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APPLICATION NUMBER:

208232Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208232 /SN0031
Link to EDR	\\\\Cdsub1\\evsprod\\NDA208232\\208232.enx
Submission Date	24 Dec 2019
Submission Type	505(b)(2) / Resubmission
Brand Name	MYCAPSSA
Generic Name	Octreotide
Dosage Form and Strength	Capsules: • 20 mg
Route of Administration	Oral
Proposed Indication	Long-term maintenance treatment in acromegaly patients (b) (4)
Applicant	Chiasma, Inc
Associated IND	IND- (b) (4)
OCP Reviewer	Suryanarayana Sista, PhD
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1. EXECUTIVE SUMMARY

The original NDA submission for MYCAPSSA® (octreotide) delayed-release capsule for long-term maintenance treatment of patients with acromegaly was made on 12 June 2015. The application received a Complete Response Letter (CRL) (Reference ID: 3918130) on 15 April 2016, in which the Agency listed two deficiencies (one related to Active Pharmaceutical Ingredient (API) manufacturing, the other related to the clinical program), and determined that the NDA was not approvable in its form at that time. To address deficiency #2 in the CRL, the Applicant completed an additional clinical efficacy and safety study (Study OOC-ACM-303). This study protocol was agreed to through a Special Protocol Assessment (SPA).

In the current NDA resubmission, the Applicant provided a complete response to the issues identified in the CRL.

Mycapssa, which will be available as an oral capsule, is indicated for long-term maintenance therapy in acromegaly patients in whom prior treatment with somatostatin analogs has been shown to be effective and tolerated.

Currently marketed products for the indication of Acromegaly are the following list of drugs:

1. Octreotide
 - i. Sandostatin injection (subcutaneous (s.c.) or intramuscular (i.m.))
 - ii. Sandostatin LAR injection (i.m. only)
 - iii. Octreotide acetate injection (multiple ANDAs)
2. Lanreotide
 - i. Somatuline Depot (s.c.)
3. Pasireotide
 - i. Signifor LAR (i.m. only)
4. Cabergoline
 - i. Multiple ANDAs
5. Bromocriptine
 - i. Parlodel (oral)
6. Pegvisomant
 - i. Somavert (s.c.)

This submission is a 505 (b)(2) NDA application referencing Sandostatin sub-cutaneous injection (NDA 019667). If approved, Mycapssa will be the first oral octreotide formulation to enter the market.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in the resubmission of NDA 208232 and found it acceptable to support approval of MYCAPSSA for the long-term maintenance therapy in acromegaly patients (b) (4).

(b) (4). Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The primary evidence of effectiveness for the proposed dosing regimen were obtained from data from an efficacy and safety study (Study OOC-ACM-303) that was agreed to through a Special Protocol Assessment (SPA). Fifty-one percent of patients treated with MYCAPSSA maintained their baseline response levels (IGF-1 $\leq$ 1 times upper limit of normal (ULN)) at 9 months vs. 11% who maintained their response on placebo at the end of the 9-month double-blind placebo controlled (DPC) period
General dosing instructions	Take MYCAPSSA with a glass of water on an empty stomach, at least 1 hour before a meal or at least 2 hours after a meal. Mycapssa capsules should be swallowed whole and should not be crushed or chewed. - Initiate MYCAPSSA at a dose of 40 mg daily, given as 20 mg orally twice daily. - Measure insulin-like growth factor 1 (IGF-1) levels initially every two weeks. Once the maintenance dosage is achieved, monitor IGF-1 levels monthly or as indicated. - Titrate the dosage of MYCAPSSA based on IGF-1 levels and patient's signs and symptoms. - If needed, increase the dose to 60 mg daily (given as 40 mg in the morning and 20 mg in the evening) and subsequently to the maximum recommended dose of 80 mg daily (given as 40 mg twice daily). - If IGF-1 levels remain above upper normal limit while patient has been treated with maximum dose of 80 mg daily or patient cannot tolerate treatment with MYCAPSSA, discontinue MYCAPSSA and switch patient to another somatostatin analog. - Withdraw MYCAPSSA therapy periodically to assess disease activity. If IGF-1 levels increase and signs and symptoms recur, resume MYCAPSSA therapy.
Dosing based on intrinsic/extrinsic factors	- No dose adjustments are necessary based on age, race, body weight or gender - Drug Interactions: Patients taking proton pump inhibitors, H2-receptor antagonists, or antacids concomitantly may require increased doses of MYCAPSSA - Renal Impairment: In patients with mild, moderate, or severe renal impairment there is no need to adjust the starting dose of MYCAPSSA. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in normal renal function patients. There is an almost 2-folds increase in octreotide exposure in patients with end stage renal disease (ESRD). Start patients with ESRD on MYCAPSSA 20 mg orally daily. The

	maintenance dose should be adjusted thereafter based on IGF-1 levels, clinical response and tolerability. • Hepatic Impairment: Following subcutaneous administration of the drug, patients with liver cirrhosis showed prolonged elimination, with octreotide $t_{1/2}$ increasing to 3.7 hours and total body clearance decreasing to 5.9 L/hour, whereas patients with fatty liver disease showed $t_{1/2}$ increased to 3.4 hours and total body clearance of 8.2 L/hour.
Bridge between the “to-be-marketed” and clinical trial formulations	The to-be-marketed formulation is the same as the clinical trial formulation that was used in several clinical pharmacology studies. The to-be-marketed formulation was also used in all the Phase 3 clinical studies.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Each capsule of MYCAPSSA contains (b) (4) octreotide acetate corresponding to 20 mg of the free peptide octreotide.

The following is a summary of the clinical pharmacokinetics of MYCAPSSA:

Pharmacokinetics	
Absorption:	- Linear pharmacokinetics in the dose range studied (3 mg – 20 mg in healthy volunteers, 40 mg – 80 mg in acromegaly patients) - Median T_{max} - 1.67 – 2.5 hours - Relative bioavailability following single-dose (oral compared to s.c. following dose correction): 0.5% C_{max}: - Healthy volunteers (20 mg dose): 0.4 ng under fed conditions; 3.6 ng/mL under fasting conditions - Acromegaly patients (40 mg – 80 mg): 2.51 ng/mL after 40 mg, 3.83 ng/mL after 60 mg, and 5.30 ng/mL after 80 mg AUC_{last}: - Healthy Volunteers: 1.3 ng·hr/mL under fed conditions; 15.2 ng·hr/mL under fasting conditions - Acromegaly patients (40 mg – 80 mg): 8.41 ng·hr/mL after 40 mg, 14.7 ng·hr/mL after 60 mg, and 19.6 ng·hr/mL after 80 mg - Food leads to an approximately 90% decrease in extent of absorption - Bioavailability decreased 60% when Mycapssa was administered 1 hour before a reduced-size high-fat meal
Distribution:	- Volume of distribution (V_{dss}) ~ 13.6 L in healthy volunteers and estimated to be 21.6 ± 8.5 L in Acromegaly patients - In healthy subjects, 65% bound in the plasma mainly to lipoprotein and, to a lesser extent, to albumin. Mean percentage of drug bound in Acromegaly patients is 41.2%.
Elimination:	- Total body clearance: 7 L/h - 10 L/h in healthy subjects, and about 18 L/h in Acromegaly patients. $t_{1/2}$ ~ 2-4 h in healthy subjects, and ~3.2 – 4.5 hours at steady state in Acromegaly patients
Pharmacodynamics	
Acromegaly Patients	Serum growth hormone (GH) concentrations were reasonably constant over the 2.5 to 4-hour period after dosing in all 3 dosing cohorts (40-mg, 60-mg and 80-mg). Response was defined as insulin-like growth factor 1 (IGF-1) < 1 times ULN adjusted for age and an integrated GH level over 2 hours < 2.5 ng/mL. There does not seem to be a relationship between octreotide AUC_{2-4hr} and GH average steady-state concentrations (C_{ave}) or normalized IGF-1 levels

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed starting dose of MYCAPSSA is as follows:

Take MYCAPSSA with a glass of water on an empty stomach, at least 1 hour before a meal or at least 2 hours after a meal.

Switch patients currently taking somatostatin analog therapy to oral MYCAPSSA 40 mg daily, given as 20 mg orally twice daily.

Adjust the dosage based on insulin-like growth factor 1 (IGF-1) and clinical signs and symptoms as follows:

- Measure insulin-like growth factor 1 (IGF-1) levels initially every two weeks. Once the maintenance dosage is achieved, monitor IGF-1 levels monthly or as indicated.
- Titrate the dosage of MYCAPSSA based on IGF-1 levels and patient's signs and symptoms.
- If needed, increase the dose to 60 mg daily (given as 40 mg in the morning and 20 mg in the evening) and subsequently to the maximum recommended dose of 80 mg daily (given as 40 mg twice daily).
- If IGF-1 levels remain above upper normal limit while patient has been treated with maximum dose of 80 mg daily or patient cannot tolerate treatment with MYCAPSSA, discontinue MYCAPSSA and switch patient to another somatostatin analog.
- Withdraw MYCAPSSA therapy periodically to assess disease activity. If IGF-1 levels increase and signs and symptoms recur, resume MYCAPSSA therapy.
- Patients taking proton pump inhibitors, H2-receptor antagonists, or antacids concomitantly may require increased doses of MYCAPSSA

2.2.2 Therapeutic individualization

Age, Race, Body Weight and Gender:

A formal population PK of Mycapssa was not performed. However, based on analysis of pooled data for the 20 mg Mycapssa oral administration and 0.1 mg Sandostatin administration in healthy volunteers, and a separate analysis of acromegaly patients from the PK sub-study of the Phase 3 trial, no dose adjustments are necessary based on age, race, body weight or gender.

Dosing Adjustment Due to Drug Interactions:

Proton pump inhibitors (PPIs), H2-receptor antagonists, and antacids may lead to a higher dosing requirement of MYCAPSSA to achieve therapeutic levels.

Renal Impairment:

In patients with mild, moderate, or severe renal impairment there is no need to adjust the starting dose of MYCAPSSA. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in patients with normal renal function. There is a significant increase in octreotide exposure in patients with end stage renal disease (ESRD). Patients with ESRD should be started on a lower starting dose of 20 mg daily. The maintenance dose should be adjusted thereafter based on IGF-1 levels, clinical response and tolerability.

Hepatic Impairment:

Patients with liver cirrhosis and patients with fatty liver disease showed prolonged elimination of octreotide following subcutaneous administration of drug.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following preliminary labeling concepts be included in the final package insert:

Label Section	Acceptable to OCP?			Recommendation
	A	AWE	U	
7 DRUG INTERACTIONS	☐	☐	☒	Present the drug-drug interaction information in a table format to include impact and recommend mitigation strategies for significant drug-drug interactions.
8 USE IN SPECIFIC POPULATIONS 8.6 Renal Impairment	☐	☒	☐	Add <i>"There is an almost 2-folds increase in octreotide exposure in patients with end stage renal disease (ESRD). Patients with ESRD should be started on a lower starting dose (recommended 20 mg QD). The maintenance dose should be adjusted thereafter based on clinical response and tolerability"</i>.
8.7 Hepatic Impairment	☐	☐	☒	Replace with <i>"Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide t_{1/2} increasing to 3.7 hours and total body clearance decreasing to 5.9 L/hour, whereas patients with fatty liver disease showed t_{1/2} increased to 3.4 hours and total body clearance of 8.2 L/hour"</i>
12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics	☐	☒	☐	Add words in italics In healthy subjects, similar <i>systemic exposure (AUC)</i> was observed between a single dose oral administration of MYCAPSSA (20 mg octreotide acetate), and a single dose of subcutaneous Sandostatin IR (0.1 mg octreotide acetate). <i>Peak octreotide levels (C_{max}) were 33% lower following oral administration compared to the subcutaneous route. Absorption time was longer following oral administration compared to the subcutaneous route; peak concentrations were reached at a median of 1.67–2.5 hours after 20 mg MYCAPSSA administration compared to 0.5 hours for the subcutaneous administration (see Error! Reference source not found.)</i>.
12.3 Pharmacokinetics	☐	☐	☒	<i>Effect of Food on Oral Absorption</i> - Add value for C_{max} and delete 90% confidence intervals - Delete "In a Phase 3 clinical study in acromegaly patients, MYCAPSSA was effective when administered

