4) do not pose a genotoxic risk (b) (4)

Methods

Two octreotide degradants, (b) (4) were evaluated using 2 (Q)SAR prediction methodologies, rule-based DEREK 4.0.6 Nexus 1.7.6 and statistical-based Leadscope Model Applier version 3.2.4-1.

Results

Derek evaluation resulted in no evidence to support or oppose carcinogenicity and both compounds were predicted to be inactive for mutagenicity. Thus, there were no positive Derek alerts for genotoxicity, mutagenicity or carcinogenicity.

Leadscope predictions were negative for genotoxicity potential for (b) (4). There were no positive alerts for positive predictions of mutagenicity.

The overall weight of evidence indicates that there is not a genotoxic risk for carcinogenicity, genotoxicity or mutagenicity with either of the 2 degradant (b) (4) examined. The results of both prediction methodologies complement each other and do not indicate a genotoxic risk.

11 Labeling Review

Section 8 Use in Specific Populations

Section 8.1 Pregnancy

Excerpt 1: Sponsor's Proposed Section 8.1 Text - Animal Data

8.1 Pregnancy

Risk Summary

(b) (4)

Data

(b) (4)

Animal Data

(b) (4)

(Excerpted from Sponsor's package)

Reviewer's Comments

The Risk Summary section should refer to the animal data, as suggested below in black font (the sponsor's text is in blue). The Animal Data paragraph is repetitive in that the same data are discussed in section 13.1. See Section 13.1 Reviewer's Comments for a complete discussion of the determination of the safety margins for Mycapssa. A statement should be added to clarify the origination of the safety margin determination, which is based on body surface area of octreotide acetate subcutaneous injection which has comparable systemic exposure levels to oral administration of Mycapssa. Reviewer's text additions are noted in black and deletions are noted with a strike through the sponsor's blue text.

Reviewer's Proposed Section 8.1 Text

Risk Summary

(b) (4)

(b) (4)

Data

(b) (4)

Animal Data

(b) (4)

Section 8.2 Lactation

Data

(b) (4)

(Excerpted from Sponsor's package)

Reviewer's Comments

There are no animal data investigating the presence of octreotide in nursing dams, milk or effects on nursing offspring. From a nonclinical standpoint, this statement is not needed.

Section 8.3 Females and Males of Reproductive Potential

Excerpt 2: Sponsor's Proposed Section 8.3 Text

Infertility

Injectable octreotide acetate did not impair fertility in rats at doses up to 1000 µg/kg/day, which represents 7× the human exposure based on body surface area.

(Excerpted from Sponsor's package)

Reviewer's Comments
This paragraph is repetitive in that the same data are discussed in section 13.1. See Section 13.1 Reviewer's Comments for comments on the safety margin. From a nonclinical standpoint, this section is not needed. However, if other disciplines chose to retain it, then it should be noted that fertility studies for octreotide acetate were performed with the SC injectable formulation, not with Mycapssa. Also, a statement should be added to clarify the origination of the safety margin determination, which is based on body surface area of octreotide acetate subcutaneous injection which has comparable systemic exposure levels to oral administration of Mycapssa. Reviewer's text additions are noted in black and deletions are noted with a strike through the sponsor's blue text.

Reviewer's Proposed Section 8.3 Text
No fertility studies in animals have been conducted with MYCAPSSA. (b) (4)

(b) (4)

(b) (4)

Section 12 Clinical Pharmacology

Excerpt 3: Sponsor's Proposed Section 12 Text

(b) (4)

(Excerpted from Sponsor's package)

Reviewer's Comments
The sponsor's proposed text (Excerpt 3) is supported by the nonclinical pharmacology studies and is considered to be acceptable.

Section 12.1 Mechanism of Action

Excerpt 4: Sponsor's Proposed Section 12.1 Text

(b) (4)

Octreotide exerts pharmacologic actions similar to the natural hormone somatostatin, but is a more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin it also suppresses luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

(Excerpted from Sponsor's package)

Reviewer's Comments

(b) (4)

(b) (4)

(b) (4)

(b) (4). Overall, this statement is not considered to be current or consistent with the LD label; therefore, this statement should be omitted. Reviewer's deletions are noted with a strike through the sponsor's blue text.

Paragraph 2 is consistent with the current Sandostatin label and is considered to be acceptable.

Reviewer's Proposed Section 12.1 Text

(b) (4)

Octreotide exerts pharmacologic actions similar to the natural hormone somatostatin, but is a more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin it also suppresses luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide."