				<i>at least 1 hour prior to a meal or at least 2 hours after a meal" as this sentence does not describe food effect.</i>
12.3 Pharmacokinetics	☐	☒	☐	<i>Patients with Renal Impairment</i> – addition of sentence in <i>italics</i>. Exposure in patients with severe renal impairment was not substantially different from that of the matched controls. Following oral administration of a single dose of 20 mg MYCAPSSA to patients with severe renal impairment (eGFR 15–29 mL/min/1.73m²) and patients with end-stage renal disease (ESRD) requiring dialysis, patients with ESRD on dialysis <i>had a 46% decrease in clearance with a corresponding 87% increase in AUC and 85% increase in t_{1/2} compared to matched healthy subjects. ESRD patients had higher mean plasma concentrations than did those with severe renal impairment with higher mean values for C_{max} (9.30 ng/mL compared to 6.13 ng/mL in the matched controls), AUC_{0–5} (68.0 h·ng/mL compared to 32.2 h·ng/mL in the matched controls), AUC_{inf} (69.5 h·ng/mL compared to 32.4 h·ng/mL in the matched controls), and t_{1/2} (7.09 hr compared to 3.84 hr in the matched controls), consistent with the known effect of renal impairment on octreotide exposure.</i>
12.3 Pharmacokinetics	☐	☐	☒	<i>Add a section on Drug-Drug Interactions and describe the magnitude of the interactions in a tabular format</i>

A = Acceptable; AWE=Acceptable with minor edits; U=Unacceptable/substantive disagreement (must provide comment);

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

For a comprehensive Clinical Pharmacology review including the regulatory history for the original NDA submission, please refer to the review in DARRTS (Reference ID: 3914351, dated: 08 Apr 2016). The original NDA submission received a CR letter, which listed 2 deficiencies. The first deficiency was related to facilities while the second deficiency was stated as follows:

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

The following paragraphs provide a summary of our rationale for the deficiency described in item number 2.

The data in the application demonstrate that Mycapssa and Sandostatin IR (listed drug) are not bioequivalent. Specifically, the relative systemic exposure, based on the least squares means for AUC_{0-t}, of octreotide from the single-dose 20 mg fasted dose of Mycapssa relative to the 0.1 mg s.c. dose of octreotide was 0.97 with very wide confidence intervals of 73% – 128% for AUC_{0-t}. Similarly, the C_{max} with a point estimate of 0.64 and 90% confidence intervals of 45.29% -89.78% failed to meet the bioequivalence criteria. A comparative pharmacokinetic (PK) study evaluating the proposed twice daily (BID) dosing regimen of Mycapssa compared to the three times daily (TID) dosing of Sandostatin was not conducted. Finally, you did not characterize the Mycapssa dose-response relationship or the pharmacodynamic (PD) comparability (growth hormone and IGF-1) between Mycapssa and Sandostatin injection in your application.

Although meeting strict criteria for bioequivalence is not required for products reviewed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, absence of bioequivalence between Mycapssa and the listed drug necessitated that you demonstrate the safety and effectiveness of Mycapssa with data generated in study CH-ACM-01. ...To address the deficiency listed in item number 2, you will need to provide substantial evidence that Mycapssa will have the effect it purports to have under the conditions of use recommended in labeling for patients with acromegaly in a new clinical trial. The study design, conduct of the study and primary analysis should minimize biases to the extent possible to ensure the effect size captured is attributable to Mycapssa and not to a confounder. We strongly recommend that your study be randomized, double-blind and controlled. The trial should enroll patients from the United States and be of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment. ... " (See DARRTS, Reference ID 3918130, dated 15 APR 2016 for complete letter).

No new Clinical Pharmacology studies were submitted in the current resubmission. The following summary is a brief overview of the regulatory history since the CR action and the resubmission, and findings from the additional clinical efficacy and safety study (Study OOC-ACM-303) that the Applicant conducted. This new clinical study did not assess octreotide plasma concentrations in patients.

The regulatory communication history between the CR action and NDA resubmission is summarized below:

Dates	Communication/Meeting Type	Key Communication Points
08 Jun 2016	End-of-Review meeting	• Discussion of deficiencies outlined in the Agency's CR letter
06 Jan 2017	Type C Meeting Written Response	• Agency disagreed with design of proposed study, OOC-ACM-302-4 • During the Type C Guidance Teleconference, the Agency agreed that SPA agreement would be the most appropriate path forward for the Applicant
04 Aug 2017	SPA Agreement Letter	• Agency agreed that Study OOC-ACM-303 (protocol Version 5.0) was adequately designed to potentially address the

		deficiency listed in item number 2 of the Complete Response Letter
04 May 2018	Type C Meeting Written Response	In the review of the original submission of NDA 208232, OCP had recommended a complete response because (a) single oral dose of Mycapssa 20 mg did not demonstrate bioequivalence to single dose of Sandostatin 0.1 mg administered subcutaneously, (b) there was no characterization of MYCAPSSA dose-response or pharmacodynamic (PD) comparability (GH and IGF-1) between Mycapssa and Sandostatin. Even though the CR letter had noted that a comparative PK study evaluating the proposed twice daily (BID) dosing regimen of Mycapssa compared to the three times daily (TID) dosing of Sandostatin was not conducted, and that the Applicant did not characterize the Mycapssa dose-response relationship or the PD comparability (GH and IGF-1) between Mycapssa and Sandostatin injection in their application, during the Type C meeting, the Agency agreed that no additional clinical pharmacology studies need to be included in the NDA resubmission since Study OOC-ACM-303 conducted under an approved SPA was going to evaluate IGF-1 and GH under previously agreed criteria to demonstrate efficacy and safety.
08 Oct 2018	Type B Pre-NDA Meeting Comments	Agency informed the Applicant that the Agency did not agree that the results of Study CH-ACM-01 from the original NDA submission, and therefore was not necessary for resubmission The Applicant pointed out that in a Type C letter the Agency agreed that ISS and ISE will include the results from both studies CH-ACM-01 and OOC-ACM-303

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Octreotide is a synthetic octapeptide analog of human somatostatin, displaying a high affinity for somatostatin receptor subtypes 2 and 5. Octreotide exerts pharmacologic actions similar to the natural hormone somatostatin, but is a more potent inhibitor of GH, 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.
Active Moieties	Octreotide
Pharmacodynamics	Single-dose PK study conducted in healthy volunteers evaluating the pharmacodynamic effects of MYCAPSSA, inhibition of GH (as measured by C_{avg}) was observed in all subjects receiving MYCAPSSA, as compared to their GH levels prior to MYCAPSSA. MYCAPSSA maintained GH and IGF-1 levels in patients with acromegaly.
General Information	
Bioanalysis	Octreotide: Octreotide concentrations in plasma and serum were determined using validated high-performance liquid chromatography with mass spectrometric detection (HPLC-MS/MS). The validation range was 50 – 2000 pmol/L, with the lower limit of quantification (LLOQ) being 50 pmol/L.

	GH: GH was assayed by a sandwich type IDS-iSYS hGH immunoassay with detection by chemiluminescence. Growth hormone molecules were captured by a biotinylated monoclonal anti-GH antibody, which binds then to streptavidin-coated magnetic particles. After incubation and a washing step, an acridinium-labelled anti-GH antibody was added to give a directly proportional chemiluminescence signal, initiated by the triggers hydrogen peroxide and sodium hydroxide. The lower limit of quantification (LOQ) set by the instrument software for the determination of GH was 0.05 ng/mL. IGF-1: IGF-1 was assayed by a sandwich type IDS-iSYS IGF-1 immunoassay with detection by chemiluminescence. The free IGF-1 was captured by a biotinylated monoclonal anti-IGF-1 antibody, which binds then to streptavidin-coated magnetic particles. To generate a signal, an acridinium-labeled anti-IGF-1 antibody was added to give a directly proportional chemiluminescence signal, initiated by the triggers hydrogen peroxide and sodium hydroxide. The lower limit of quantification (LOQ) set by the instrument software for the determination of IGF-1 was 10 ng/mL.
Effect of Intrinsic Factors on Pharmacokinetics	Information on the intrinsic factors affecting the pharmacokinetics of octreotide was pooled from several 7 Phase 1, studies. Only data from the 20 mg Mycapssa administered under fasting conditions and 0.1 mg Sandostatin administered subcutaneously were pooled due to similarity in total exposure. The data from phase 3 sub-study was also explored to determine if there were any factors affecting the PK of octreotide. Based on pooled analysis and phase 3 sub-study data, no notable differences in octreotide exposure were observed across age groups, between sexes, across race groups, or by body weight.
Dose Proportionality	Dose proportionality was observed between the Mycapssa doses evaluated, 3 mg – 80 mg.
Renal or Hepatic Impairment	Renal Impairment: In patients with mild, moderate, or severe renal impairment there is no need to adjust the starting dose of MYCAPSSA. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in nonrenal patients. In Study CHI-007, patients with severe renal impairment (SRI) showed that SRI subjects had a longer mean $t_{1/2}$ of 5.90 hours for oral octreotide acetate compared to 3.1 hours for Sandostatin. It is not clear if this difference would lead to any significant accumulation differences of octreotide between oral octreotide and Sandostatin in SRI patients at steady-state. Hepatic impairment: Patients with liver cirrhosis and patients with fatty liver disease showed prolonged elimination of octreotide following subcutaneous administration of drug
Pediatric	Safety and efficacy of octreotide acetate in the pediatric population have not been studied.
Drug-Drug Interaction	Proton pump inhibitors (PPIs), H2-receptor antagonists, and antacids may lead to a higher dosing requirement of MYCAPSSA to achieve therapeutic levels The pharmacological effects of somatostatin analogs may alter the intestinal absorption of concomitant drugs or alter nutrient absorption. Concomitant administration of MYCAPSSA (octreotide) capsules with cyclosporine has been shown to decrease blood levels of cyclosporine; this is consistent with the known effects of injectable somatostatin analogs. Concomitant administration of MYCAPSSA with levonorgestrel or digoxin may lead to decreased blood levels of levonorgestrel and digoxin. Concomitant administration of MYCAPSSA with lisinopril may result in increased blood levels of lisinopril.

Absorption	
Bioavailability	Comparison of PK parameters following 20 mg oral dose of octreotide and 0.1 mg Sandostatin s.c. showed that the geometric mean ratios (Mycapssa/Sandostatin) for AUC_{0-4} and $AUC_{0-\infty}$ were 95.1% and 95.4%, respectively. The C_{max} ratio was 66.7%.
T_{max}	The time to maximum octreotide concentration was 2.5 hours following 20 mg oral octreotide administered under fasting conditions, compared to a T_{max} of 0.5 hours following subcutaneous administration of 0.1 mg of Sandostatin. Following administration of oral octreotide under fed conditions, the T_{max} was delayed to 3 hours.
ADME	
Distribution	Volume of distribution (V_{dss}) is ~ 13.6 L in healthy volunteers and estimated to be 21.6 ± 8.5 L in Acromegaly patients. In healthy subjects, 65% bound in the plasma mainly to lipoprotein and, to a lesser extent, to albumin. Mean percentage of drug bound in Acromegaly patients is 41.2%.
Elimination	The total body clearance of octreotide is estimated to be 7 L/h - 10 L/h in healthy subjects, and about 18 L/h in Acromegaly patients. The $t_{1/2}$ for elimination of octreotide is ~ 2-4 h in healthy subjects, and ~3.2 – 4.5 hours at steady state in Acromegaly patients.
Metabolism	No definitive ADME studies in humans have been performed with MYCAPSSA.
Excretion	According to data obtained with the immediate-release formulation, Sandostatin sc injection, approximately 32% of the dose is excreted unchanged in the urine.

3.3 Clinical Pharmacology Review Questions

3.3.1 *To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?*

The Clinical Pharmacology program included 12 completed clinical studies providing information on the safety, tolerability, pharmacokinetic, and pharmacodynamic properties of octreotide. All of the 12 studies contributed towards the pharmacokinetics of oral octreotide. Two (2) studies contributed towards pharmacodynamic information, 5 studies contributed towards information on drug-drug interaction. The data from one phase 3 safety/efficacy studies (Study OOC-ACM-303, conducted under a SPA agreement) provided evidence of effectiveness of MYCAPSSA. It showed that in acromegaly patients who responded to and tolerated treatment with somatostatin analogs, long-term maintenance treatment with oral octreotide, maintained control of GH and IGF-1 levels (see Clinical review by Dr. Doi in DARRTS).

For full details on the Clinical Pharmacology information of MYCAPSSA, refer to the review of the original NDA submission in DARRTS (Reference ID: 3914351, dated: 08 Apr 2016).

3.3.2 *Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?*

The standard of care, Sandostatin, is administered at a dose of 0.1 mg thrice daily subcutaneously. MYCAPSSA 20 mg is proposed to be dosed twice a day orally. In a head-to-head comparison of 20 mg MYCAPSSA and 0.1 mg Sandostatin (Study CHI-002), bioequivalence was not established between the two products. While AUC_{0-4} was comparable, it failed to meet the criteria for bioequivalence determination. The ratio of least squares means (test/ref) for AUC_{0-4} was 0.97 with 90% confidence intervals of 73.03% - 128.37%. Similarly, C_{max} with a point estimate of 0.64 and 90% confidence intervals of 45.29% - 89.78% failed to meet the bioequivalence criteria. In this study, pharmacodynamic comparison of growth hormone and IGF-1 concentration, that would have lent support to the safety and efficacy, was not carried out. These points were outlined in the CR recommendation in the original OCP review (see Reference ID: 3914351, dated: 08 Apr 2016). Following the CR action, the Applicant agreed

to conduct a Phase 3 study (OOC-ACM-303) according to a SPA agreement, which would mitigate the concerns raised in the CR letter.

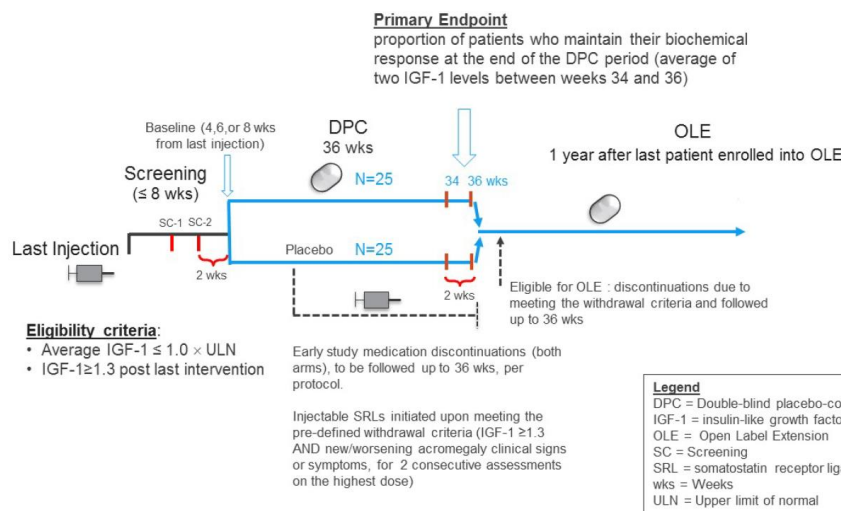
The primary objective of Study OOC-ACM-303 was to assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly who previously demonstrated biochemical control on Somatostatin receptor ligands (SRLs). Assessment of maintenance of biochemical control, based on GH with octreotide capsules compared to placebo was a secondary objective.

The study consisted of a screening period, a double-blind placebo-controlled (DPC) period, an open-label extension (OLE) period and a follow-up period for patients who discontinued study drug early during the DPC period. During the DPC period of 36 weeks, the octreotide capsule dose/ placebo was titrated up per Investigator's discretion based on significantly increased IGF-1 levels compared to baseline (average of the 2 assessments within 2 weeks prior to randomization), worsening of acromegaly signs/symptoms, or both. The Applicant recommended any one of the following guiding rules for dose escalation:

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

Dose escalation was performed in a stepwise manner from 1 capsule bid; equivalent to 40 mg/day), to 2 capsules in the morning and 1 capsule in the evening/night (equivalent to 60 mg/day), to 2 capsules bid (equivalent to 80 mg/day). The dose could have been escalated any time through week 24 (including week 24); thereafter the dose was to be kept stable. Patients who completed the DPC period on study drug (either octreotide capsules or placebo) were offered entry into the OLE. Patients who discontinued study medication early during the DPC period for reasons other than the pre-defined withdrawal criteria were followed per protocol until week 36.

The study design is shown below:



Evaluation of the efficacy endpoint, baseline IGF-1 and somatostatin dose-adjusted proportion of patients who maintain their biochemical response at the end of 9 months of treatment showed that 51% of patients treated with MYCAPSSA maintained their baseline response levels at 9 months vs. 11% who maintained

their response on placebo. Please refer to the statistical review by Dr. Kettermann for further details (DARRTS reference ID: 4617317, dated 01 June 2020).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Information on the intrinsic factors affecting the pharmacokinetics of octreotide was pooled from several 7 Phase 1, studies. Only data from the 20 mg Mycapssa administered under fasting conditions and 0.1 mg Sandostatin administered subcutaneously were pooled due to similarity in total exposure. The data from phase 3 sub-study was also explored to determine if there were any factors affecting the PK of octreotide. Based on pooled analysis and phase 3 sub-study data, no notable differences in octreotide exposure were observed across age groups, between sexes, across race groups, or by body weight (See DARRTS, Reference ID: 3914351, dated 08 APR 2016). Immunogenicity was assessed in Study CH-ACM-01 and there were no detectable positive anti-octreotide antibodies (Appendix 4.2).

3.3.4 Are there clinically relevant drug-drug interactions, and what is the appropriate management strategy?

Mycapssa capsule has a pH-sensitive enteric coating designed to withstand the acid environment of the stomach and deliver octreotide acetate to the small intestine for absorption. Drugs that elevate gastric pH, such as Proton pump inhibitors (PPI) have the potential of disrupting the capsule's ability to stay intact in the stomach until it reaches the small intestine for absorption. Similarly, motility inducers or inhibitors may affect the absorption pattern by changing the residence time of the capsule in the stomach. In order to address these issues, the sponsor conducted various drug-drug interaction (DDI) studies (See DARRTS, Reference ID: 3914351, dated 08 APR 2016).

According to the Sandostatin package insert "*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 growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution*". The Applicant has evaluated the effect of Mycapssa on drugs such as digoxin, lisinopril, oral contraceptives, metformin, warfarin, hydrochlorothiazide and cyclosporine.

The clinically relevant drug-drug interactions between MYCAPSSA and other drugs, and the appropriate management strategy are discussed below:

Effects of Other Drugs on MYCAPSSA

Proton Pump Inhibitors and Other Drugs Altering the pH of the Upper Gastrointestinal Tract	
<i>Clinical Impact:</i>	Concomitant administration of MYCAPSSA with esomeprazole resulted in a decrease in the bioavailability for MYCAPSSA (See Clinical Pharmacology [12.3]). Drugs that alter the pH of the upper GI tract (e.g., other PPIs, H2-receptor antagonists, and antacids) may alter the absorption of MYCAPSSA and lead to a reduction in bioavailability.
<i>Intervention:</i>	Co-administration of MYCAPSSA with esomeprazole may require higher dosing of MYCAPSSA. Similarly, co-administration of MYCAPSSA with other PPIs, H2-blockers, or antacids may require higher dosing of MYCAPSSA.

Effects of MYCAPSSA on Other Drugs

Cyclosporine	
<i>Clinical Impact:</i>	Concomitant administration of MYCAPSSA with cyclosporine resulted in a decrease in cyclosporine bioavailability
<i>Intervention:</i>	Adjustment of cyclosporine dose to maintain therapeutic levels may be necessitated.
Insulin and Antidiabetic Drugs	
<i>Clinical Impact:</i>	MYCAPSSA inhibits the secretion of insulin and glucagon.
<i>Intervention:</i>	Monitor blood glucose levels in diabetic patients upon MYCAPSSA initiation and subsequent dose adjustment. Patients receiving insulin or antidiabetic drugs agents may require dose adjustment of these therapeutic agents.
Digoxin	
<i>Clinical Impact:</i>	Concomitant administration of MYCAPSSA with digoxin resulted in a decrease in digoxin peak exposure
<i>Intervention:</i>	Digoxin has a narrow therapeutic ratio and careful assessment of clinical response and toxicity should be performed when digoxin is concomitantly administered with MYCAPSSA.
Lisinopril	
<i>Clinical Impact:</i>	Concomitant administration of MYCAPSSA increases lisinopril bioavailability
<i>Intervention:</i>	Monitor patient's blood pressure and adjust the dosage of lisinopril if needed.
Levonorgestrel	
<i>Clinical Impact:</i>	Concomitant administration of MYCAPSSA with levonorgestrel decreases levonorgestrel bioavailability
<i>Intervention:</i>	Decreased bioavailability may potentially diminish the effectiveness of combined oral contraceptives (COCs) or increase breakthrough bleeding. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when MYCAPSSA is used with COCs
Bromocriptine	
<i>Clinical Impact:</i>	Concomitant administration of MYCAPSSA with bromocriptine may increase the systemic exposure of bromocriptine
<i>Intervention:</i>	Dose adjustment of bromocriptine may be necessary.
Beta Blocker and Calcium Channel Blockers	
<i>Clinical Impact:</i>	MYCAPSSA may cause bradycardia in acromegaly patients.
<i>Intervention:</i>	Patients receiving beta blockers or calcium channel blockers may require dose adjustments of these therapeutic agents.
Drugs Metabolized by CYP 450 Enzymes	
<i>Clinical Impact:</i>	Limited published data indicate that somatostatin analogs including MYCAPSSA may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of GH.
<i>Intervention:</i>	Concomitant use with other drugs mainly metabolized by CYP3A4 that have a narrow therapeutic index (e.g., quinidine) should be used with caution and increased monitoring may be required.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 *How is MYCAPSSA identified and what are the analytical methods used to measure them in serum?*

Octreotide:

An HPLC assay with MS/MS detection was developed to detect octreotide in human serum. The assay was validated serum samples in terms of recovery, linearity, accuracy, precision and sensitivity. Please refer to the Clinical Pharmacology review of the original submission in DARRTS for details on the analytical methods and summary of validation parameters, (Reference ID: 3914351, dated: 08 APR 2016).

GH:

GH was assayed by a sandwich type IDS-iSYS hGH immunoassay with detection by chemiluminescence. Growth hormone molecules were captured by a biotinylated monoclonal anti-GH antibody, which binds then to streptavidin-coated magnetic particles. After incubation and a washing step, an acridinium-labelled anti-GH antibody was added to give a directly proportional chemiluminescence signal, initiated by the triggers hydrogen peroxide and sodium hydroxide. Please refer to the Clinical Pharmacology review of the original submission in DARRTS for details on the analytical methods and summary of validation parameters, (Reference ID: 3914351, dated: 08 APR 2016).

IGF-1:

IGF-1 was assayed by a sandwich type IDS-iSYS IGF-1 immunoassay with detection by chemiluminescence. The free IGF-1 was captured by a biotinylated monoclonal anti-IGF-1 antibody, which binds then to streptavidin-coated magnetic particles. To generate a signal, an acridinium-labeled anti-IGF-1 antibody was added to give a directly proportional chemiluminescence signal, initiated by the triggers, hydrogen peroxide and sodium hydroxide. Please refer to the Clinical Pharmacology review of the original submission in DARRTS for details on the analytical methods and summary of validation parameters, (Reference ID: 3914351, dated: 08 APR 2016).

The bioanalytical assays used for Study ACM-303 to detect serum GH and IGF-1 levels were the same as that used in the original submission, and the validation parameters remain unchanged.

According to the Applicant, sample analyses were conducted at 2 sites using the validated assays for GH and IGF-1. Human serum samples collected from study sites in Australia, Europe, Israel and New Zealand were assayed at the (b) (4)

(b) (4). Samples collected from study sites in the United States were assayed at (b) (4)

Both laboratories used the same instrumentation and the same IDS iSYS kits (b) (4) Both laboratories used calibrators and quality control samples from the kit manufacturer, often using the same lots when possible.