Section 13 Nonclinical Toxicology

Section 13.1 Carcinogenicity & Mutagenesis & Impairment of Fertility

Excerpt 5: Sponsor's Proposed Section 13.1 Text

13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of octreotide acetate.

No carcinogenic potential was demonstrated in mice treated SC with octreotide acetate for 85 – 99 weeks at doses up to 2000 µg/kg/day (8× the human exposure based on body surface area). In a 116-week SC study in rats administered octreotide acetate, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 µg/kg/day (10× the human exposure based on body surface area) compared to an incidence of 8% – 10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated SC injections at the same site. No tumors of this or any type were observed in animals treated with MYCAPSSA administered orally for up to 9 months.

There was also a 15% incidence of uterine adenocarcinomas in the 1250 µg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats, which does not occur in humans.

Octreotide acetate did not impair fertility in rats at doses up to 1000 µg/kg/day, which represents 7× the human exposure based on body surface area.

(b) (4)

(Excerpted from Sponsor's package)

Reviewer's Comments

All 5 paragraphs are consistent with the most recent label for the LD Sandostatin (March 2012). However, the exposure margins are based off of administration of the LD and not specific for Mycapssa, which is proposed to be used at a higher daily dose than the LD. However, the sponsor has demonstrated in monkeys that a SC dose of 0.1 mg/day Sandostatin results in systemic exposures comparable to a 20 mg/day dose of Mycapssa, this further suggests the clinical safety margins for Sandostatin are comparable to that of 20 mg/day Mycapssa in monkeys. Since the 20 mg/day dose in monkeys has safety margins of 1-2x $MRHD_{BSA}$, 1.5-5x $MRHD_{AUC}$, and 2.4-8x $MRHD_{Cmax}$ for the Mycapssa MRHD of 80 mg, a 20 mg/day dose of Mycapssa in monkeys results in exposures that are equal to or greater than that expected for clinical administration of

80 mg/day Mycapssa. Thus, this further suggests that the clinical safety margins for 0.1 mg/day Sandostatin are comparable to or less than that of 80 mg/day Mycapssa. Therefore, the safety margins reported in the LD label are considered to be comparable to and sufficient for clinical safety margins for 80 mg/day Mycapssa.

(b) (4)

(b) (4) Reviewer's text additions are noted in black and deletions are noted with a strike through the sponsor's blue text.

Reviewer's Proposed Section 13.1 Text

13.1 Carcinogenesis & Mutagenesis & Impairment ~~O~~of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of SC octreotide acetate.

No carcinogenicity studies have been conducted with MYCAPSSA. No carcinogenic potential was demonstrated in mice treated with SC ~~with~~ injectable octreotide acetate for 85 to 99 weeks at doses up to 2000 µg/kg/day (8× the human exposure based on octreotide acetate injection body surface area). In a 116-week SC study in rats administered injectable octreotide acetate, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 µg/kg/day (10× the human exposure based on octreotide acetate injection body surface area) compared to an incidence of 8% to 10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated SC injections at the same site. (b) (4)

(b) (4)

There was also a 15% incidence of uterine adenocarcinomas in ~~the1250 µg/kg/day~~ female rats (b) (4) (b) (4) compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats, which does not occur in humans.

No fertility studies have been conducted with MYCAPSSA. SC injectable octreotide acetate did not impair fertility in rats at doses up to 1000 µg/kg/day, which represents 7× the human exposure based on injectable octreotide acetate body surface area.

(b) (4)

Section 13.2 Animal Pharmacology and/or Toxicology

Excerpt 6: Sponsor's Proposed Section 13.2 Text

(b) (4)

(Excerpted from Sponsor's package)

Reviewer's Comments

The majority of Sponsor's proposed text for section 13.2 is not considered to be relevant to the safe prescribing and use of this product, and should be deleted. The abbreviated version below is proposed with reviewer's text additions noted in black and deletions noted with a strike through the sponsor's blue text.

Reviewer's Proposed Section 13.2 Text

(b) (4)

(b) (4)

12 Integrated Summary and Safety Evaluation

Chiasma, Inc., is seeking market approval under the 505(b)2 regulatory pathway for Mycapssa (oral octreotide acetate), an oral somatostatin analog, for the indication of long-term maintenance treatment of acromegaly (b) (4)

(b) (4)

(b) (4) The active ingredient, octreotide, is poorly absorbed from the gut, resulting in the use of subcutaneous, intramuscular, and intravenous injection drug delivery systems for prior Octreotide formulations. The sponsor has developed a new formulation of octreotide acetate for oral delivery containing TPE, which increases intestinal absorbance via inducing a transient opening of the tight junctions between cells to increase bioavailability through paracellular transit across the gastrointestinal wall.