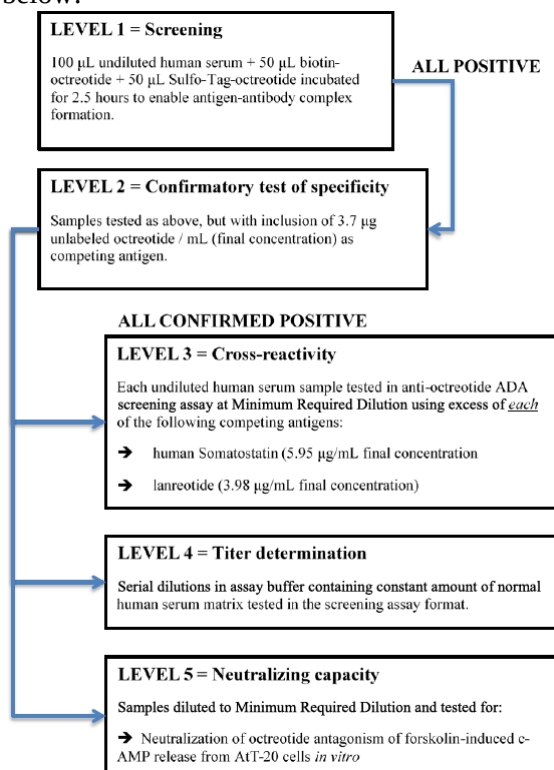
A laboratory cross-comparison study entitled, “Cross-Correlation plan for IGF-1 and hGH on the IDS ISys Between (b) (4) and (b) (4) was conducted. This laboratory cross-comparison was used to support two studies, OOC-ACM-303 and OOC-ACM-302. The method validation comparison was performed in two phases, the initial pre-phase prior to initiating of testing samples from the clinical trial and the monitoring phase to continue to demonstrate method comparison as samples from the ongoing study were being analyzed. For each analyte (IGF-1 and hGH), the (b) (4)

laboratory in (b) (4) was to collect a set of at least 40 samples (per analyte, if necessary) for the initial pre-phase and then at least 60 samples (per analyte, if necessary) for the monitoring phase per year. In first quarter 2017, a pre-study phase, consisted of 40 human serum samples prepared at the (b) (4) lab. The (b) (4) lab prepared the serum samples, split them into sub-aliquots and shipped one set of aliquots frozen to (b) (4). Both laboratories tested the sub-aliquots. The results of this phase met the acceptance criteria for both IGF-1 and GH with a Deming regression slope between 0.9-1.1 and a correlation coefficient >0.9 . Deming regression is a technique for fitting a straight line to two-dimensional data where there is measurement error in both variables, X and Y. This procedure is different from the simple linear regression where only the response variable, Y, is measured with error.

4.2 Immunogenicity

Immunogenicity testing for anti-octreotide antibodies were carried out in the Phase 3 study CH-ACM-01, that was part of the original NDA submission. Immunogenicity testing was not carried out in the SPA driven Phase 3 Study ACM-303.

The Applicant used a hierarchical test scheme to test for anti-octreotide antibodies in the Phase 3 clinical study CH-ACM-01 as shown below:



Lanreotide was included as an additional competing antigen for the cross-reactivity testing since patients may have had pre-existing antibodies induced by lanreotide.

The validation of the PK assay for octreotide included spiking of anti-octreotide positive control antibody (3.125, 12.5, and 50 µg/mL final concentration) into the human plasma test sample matrix and demonstrating that the quantitation of octreotide (0.075 to 18.8 ng/mL final concentration) was not affected by anti-octreotide antibody formation. Plasma octreotide concentrations are in the low ng/mL range, even at C_{max} , and any reduction of circulating drug levels with consequential reduction of efficacy might represent a potential risk factor associated with induction of anti-octreotide antibodies. However, in Study CH-ACM-01, drug levels were maintained during chronic treatment, combined with sustained GH and IGF-1 levels, which provided indirect evidence of an absence of induction of a clinically relevant anti-octreotide antibody response.

The double-antigen bridge assay method validated to detect anti-octreotide antibodies in human clinical samples collected during the Phase 3 study CH-ACM-01 of MYCAPSSA was based on the Meso-Scale Discovery (MSD) electrochemiluminescence (ECL) bridging format since it enabled detection of anti-drug antibodies (ADA) of different isotypes, including IgG, IgM, and IgA. Antibody positive samples were identified by comparing the sample ECL response (average value of duplicate values) with a plate-specific cut-point based on the mean ($n = 6$ replicates) negative control value for that plate adjusted by a pre-determined, assay cut-point normalization factor. An ECL value equal to or greater than the ECL cut-

point, identified the sample as a “presumptive positive,” while an ECL value less than the ECL cut-point identified the sample as negative. Following the initial antibody screen, any samples that were “presumptive positive” were then subjected to confirmatory testing by inhibition of the signal with a molar excess of unlabeled octreotide. If a sample demonstrated inhibition above the pre-validated level it was classified as a “confirmed positive” result, and a follow-up assay was then to be performed to estimate the titer (reciprocal of dilution) corresponding to the assay cut-point. Samples giving % inhibition values below the confirmatory cut-point were classified as “negative.”

The sensitivity of the assay was determined as 158.95 ng/mL based on 6 assay runs (3 assay runs by each of 2 analysts) performed during the method validation exercise. Conditions for testing cross-reactivity of anti-octreotide antibodies were validated using recombinant human somatostatin, synthetic lanreotide and synthetic leuprolide (as negative control). The clinical sample analysis included cross-reactivity testing for any confirmed positive samples detected in the anti-octreotide antibody assay. This was to enable comparison of % inhibition of the ECL signal for equimolar concentrations of octreotide, somatostatin, and lanreotide.

The assay developed to detect neutralizing capacity of anti-octreotide antibodies had very poor assay precision in the presence of 5% v/v human serum as well as lack of inhibition by a high concentration (50 µg/mL) of the anti-octreotide antibody and was deemed unsuitable for use with clinical samples. However, this may not be of clinical relevance as sample analysis showed that there were no detectable positive anti-octreotide antibodies in the Phase 3 clinical study CH-ACM-01. There does not appear to be any significant report in the literature on immunogenicity of octreotide. According to Kuriakose, et al¹, immunogenicity is associated with the route of administration of a therapeutic molecule and routes of administration that involve the skin or mucosa may carry the greatest potential for an immunological response. The authors noted that exposure via gut mucosa is generally tolerogenic, and that the probability of immune response is highest after subcutaneous injection, followed by intramuscular, intranasal, and intravenous routes. Subcutaneous administration generally localizes and prolongs the exposure of the protein to a small area within close proximity of lymph nodes, where B and T cells are present. Therefore, it was not surprising to find that there were no detectable positive anti-octreotide antibodies in the Phase 3 clinical study CH-ACM-01.

¹ Kuriakose A, Chirmule N, Nair P. Immunogenicity of Biotherapeutics: Causes and Association with Posttranslational Modifications. *J Immunol Res*. 2016;2016:1298473. doi:10.1155/2016/1298473

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	208232
Submission Date(s):	June 18, 2015
Brand Name	MYCAPSSA
Generic Name	Octreotide
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Chiasma, Inc
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Capsules: • 20 mg
Proposed Indication	Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)
Dosage & Administration	• MYCAPSSA should be taken with a glass of water on an empty stomach (ie, at least 1 hour before a meal or at least 2 hours after a meal). Drinking of water is allowed during these times. • Patients currently taking somatostatin analog therapy can be transitioned to MYCAPSSA with an initial dose of 20 mg BID given orally (20 mg morning + 20 mg evening). Blood levels of IGF-1 and clinical symptoms should be monitored. If IGF-1 is normal and clinical symptoms are controlled or response level (biochemical and symptomatic response) is maintained, continue MYCAPSSA dosage at 20 mg BID. • Dosage may be increased to 60 mg daily (40 mg morning + 20 mg evening) if IGF-1 levels increase, as determined by the physician. • Continue monitoring, applying the above algorithm for maintaining or increasing the dose up to 80 mg daily (40 mg morning + 40 mg evening).
Clinical Pharmacology Review Team	Suryanarayana Sista and Jayabharathi Vaidyanathan

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1 Executive Summary

Mycapssa (Octreotide) being developed by Chiasma, Inc. is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin.

Mycapssa, available as an oral capsule, is indicated for long-term maintenance (b) (4) in acromegaly patients (b) (4)

The proposed dosing regimen for Mycapssa is as follows:

MYCAPSSA should be taken with a glass of water on an empty stomach (i.e., at least 1 hour before a meal or at least 2 hours after a meal). Drinking of water is allowed during these times.

It is proposed that patients currently taking somatostatin analog therapy can be transitioned to MYCAPSSA with an initial dose of 20 mg BID given orally (20 mg morning + 20 mg evening). Blood levels of IGF-1 and clinical symptoms should be monitored. If IGF-1 is normal and clinical symptoms are controlled or response level (biochemical and symptomatic response) is maintained, it is proposed to continue MYCAPSSA dosage at 20 mg BID. The dosage may be increased to 60 mg daily (40 mg morning + 20 mg evening) if IGF-1 levels increase, as determined by the physician. It is proposed to continue to monitor, applying the above algorithm for maintaining or increasing the dose up to 80 mg daily (40 mg morning + 40 mg evening).

Currently marketed products for the indication of Acromegaly are the following list of drugs:

1. Octreotide
 - o i. Sandostatin injection (s.c. or i.m.)
 - o ii. Sandostatin LAR injection (i.m. only)
 - o iii. Octreotide acetate injection (multiple ANDAs)
2. Lanreotide
 - o i. Somatuline Depot (s.c.)
3. Pasireotide
 - o i. Signifor LAR (i.m. only)
4. Cabergoline
 - o i. multiple ANDAs
5. Bromocriptine
 - o i. Parlodel (oral)
6. Pegvisomant
 - o i. Somavert (s.c.)

This submission is a 505 (b)(2) NDA application referencing Sandostatin sub-cutaneous injection. If approved, Mycapssa will be the first oral octreotide formulation to enter the market.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 08/14/2015 under NDA 208232 and recommends a complete response with the following comments.

- (a) Single oral dose of Mycapssa 20 mg is not bioequivalent to single dose of Sandostatin 0.1 mg administered subcutaneously. The relative systemic exposure, based on the least squares means for AUC_{0-t} of octreotide from the 20 mg fasted dose of Mycapssa relative to the 0.1 mg s.c. dose

of octreotide was 97% with very wide confidence intervals of 73% – 128% for AUC_{0-t} . Similarly C_{max} with a point estimate of 0.64 and 90% confidence intervals of 45.29% - 89.78% failed to meet the bioequivalence criteria. The sample size used in the comparative study was small for a drug that exhibits large intra-subject variability. A comparative pharmacokinetic (PK) study evaluating the proposed BID dosing regimen of Mycapssa and the TID dosing of Sandostatin was not conducted.

- (b) There was no characterization of Mycapssa dose-response or pharmacodynamic (PD) comparability (growth hormone and IGF-1) between Mycapssa and Sandostatin. Information regarding the PK/PD comparability with Sandostatin will be beneficial towards interpretation of the Phase 3 results.
- (c) Data supporting other aspects of clinical pharmacology (e.g., studies in renal/hepatic impairment, and food effect) of oral octreotide are acceptable. Data from the drug interaction studies are acceptable though some of the drug interaction studies that used the “cocktail” approach are deficient in design (limited PK sampling time of only 0-5 h).
- (d) The applicant should conduct a dedicated steady-state PK/PD study in acromegaly patients and evaluate PD (GH and IGF-1) comparability between b.i.d. Mycapssa and t.i.d. Sandostatin.

A Required Inter-Divisional Level Briefing was held on April 06, 2016 to discuss the review team’s recommendations. Attendees included Drs. Chandrahas Sahajwalla, Shiew-Mei Huang, Mehul Mehta, John Lazor, Suresh Doddapaneni, Hae Young Ahn, Raj Madabushi and Lei Zhang from OCP, Drs. Jean-Marc Guettier, Marina Zemskova and Smita Abraham from Office of New Drugs and Jennifer Johnson from OND.

1.2 Phase IV Commitments

N/A

1.3 Summary of Important Clinical Pharmacology Findings

The drug product Mycapssa capsules is a white, size “0” hard gelatin capsule, (b) (4) enteric-coated and imprinted in black with “OT” on one half of the capsule and “20” on the other half. Each capsule contains (b) (4) octreotide acetate corresponding to 20 mg of the free peptide octreotide.

Key pharmacokinetic and pharmacodynamic properties of Mycapssa are summarized in [Table 1](#).

Table 1 Highlights of Pharmacokinetics

Pharmacokinetics	
Absorption	- Linear pharmacokinetics in the dose range studied (3 mg – 20 mg in healthy volunteers, 40 mg – 80 mg in acromegaly patients) - Median T_{max} - 1.67 – 2.5 hours - Relative bioavailability following single-dose (oral compared to s.c.) : 0.5% C_{max}: - Healthy volunteers (20 mg dose): 0.4 ng under fed conditions; 3.6 ng/mL under fasting conditions - Acromegaly patients (40 mg – 80 mg): 2.51 ng/mL after 40 mg, 3.83 ng/mL after 60 mg, and 5.30 ng/mL after 80 mg AUC_{last}: - Healthy Volunteers: 1.3 ng·hr/mL under fed conditions; 15.2 ng·hr/mL under fasting conditions

	○ Acromegaly patients (40 mg – 80 mg): 8.41 ng·hr/mL after 40 mg, 14.7 ng·hr/mL after 60 mg, and 19.6 ng·hr/mL after 80 mg • Food leads to an approximately 90% decrease in extent of absorption • Bioavailability decreased 60% when Mycapssa was administered 1 hour before a reduced-size high-fat meal
Distribution	• Volume of distribution (V_{dss}) ~ 13.6 L in healthy volunteers and estimated to be 21.6 ± 8.5 L in Acromegaly patients • In healthy subjects, 65% bound in the plasma mainly to lipoprotein and, to a lesser extent, to albumin. Mean percentage of drug bound in Acromegaly patients is 41.2%.
Metabolism and Elimination	• Total body clearance: 7 L/h - 10 L/h in healthy subjects, and about 18 L/h in Acromegaly patients. • $t_{1/2}$ ~ 2-4 h in healthy subjects, and ~3.2 – 4.5 hours at steady state in Acromegaly patients
Pharmacodynamics	
Acromegaly Patients	• Serum GH concentrations were reasonably constant over the 2.5 to 4 hour period after dosing in all 3 dosing cohorts (40-mg, 60-mg and 80-mg). Response was defined as IGF-1 < 1.3 times ULN adjusted for age and an integrated GH level over 2 hours < 2.5 ng/mL. There does not seem to be a relationship between octreotide AUC_{2-4hr} and GH Cave or normalized IGF-1 levels

1.3.1 Dose/exposure-response relationship for efficacy

The pharmacodynamic (PD) profile following administration of Mycapssa throughout the dosing interval was not characterized. The sponsor measured growth hormone (GH) levels in patients for a period of 2-4 h post-dose. This limited GH response obtained had no clear relationship with octreotide AUC₂₋₄ at all three dose levels 40 mg (20 mg bid), 60 mg (40 mg AM, 20 mg PM) or 80 mg (40 mg bid) evaluated in the study ([Figure 1a](#)).

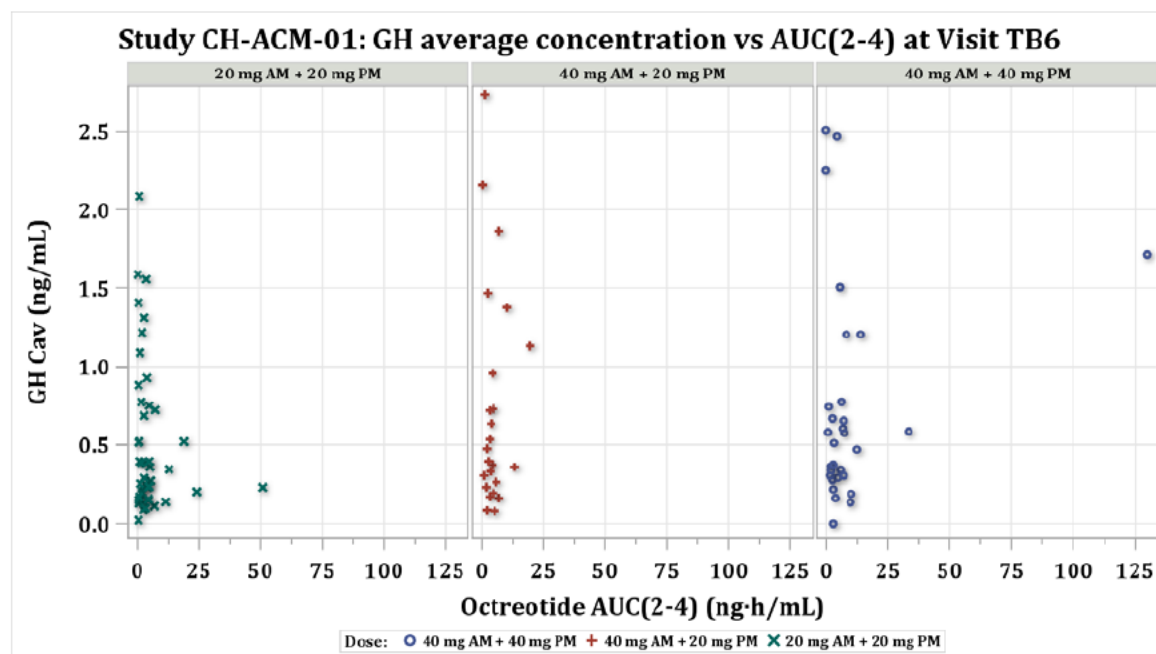


Figure 1a Exposure-response relationships for octreotide

In NDA 019667, the innovator, Novartis (Sandoz) had shown the 24-hour growth hormone profile following a single 100 µg intravenous or subcutaneous injection ([Figure 1b](#)). The GH levels stay reduced for approximately 8 hours post-injection and then start coming back to baseline, an observation that led to the t.i.d regimen decision for Sandostatin. Such information for dosing interval decision based on growth

hormone profiles is lacking from the current application and it is difficult to estimate the duration of action of a Mycapssa 20 mg dose.

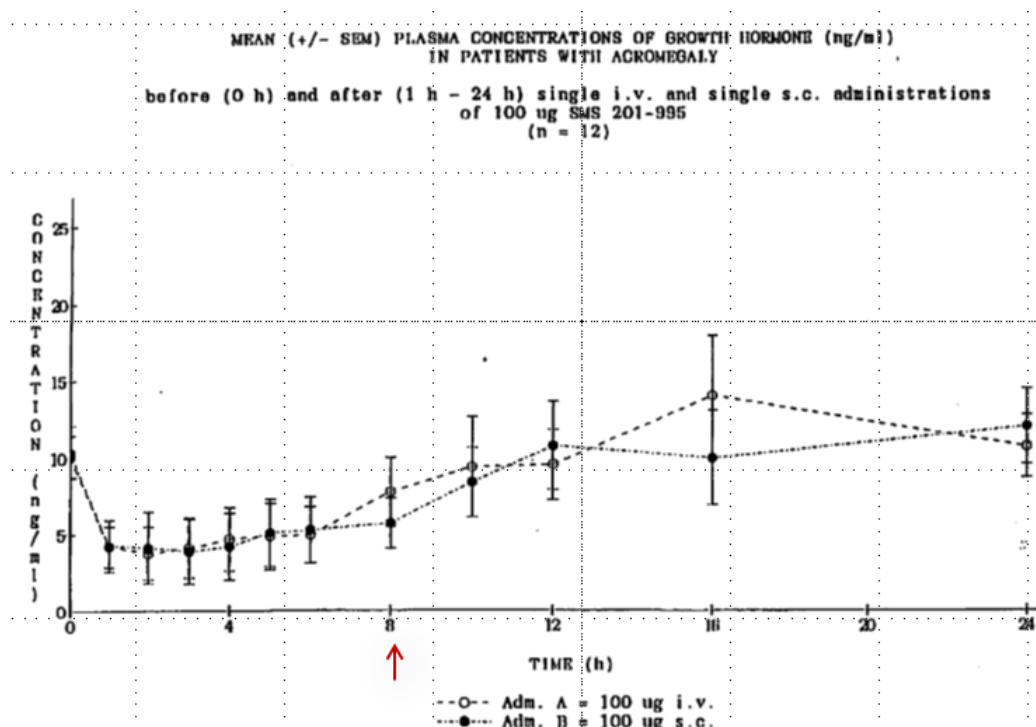


Figure 1b Plasma Growth Hormone concentrations following a single Sandostatin 100 µg dose administered either intravenously or subcutaneously

(Source: NDA 019667 for Sandostatin)

1.3.2 Intrinsic Factors

- **Age, Race, Body Weight and Gender:** A formal population PK of Mycapssa was not performed. However, based on analysis of pooled data for the 20 mg Mycapssa oral administration and 0.1 mg Sandostatin administration in healthy volunteers, and a separate analysis of acromegaly patients from the PK sub-study of the Phase 3 trial, no dose adjustments are necessary based on age, race, body weight or gender.

1.3.3 Drug-Drug Interactions:

The effect of other drugs on Mycapssa and the effect of Mycapssa on other drugs, as well as the findings are listed in [Table 2](#) below:

Table 2 Effect of Co-administered Drugs on Mycapssa Exposure, and Effect of Mycapssa on the Exposure of Co-Administered Drugs

Co-administered Drug	Dosing of Co-administered Drug	Dosing of Mycapssa	Effect on PK		Recommendation
			AUC	C _{max}	
Effect of Other Drugs on Mycapssa					
Esomeprazole	40 mg	20 mg	↓41%	↓45%	Monitor patient's IGF-1 and adjust dose as necessary
Loperamide	4 mg	40 mg	↓5%	↓9%	No dosage adjustment of Mycapssa is needed when co-administering with Loperamide
Metoclopramide	20 mg	40 mg	↓13%	↓5%	No dosage adjustment of Mycapssa is needed when co-administering with Metoclopramide
Effect of Mycapssa on Other Drugs					
Lisinopril	20 mg	40 mg	↑40%	↑50%	Dose of Lisinopril may need to be adjusted when administered concomitantly with Mycapssa
Digoxin	0.5 mg	40 mg	↔	↓37%	Digoxin is a narrow therapeutic index drug and is monitored in patients. As concomitant administration of Mycapssa with digoxin may result in decreased blood levels of digoxin, patients taking these drugs concomitantly should be monitored appropriately.
Warfarin	7.5 mg	40 mg	↔	↔	Overall, no dosage adjustment for warfarin is recommended when co-administering with Mycapssa
Hydrochlorothiazide	100 mg	40 mg	↓18%	↓9%	No dosage adjustment for hydrochlorothiazide is recommended when co-administering with Mycapssa
Metformin	850 mg	40 mg	↓5%	↑11%	No dosage adjustment for metformin is recommended when co-administering with Mycapssa
Ethinyl Estradiol/Levonorgestrel	EE: 0.06 mg LN: 0.30 mg	40 mg	EE: ↔	EE: ↔	Patients using oral contraceptives containing levonorgestrel should be advised to use an alternative contraceptive method
			LN: ↓24%	LN: ↓38%	
Cyclosporine	300 mg	40 mg	↓62%	↓71%	Coadministration of cyclosporine with Mycapssa should be avoided

1.3.4 Volume of Water Administered, Meal Size and Posture:

- **Volume of Water Administered:**

The bioavailability of octreotide is reduced by 12% when administered with 75 mL of water instead of 240 mL (8 oz.) of water.

- **Meal Size and Posture:**

Compared to administration in the semi-sitting position, administration of oral octreotide acetate in the morning in a standing position resulted in a decrease in the mean plasma concentrations. When Mycapssa is administered 1 hour before a high-fat meal, 30 minutes before a reduced size of a high-fat meal, 1 hour after a high-fat meal or 2 hours after a high-fat meal, the bioavailability is decreased by more than 80%. When Mycapssa is administered 1 hour before a reduced size high-fat meal, bioavailability is decreased by more than 40%.