For the safety of the octreotide, the sponsor is relying on previous findings of safety for the LD, Sandostatin Injection that was approved under NDA #019667 and included a comprehensive nonclinical safety evaluation including acute, subchronic, chronic toxicity, and carcinogenicity studies, as well as reproduction and mutagenicity studies in mice, rats, rabbits, dogs, and monkeys. Nonclinical studies conducted by Chiasma under this NDA application focus on the characterization and development of the TPE formulation to promote the oral bioavailability of octreotide in animals. The sponsor conducted 4 GLP-compliant toxicology studies in cynomolgus monkeys with octreolin capsules including a 28-day study, a 13-week study, a chronic 9-month study, and a 28-day bridging study. In all 4 studies, no new drug-related toxicities were identified and the toxicology findings with oral octreotide acetate and the TPE formulation were considered to be comparable to the LD Sandostatin injection. The chronic 9-month study supports long-term oral administration with safety margins of 1-2x $MRHD_{BSA}$, 1.5-5x $MRHD_{AUC}$ and 2.4-8x $MRHD_{Cmax}$.

The 28-day bridging study evaluated the Mycapssa final drug product (lot #3165K12A) formulation stored under stress conditions. Lot #3165K12A was one of 17 lots administered to acromegaly patients in the pivotal Phase 3 study #CH-ACM-01, wherein patients received Mycapssa for 7 months and an optional additional 6 months. Overall, lot #3165K12A is considered to be a reasonable representation of the Mycapssa commercial drug product. The 28-day bridging study NOAEL was equivalent to clinical exposures and the only remarkable finding was potentially treatment-related, yet non-adverse, ECG parameter changes in 50% of monkeys that were consistent with sinus bradycardia observed with clinical administration of octreotide acetate. Since this finding does not represent a new toxicological finding, the safety profile of octreotide acetate and TPE administration with stress-induced impurities and degradation products is considered to be comparable to the LD Sandostatin. Thus, the 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.

The sponsor's identification and qualification of degradation products and impurities are in accordance with the Guidance for Industry Q3A Impurities in New Drug Substances. Seven degradants above the identification threshold were identified and further evaluated using 2 independent and complementary QSAR methodologies that were knowledge based or statistically based, which is in accordance with the Guidance for Industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in

Pharmaceuticals to Limit Potential Carcinogenic Risk. All 7 of the assessed degradation products were found to be negative for genotoxic potential.

All 4 novel excipients, as well as the 1 excipient above the current IIG maximum, of the TPE formulation were qualified in the sponsor's GLP toxicology studies in monkeys. In the 9-month toxicology study, all excipients, except for Acryl-EZE, were assessed at clinically relevant or higher levels and are considered to be qualified. The percentage of Acryl-EZE (b) (4) used in the 28-day bridging monkey study was identical to the clinical formulation, and the Acryl-EZE dose in monkeys was considered to be equivalent to the clinical dose of Acryl-EZE in 4 capsules. Thus, the amount of Acryl-EZE in the final drug product formulation was considered to be qualified in the monkey bridging study. Together, all excipients were qualified in the monkey toxicology studies and the nonclinical data support long-term oral administration of the TPE formulation.

The overall weight of evidence indicates that the excipients and potential impurities and degradation products in Mycapssa are unlikely to present any potential risk for genotoxicity, mutagenicity, or carcinogenicity. Furthermore, the sponsor's characterization of the drug product excipients, impurities and degradation products are considered to be sufficient and hazard assessment of the TPE formulation and Mycapssa impurities/degradation products are considered to be complete.

In summary, the nonclinical toxicological profile of Mycapssa is comparable to that of the LD Sandostatin. Furthermore, the nonclinical data indicate that there is not a significant safety concern for the new excipients of the TPE formulation or for Mycapssa's anticipated impurities or degradation products. Therefore, the nonclinical data are sufficient to support approval of the proposed dose of Mycapssa in acromegaly patients.

13 Appendix/Attachments

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/s/

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02/23/2016

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02/23/2016
Nonclinical Recommendation for Approval.