1.3.4.1 Specific Population

1.3.4.1.1 Hepatic Impairment

Mycapssa, administered as a single-dose administration (10 mg or 20 mg) in 18 subjects with cirrhosis and portal hypertension was associated with a decrease of at least 10% in hepatic venous pressure gradient (HVPG) or reduction to below 12 mmHg in 61% of subjects. A dose-related but greater than dose-proportional increase was observed in the mean plasma octreotide concentrations after administration of 10 mg and 20 mg MYCAPSSA. Pharmacokinetics of Mycapssa in subjects with cirrhosis appeared to be similar to the PK in healthy subjects administered the same dose. No dose adjustment is recommended in patients with Child Pugh A and B classification. Mycapssa dose may be titrated upward based on clinical response. However, careful monitoring of patients with Child Pugh C liver cirrhosis is recommended while initiating treatment with Mycapssa.

1.3.4.1.2 Renal Impairment

The pharmacokinetics of oral octreotide was not evaluated in patients with mild or moderate renal impairment. In patients with severe renal impairment, total exposure (AUC) was increased by 14%, and peak exposure (C_{max}) was decreased by 14%, T_{max} increased 2-folds, with a corresponding 13% decrease in apparent clearance. This was not substantially different from that of the matched controls. Subjects with end stage renal disease (ESRD) on dialysis had a 46% decrease in clearance with a corresponding 87% increase in AUC and 85% increase in $t_{1/2}$ compared to matched healthy subjects. Subjects with ESRD on dialysis had higher mean plasma concentrations than did those with severe renal impairment (eGFR 15 – 29 mL/min/1.73 m²) with higher mean values for C_{max} , AUC_{0-t}, AUC_{inf}, and $t_{1/2}$, consistent with an effect of renal impairment on octreotide clearance.

The sponsor recommends that there is no need to adjust the starting dose of Mycapssa in patients with mild, moderate, or severe renal impairment. The maintenance dose should be adjusted thereafter based on clinical response and tolerability. *Due to the almost 2-folds increase in exposure in ESRD patients, they should be started on a lower starting dose (recommended 20 mg QD). The maintenance dose should be adjusted thereafter based on clinical response and tolerability.*

1.3.4.1.3 Geriatric Population

The responder rate of 77% in the subgroup of age greater than 65 years was similar to the responder rate of 62% in the age subgroup 65 years or less. Additionally, the safety profile of Mycapssa in elderly patients was consistent with that of the general study population, and no new safety signals were observed. . No dose adjustment is recommended in geriatric patients.

1.3.4.1.4 Pediatric Population

The safety and effectiveness of Mycapssa has not been established in pediatric patients.

2 Question-Based Review (QBR)

2.1 General Attributes

- Mycapssa (octreotide) capsule is an oral somatostatin analog indicated for long-term maintenance treatment in acromegaly patients (b) (4)

(b) (4)

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

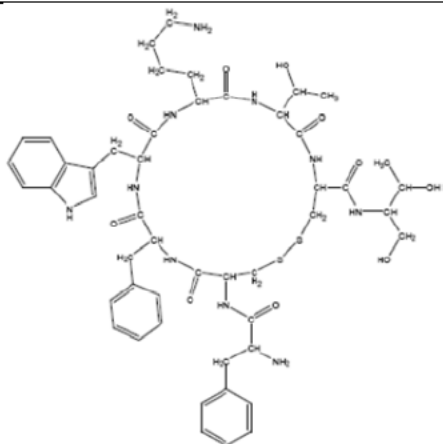
Date	Action
March 2, 2010	Sponsor submitted a Pre-IND request, which was denied
June 17, 2010	Orphan drug designation was granted for the treatment of acromegaly by the Office of Orphan Products Development
August 30, 2010	Written responses to Pre-IND request were issued
November 9, 2010	Sponsor opened its IND 108163
December 9, 2010	IND was placed on partial clinical hold due to inadequate nonclinical data to support multiple-dose studies
March 4, 2011	Sponsor submitted a complete response to clinical hold
March 30, 2011	Clinical hold removed
August 9, 2011	An End-of-Phase 2 (EOP2) meeting was held
September 8, 2011	EOP2 minutes issued
September 15, 2011	Sponsor submitted an amendment which contained toxicology information from a 3-month oral capsule dose toxicology study in cynomolgus monkeys, an excipient assessment report evaluating the excipients sodium caprylate and glyceryl tricaprylate, and responses to nonclinical comments from the EOP2 meeting minutes.
November 3, 2011	Response advice letter to amendment was issued
December 31, 2012	Sponsor submitted a request for proprietary name review of its proposed trade name "Octreolin"
March 25, 2013	Sponsor submitted a withdrawal request for proprietary name review
March 28, 2013	Sponsor submitted an amendment containing a toxicity report for Study 1300-009 entitled, "Octreolin: A 9-Month Oral Capsule Dose Toxicity Study in Cynomolgus Monkeys," as well as a request for a waiver of carcinogenicity studies.
May 30, 2013	Letter of agreement with this waiver request was issued
April 26, 2013	An amendment for a new protocol for Study CHI-007, entitled, "A Phase I, Open-label Study to Evaluate the Safety and Pharmacokinetics of 40 mg Oral Octreotide Acetate in Subjects with End-stage Renal Disease (ESRD) and Subjects with Severe Renal Impairment, Compared to Matched Normal Health Subjects" was submitted
June 28, 2013	Response advice letter for protocol amendment was issued
September 20, 2013	Sponsor submitted a guidance meeting request to discuss product development issues with Agency CMC personnel
October 7, 2013	A Written Responses-Only (WRO) meeting granted letter was issued
November 22, 2013	WRO letter was issued
October 18, 2013	Sponsor submitted an amendment on October 18, 2013, which contained a statistical analysis plan, a PK/PD analysis plan and an updated Phase 3 protocol for Study CH-ACM-01 entitled, "Phase 3 Efficacy and Safety of Oral Octreotide Acetate in Patients with Acromegaly Who Are Currently Receiving Parental

Date	Action
	Somatostatin Analogs”
January 31, 2014	Sponsor submitted a follow-up amendment seeking feedback regarding alcohol-induced dose dumping
February 20, 2014	Response advice letter was issued for study CH-ACM-01
March 10, 2014	Response advice letter was issued for alcohol-induced dose dumping
March 11, 2014	IND application was transferred from Chiasma, Inc. to Genentech
March 12, 2014	New sponsor (Genentech) requested a Pre-NDA meeting
April 3, 2014	Meeting granted letter issued
April 11, 2014	Background materials submitted by the sponsor
May 19, 2014	Preliminary comments were sent to the sponsor by electronic mail
May 20, 2014	Sponsor sent clarification responses to relevant FDA requests included in the preliminary comments
May 21, 2014	Pre-NDA meeting held
June 20, 2014	Pre-NDA meeting minutes issued
August 8, 2014	IND application was transferred from Genentech back to Chiasma, Inc., the original application holder
October 3, 2014	Chiasma, Inc. requested another Pre-NDA meeting to discuss their plans for submission of an NDA via the 505(b)(2) regulatory pathway for the treatment of acromegaly and to gain clarity on outstanding issues from previous interactions with FDA since complete results from Phase 3 Study CH-ACM-01 were available
October 27, 2014	Meeting granted letter issued after the Division re-classified this meeting as a type C guidance meeting to be conducted via teleconference
November 6, 2014	Sponsor submitted a meeting background package
December 4, 2014	FDA sent preliminary comments on the background package to the sponsor via electronic mail
December 8, 2014	Type C guidance meeting held
January 8, 2015	Official meeting minutes of Type C meeting issued
January 20, 2015	Sponsor issued corrections (key grammatical errors) to FDA’s meeting minutes
February 13, 2015	Sponsor submitted a request for proprietary name review of its proposed trade name Mycapssa
March 10, 2015	Agency acknowledgement of grammatical errors in the January 8, 2015 meeting minutes
June 12, 2015	NDA 208232 submitted for oral octreotide
July 30, 2015	Agency notified sponsor that proposed proprietary name, Mycapssa is conditionally acceptable
August 28, 2015	Sponsor was notified that NDA application is sufficiently complete to permit a substantive review

2.1.2 What are the highlights of the Mycapssa drug product as they relate to clinical pharmacology review?

The physical and chemical properties of octreotide are summarized in [Table 3](#) below.

Table 3 Physicochemical Properties of Octreotide

	Octreotide
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 Acetate salt
Chemical Abstracts Service (CAS) Registry Number (RN)	79517-01-4
Physical Description	White to off-white powder
Molecular Formula	C ₄₉ H ₆₆ N ₁₀ O ₁₀ S ₂
Molecular Weight	1019.3 g/mol
Structural Formula	
Solubility	Octreotide acetate is soluble in water, freely soluble in methanol, and very slightly soluble in acetonitrile and dichloromethane
Hygroscopicity	Octreotide acetate is a hygroscopic material
Specific Optical Rotation	($[\alpha]_D^{20}$), 2 mg/mL in 1% v/v glacial acetic acid in water. Calculated with reference to the anhydrous, acetic acid free substance, the results are between -14.5° and -18.5°

2.1.3 What is the composition of to-be-marketed formulation of Octreotide?

The sponsor provided description of octreotide drug product is shown in the highlighted box below:

The drug product octreotide capsules is a white, size 0 hard gelatin capsule, (b) (4) enteric coated and imprinted in black with “OT” on one half of the capsule and “20” on the other half. Each capsule contains (b) (4) (b) (4) octreotide acetate corresponding to 20 mg of the free peptide octreotide.

According to the sponsor, the technology they used in formulating Mycapssa capsule is a proprietary mixture of excipients, collectively called Transient Permeability Enhancer (TPE®), which enhances the intestinal absorption of drug molecules with limited permeability and low oral bioavailability. Mycapssa was formulated as a single-strength enteric-coated (b) (4) hard gelatin capsule containing 20 mg of octreotide (calculated as free base) for oral administration. The formulation composition is shown in [Table 4](#)

Table 4 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)	(b) (4)
Sodium caprylate	NF/Ph. Eur.			
Polysorbate 80	NF/Ph. Eur.			
Glycerol monocaprylate (b) (4)	Ph. Eur.			
Glycerol tricaprylate (GTC)	Manufacturer's			
Magnesium chloride	USP/Ph. Eur.			
			(b) (4)	
Capsule Fill Weight				
Capsule Shell (Body & Cap) ^e				
Hard gelatin capsule, size 0 (b) (4)	Manufacturer's	Capsule shell		(b) (4)
Gelatin (b) (4)	NF/Ph. Eur.		(b) (4)	
	NF/Ph. Eur.			
Acryl-EZE ^g	Manufacturer's		(b) (4)	
Print Ink				
Opacode ^h (b) (4) ink	Manufacturer's		(b) (4)	
Theoretical Finished Unit Weight				
				(b) (4)

(Source: Mycapssa NDA eCTD module 3.2.P.1; Description and Composition of the Drug Product [32p1] Table 1, page 2)

2.1.4 What are the proposed mechanism of action and therapeutic indications?

The mechanism of action of octreotide as described in the product label for Sandostatin is as follows:

“Octreotide exerts pharmacologic actions similar to the natural hormone somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.”

Further supplementation of this information from the sponsor with information from published literature is shown in the highlighted box below:

Acromegaly is caused by pituitary hyper secretion of Growth Hormone (GH). At the liver, GH stimulates secretion of Insulin-like Growth Factor 1 (IGF-1), which mediates many of the peripheral somatic effects of GH¹. The primary objective of medical treatment of acromegaly is to reduce mortality and ameliorate symptoms by normalizing IGF-1 and GH levels. The effect of somatostatin analogues, eg, octreotide, is mediated through a direct receptor-mediated inhibition of GH secretion. Subsequently, the reduced systemic GH levels, over time translate into a decline of circulating IGF-1 levels.

2.1.5 What are the proposed dosages and routes of administration?

Mycapssa will be available as an oral capsule. The following dosing recommendations are proposed by the sponsor:

- Mycapssa should be taken with a glass of water on an empty stomach (i.e., at least 1 hour before a meal or at least 2 hours after a meal). Drinking of water is allowed during these times.
- Patients currently taking somatostatin analog therapy can be transitioned to Mycapssa with an initial dose of 20 mg BID given orally (20 mg morning + 20 mg evening). Blood levels of IGF-1 and clinical symptoms should be monitored. If IGF-1 is normal and clinical symptoms are controlled or response level (biochemical and symptomatic response) is maintained, continue Mycapssa dosage at 20 mg BID.
- Dosage may be increased to 60 mg daily (40 mg morning + 20 mg evening) if IGF-1 levels increase, as determined by the physician.
- Continue monitoring, applying the above algorithm for maintaining or increasing the dose up to 80 mg daily (40 mg morning + 40 mg evening).

2.1.6 Was any OSIS (Office of Study Integrity and Surveillance) inspection requested for any of the clinical studies?

Though the batch sizes of clinical trial material used in the clinical studies were small (approximately (b) (4) capsules) compared to a typical NDA application, this product has an orphan indication which waives the general SUPAC requirement of at least (b) (4) units or (b) (4) % of commercial batch size. An OSIS inspection was not requested.

¹ Katznelson L. Diagnosis and treatment of acromegaly. *Growth Horm IGF Res* 2005; 15 Suppl A:S31-S35.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies and the clinical studies used to support dosing or claims?

The clinical pharmacology program included 12 completed clinical studies providing information on the safety, tolerability, pharmacokinetic, and pharmacodynamic properties of octreotide. All of the 12 studies contributed towards the pharmacokinetics of oral octreotide. Two (2) studies contributed towards pharmacodynamic information, 5 studies contributed towards information on drug-drug interaction.

A list of all completed clinical pharmacology studies is provided in [Table 5](#)

Table 5 Overview of studies with pharmacokinetic and pharmacodynamic assessments relevant to the clinical pharmacology of Mycapssa

Study Identifier/ (eCTD Module)	Study Design	Study Objective(s)	Number of Subjects/ Treatment
Bioavailability and Food-Effect			
CHI-001 (5.3.1.2)	Stage 1: Single-dose, randomized, 2-way, 2-period, 2-sequence crossover Stage 2: Single-dose, open-label, 2-period, dose escalation	To assess the safety and tolerability of a single dose of oral octreotide acetate in healthy male subjects at 3 escalating doses, to evaluate the PK profile of octreotide after each single oral dose of oral octreotide acetate, and to compare the safety and octreotide PK profiles of oral octreotide acetate with a single s.c. injection of octreotide (Sandostatin $\square$ IR)	12 Male Healthy Volunteers Stage 1: Octreotide acetate 3 mg (single oral dose of 1 $\times$ 3 mg capsule) Octreotide acetate for injection (Sandostatin, Novartis) (single s.c. dose of 0.1 mg) Stage 2: Octreotide acetate 10 mg (single oral dose of 1 $\times$ 10 mg capsule) Octreotide acetate 20 mg (single oral dose of 2 $\times$ 10 mg capsule)
CHI-002 (5.3.1.1)	Stage 1: Single-dose, open-label, randomized, 2-way, 2-period, 2-sequence crossover Stage 2: Single-dose, open-label	Primary: To assess the effect of high-fat meal on the BA of octreotide from octreotide acetate oral 20 mg capsules following a single dose administration; to compare the PK profiles of octreotide from the octreotide acetate single oral dose with a reference single s.c. injection of 0.1 mg octreotide (Sandostatin® IR) Secondary: To assess the safety of the study drugs.	24 Healthy Volunteers (13 Male, 11 Female) Octreotide acetate (20 mg, oral capsule, qd) under fasted conditions Octreotide acetate (20 mg, oral capsule, qd) with a standardized high-fat, high-calorie meal Octreotide acetate (Sandostatin; 0.1 mg s.c. injection, qd)
OCT-01 (5.3.1.1)	Single-blind, partially-randomized, 3-way crossover, 4-period	Primary: To estimate the effect of (a) a light meal (ie, snack) post-dose and (b) full standardized meal pre- and post-dose on the absorption of octreotide from oral octreotide acetate compared to a control fasting condition Secondary: To assess the safety of oral octreotide acetate during the study period	24 Healthy Volunteers A: Octreotide acetate oral capsule 20 mg, 1 hour prior to full test meal B: Octreotide acetate oral capsule 20 mg, 1 hour after full test meal C: Octreotide acetate oral capsule 20 mg, 30 minutes prior to light test meal D: Octreotide acetate oral capsule 20 mg, after a 10-hour fast
PK/PD			
CHI-004 (5.3.4.1)	Open-label, partially randomized, 4-period, 2-sequence crossover	Primary: To assess the duration of oral octreotide acetate-induced intestinal permeability after a single dose of oral octreotide acetate 20 mg using the L/M assay. Secondary: To evaluate the PK profile of octreotide after a single dose of oral octreotide acetate 20 mg; to assess the safety and tolerability of oral octreotide acetate 20 mg in healthy subjects. Exploratory: To evaluate the effect of oral octreotide acetate 20 mg on plasma GH levels; to evaluate the effect of oral octreotide acetate 20 mg on GH plasma levels after induction by GHRH using the GHRH-Arginine test.	Healthy Volunteers (11 Male, 13 Female) Safety analysis: 24; PK: 19; PK/PD: 16; Intestinal permeability analysis: Treatment A, 20; Treatment B, 23; Treatment C, 19; Treatment D, 15 Octreotide acetate (20 mg, oral capsule, qd) plus L/M test at 2 hours post-dose Octreotide acetate (20 mg, oral capsule, qd) plus L/M test at 5.5 hours post-dose Octreotide acetate (20 mg, oral capsule, qd) plus L/M test at 10 hours post-dose L/M test and GHRH/Arginine test
Drug-Drug Interaction			
CHI-005	Open-label, non-	Primary: To evaluate the influence of	14 Healthy Volunteers

Study Identifier/ (eCTD Module)	Study Design	Study Objective(s)	Number of Subjects/ Treatment
(5.3.2.2)	randomized, 2-period	concomitant PPI administration on the PK and BA of octreotide after administration of oral octreotide acetate in healthy male and female subjects; Secondary: To assess the safety of concomitant administration of oral octreotide acetate and PPI.	Day 0: Octreotide acetate (20 mg, oral capsule, qd) under fasted conditions Days 2–6: Nexium® (esomeprazole) 40 mg delayed-release tablet at least 1 hour before a meal Day 7: One octreotide acetate (20 mg, oral capsule) and 1 Nexium 40 mg tablet under fasted conditions
CHI-006 (5.3.2.2)	Single-blind, randomized, placebo controlled, 2-way (males) or 4-way crossover (females)	Primary: To evaluate the influence of oral octreotide acetate 40 mg on the absorption, PK, and BA of concomitantly administered oral probe drugs, warfarin, HCTZ, metformin, and estradiol (from levonorgestrel/ethinyl estradiol) in healthy subjects. Secondary: To assess the safety of a single dose of oral octreotide acetate 40 mg when administered concurrently with warfarin, HCTZ, metformin and estradiol	20 Healthy Volunteers (6 Male, 14 Female) A: 19; B: 19, C: 14, D: 14 A: Oral octreotide acetate 40 mg(2 x 20 mg) +warfarin 7.5 mg, HCTZ 25 mg (4 tablets), and metformin 850 mg B: Placebo +warfarin 7.5 mg, HCTZ 25 mg (4 tablets), and metformin 850 mg C (females only): Placebo + levonorgestrel/ethinyl estradiol 0.150 mg/0.030 mg (2 tablets for total dose of ethinyl estradiol of 0.06 mg) D (females only): Oral octreotide acetate 40 mg (2 x 20 mg) + levonorgestrel/ethinyl estradiol 0.150 mg/0.030 mg (2 tablets for total dose of ethinyl estradiol of 0.06 mg)
OCT-02 (5.3.3.4)	Single-blind, randomized, placebo-controlled, 4-period, 2-sequence crossover	Primary: To evaluate the influence of oral octreotide acetate on the PK profile and BA of concomitantly administered oral drugs (lisinopril and digoxin) in healthy subjects. To investigate if the volume of ingested water, administered concomitantly with oral octreotide acetate, affects the BA of octreotide from oral octreotide acetate. To obtain the PK profile of oral octreotide acetate 40 mg under fasting conditions. Secondary: To assess the safety of a single dose of oral octreotide acetate 40 mg. To assess the safety of a single dose of oral octreotide acetate when given with selected drugs.	18 Healthy Volunteers A: Octreotide acetate oral capsule 40 mg (2 x 20 mg) +240 mL water B: Octreotide acetate oral capsule 40 mg (2 x 20 mg) +75mL water C: Octreotide acetate oral capsule 40 mg (2 x 20 mg) +240 mL water + digoxin 0.5 mg+ lisinopril 20 mg D: Placebo +240 mL water + digoxin 0.5 mg+ lisinopril 20 mg
OCT-03 (5.3.3.4)	Open-label, randomized, 5-period, 3-sequence crossover	Primary: To evaluate the effects of concomitantly administered metoclopramide on the absorption, PK, and BA of octreotide from oral octreotide acetate. To evaluate the effects of concomitantly administered loperamide on the absorption, PK, and BA of octreotide from oral octreotide acetate. To evaluate the effects of body posture (sitting or standing) on the absorption, PK, and BA of octreotide from oral octreotide acetate. To evaluate the absorption of octreotide from oral octreotide acetate when administered at night, prior to going to bed. Secondary: To assess the safety of a single dose of oral octreotide acetate when given with metoclopramide or loperamide	18 Healthy Volunteers A: Octreotide acetate oral capsules 40 mg (2 x 20 mg) in the morning, sitting B: Octreotide acetate oral capsules 40 mg (2 x 20 mg) in the morning, standing C: Metoclopramide tablets 20 mg oral (2 x 10 mg) 2 hours prior to octreotide acetate oral capsules 40 mg (2 x 20 mg) in the morning, sitting D: Loperamide capsules 4 mg oral (2 x 2 mg) 2 hours prior to octreotide acetate oral capsules 40 mg (2 x 20 mg) in the morning, sitting E: Octreotide acetate oral capsules 40 mg (2 x 20 mg) at night prior to going to bed, sitting followed by lying down
OCT-04 (5.3.3.4)	Single-blind, randomized, placebo controlled, 2-period, 2-sequence crossover	Primary: To evaluate the influence of oral octreotide acetate 40 mg on the absorption, PK, and BA of cyclosporine in healthy subjects. Secondary: To assess the safety of a single dose of oral octreotide acetate 40 mg when administered concurrently with cyclosporine	18 Healthy Volunteers A: Oral octreotide acetate 40 mg (2 x 20 mg) + cyclosporine, 300 mg B: Placebo + cyclosporine, 300 mg (3 x 100 mg)
Special Population Studies			
Renal Impairment			
CHI-007 (5.3.3.3)	Open-label, parallel-design study	To evaluate the PK of a single dose of 40 mg oral octreotide acetate in both severe renal	4 severely renally impaired, (Stage 4); 4 ESRD (Stage 5); 4 Healthy

Study Identifier/ (eCTD Module)	Study Design	Study Objective(s)	Number of Subjects/ Treatment
		impairment (defined as eGFR between 15 and 29 mL/min/1.73 m ²) and of ESRD on dialysis (Stage 5, dosed with study medication on their off dialysis day), in comparison to the PK profile of matched (gender, age, weight) control subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m ²). To assess the safety and tolerability profile of a single dose of 40 mg oral octreotide acetate in severely renally impaired subjects, subjects with ESRD on dialysis, and normal healthy subjects.	40 mg (2 × 20 mg) oral octreotide acetate enteric-coated capsules
Hepatic Impairment			
CH-PHT-01 (5.3.3.3)	Open-label, 2-period, dose-finding study	To evaluate the PK profile of oral octreotide acetate in subjects with cirrhosis and portal hypertension after single administration. To assess the safety and tolerability of oral octreotide acetate in subjects with cirrhosis and portal hypertension. To evaluate the effect of oral octreotide acetate on the HVPG in subjects with cirrhosis and portal hypertension.	18 Subjects with stable liver cirrhosis referred for the measurement of HVPG (6 in Group 1 and 12 in Group 2) Group 1: Oral octreotide acetate 10 mg (1 × 10 mg) Group 2: Oral octreotide acetate 20 mg (2 × 10 mg, 3 subjects; 1 × 20 mg, 9 subjects)
Phase 3 Efficacy and Safety			
CH-ACM-01 (5.3.5.1)	Open-label, maintenance of response, baseline-controlled, withdrawal study	Primary: To determine the effect of oral octreotide acetate therapy on IGF-1 levels and GH levels, as measures of response. Secondary: To assess the safety and tolerability of oral octreotide acetate in subjects with acromegaly. To compare the effect of oral octreotide acetate therapy on IGF-1 levels and GH levels with that of parenteral therapy with somatostatin analogs. Exploratory: To assess treatment satisfaction with parenteral vs. oral somatostatin analog therapy. To assess the rate of patients who needed to return to parenteral therapy. To determine the PK profile of oral octreotide acetate during chronic treatment.	155 Adult Acromegaly Patients Individual dose titration based on IGF-level from 40 mg/day to 80 mg/day, as follows: • Oral octreotide acetate, 40 mg/day (20 mg bid) • Oral octreotide acetate, 60 mg/day (40 mg in morning and 20 mg in the evening) • Oral octreotide acetate, 80 mg/day (40 mg bid)

BA = bioavailability; bid = twice-daily dosing; DDI = drug-drug interaction; ESRD = end stage renal disease; eGFR = estimated glomerular filtration rate; GH = growth hormone; GHRH = growth hormone releasing hormone; HCTZ = hydrochlorothiazide; HVPG = hepatic venous pressure gradient; IGF-1 = insulin-like growth factor 1; NSBB = non-selective β-blockers; L/M = lactulose/mannitol; PD = pharmacodynamics(s); PK = pharmacokinetics; qd = once-daily dosing; s.c. = subcutaneous;

2.2.2 *Is the active moiety in plasma/serum appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes.

PK:

Octreotide was quantitated by a high-performance liquid chromatography with mass spectrometric detection (HPLC-MS/MS) using a stable isotope [¹³C₆Phe³] octreotide as the internal standard.

PD:

Growth Hormone:

Human Growth Hormone (GH) was assayed by an IDS-iSYS hGH assay, which is a sandwich type immunoassay. The assay's detection principle is chemiluminescence.

IGF-1:

IGF-1 was assayed by the IDS-iSYS IGF-1, which is a sandwich type immunoassay; the detection principle is chemiluminescence.

2.3 Exposure Response

2.3.1 What data contributed to the selection of the phase 3 doses?

The sponsor's rationale for selecting the 20 mg oral dose of octreotide as an equivalent of the 0.1 mg subcutaneous dose of Sandostatin, is as follows: "Based on a review by Chanson et al², a 500 µg/day infusion of octreotide to healthy volunteers suppressed growth hormone concentrations to < 0.25 µg/L, a concentration indicative of effect in patients with pituitary tumors. This was associated with a plasma octreotide concentration between 0.5-1 ng/mL.

Based on this hypothesis, the duration of plasma concentrations of 1 ng/mL for the 4 treatments in study CHI-001 (Oral Mycapssa 3 mg, 10 mg, 20 mg, and Sandostatin 0.1 mg S.C.) was calculated as the difference between the times of the first concentration of 1 ng/mL and the first concentration < 1 ng/mL. The sponsor determined from study CHI-001 that a dose of Mycapssa 20 mg was comparable to a 0.1 mg s.c. dose of octreotide (Sandostatin) in systemic exposure (AUC, [Table 7](#)) and duration of time with plasma octreotide concentrations of 0.5 or 1 ng/mL ([Table 6](#)).

Table 6: Summary of the Time above 0.5 ng/mL for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Mycapssa 3 mg, 10 mg, and 20 mg to Healthy Volunteers under Fasted Conditions

Parameter*	Octreotide 0.1 mg SC	Octreolin 3 mg PO	Octreolin 10 mg PO	Octreolin 20 mg PO
Time ≥ 0.5 ng/mL (h)	5.92 (12) [4.92 – 7.92]	0.66 (3) [0.66 – 1.67]	3.34 (12) [0.34 – 7.67]	7.33 (9) [1.66 – 23.0]
Time ≥ 1 ng/mL (h)	3.92 (12) [2.92 – 4.92]	—†	1.34 (9) [0.33 – 5.00]	4.17 (8) [0.33 – 11.0]

*Median (N) [Range].

†There were no concentrations ≥ 1 ng/mL.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCHI-001, Table 9, Page 48 Figure 10)

2.3.2 What are the characteristics of the exposure-response relationships for effectiveness?

The effectiveness of Mycapssa for maintenance therapy for patients maintained on injectable somatostatin analogs was investigated in a Phase 3 study. Overall response to Mycapssa was 65% at 7 months and 62% at 13 months, compared to 89% on injectable therapy at baseline. For complete details about the efficacy analysis, please refer to the review by Drs. Smita Abraham and Anna Kettermann in DAROTS. The relationship between the individual subject growth hormone steady-state average concentration (GH C_{av}) and octreotide AUC₂₋₄ was investigated ([Figure 2](#)) in the Phase 3 PK sub-study. There appeared to be

² Chanson P, Timsit J, Harris AG. Clinical pharmacokinetics of octreotide. Therapeutic applications in patients with pituitary tumours. *Clin Pharmacokinet* 1993; 25(5):375-391.

a slight trend toward a lower GH C_{av} with increasing AUC_{2-4} for the 60 mg cohort, however, there were no apparent relationships for the other 2 cohorts. The values of GH C_{av} - 1 and 2.5 ng/mL that define GH response categories are represented by horizontal lines on [Figure 2](#). Overall, there does not seem to be a relationship between GH C_{av} and octreotide AUC_{2-4} among responders and non-responders based on GH C_{av} in [Figure 2](#). This was consistent with the applicant's findings.

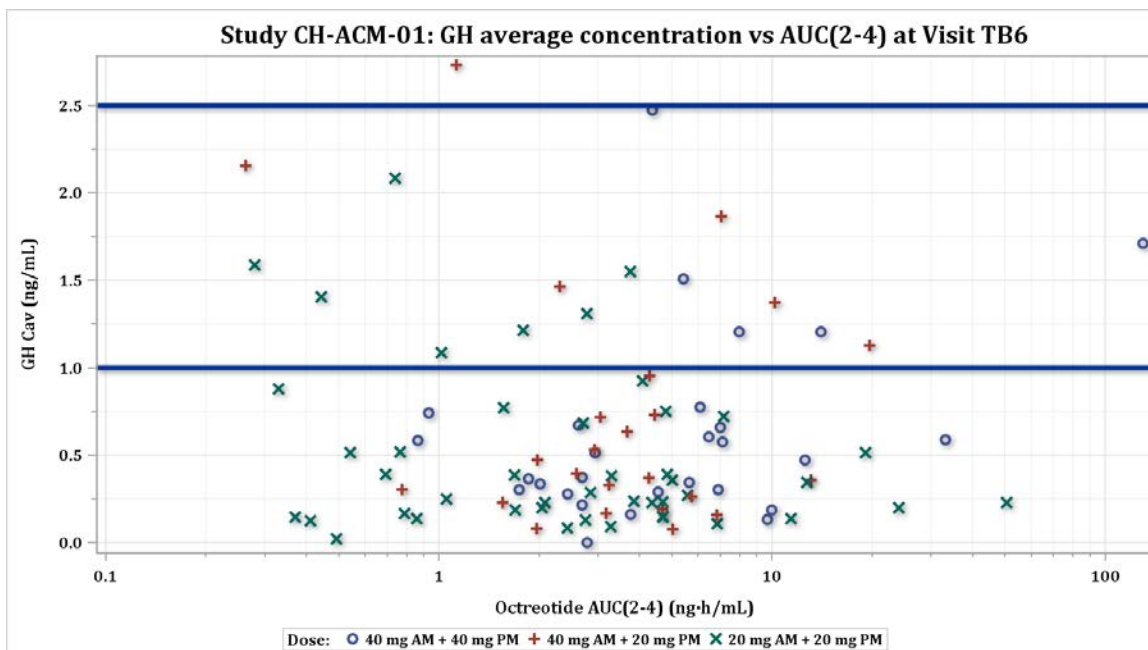


Figure 2. Individual subject GH C_{av} at EOT versus octreotide AUC_{2-4} at Visit TB6/EOT after oral octreotide administration of 40 mg as 20 mg BID, 60 mg as 40 mg AM & 20 mg PM, or 80 mg as 40 mg BID to patients with acromegaly.

(Source: eCTD Module 5.3.5.1, Clinical Trial Report for StudyCH-ACM-01, Appendix 16.1.13 Other Reports, Efficacy and Safety of Oral Octreolin® in Patients with Acromegaly Who Are Currently Receiving Parenteral Somatostatin Analogs, Figure 4, Page 20)

Similarly, there was no apparent relationship between normalized IGF-1 and AUC_{2-4} at Visit TB6/EOT (based on the reserved GH samples), either in the general population or within responders group ([Figure 3](#)). There was an almost complete overlap among the 3 cohorts (all, responders, non-responders). (IGF-1 response categories — 1 and $1.3 \times$ ULN is represented by the horizontal lines).

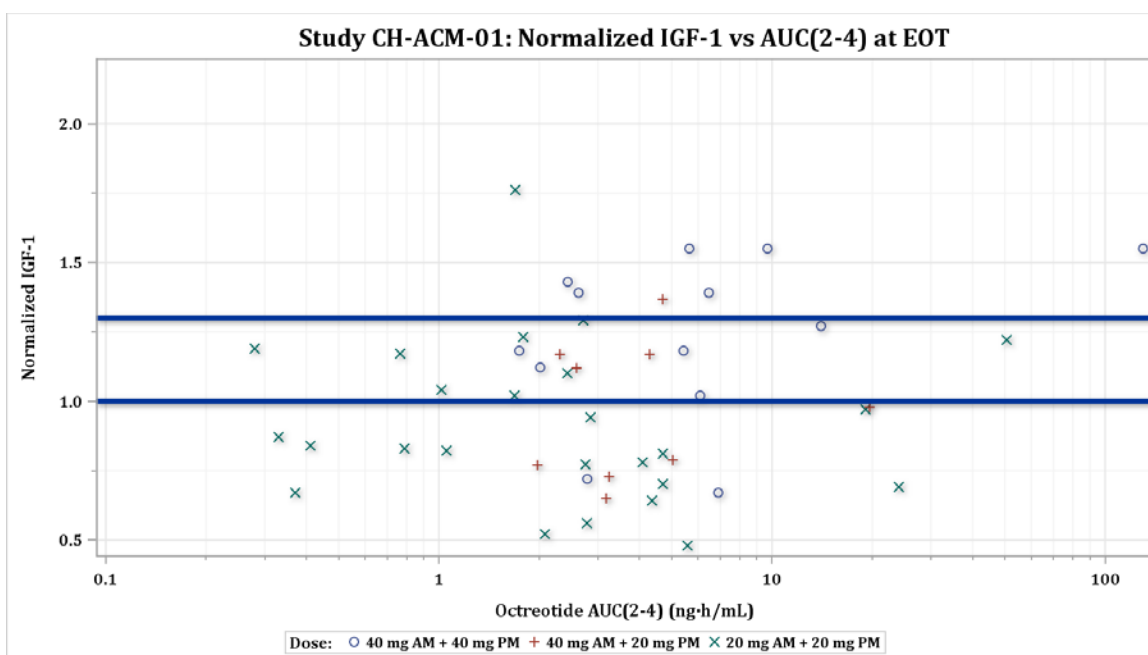


Figure 3. Individual subject normalized IGF-1 levels at EOT versus octreotide AUC2-4 at Visit TB6/EOT after Mycapssa administration of 40 mg as 20 mg BID, 60 mg as 40 mg AM & 20 mg PM, or 80 mg as 40 mg BID to patients with acromegaly — all evaluable subjects.

2.3.3 What are the characteristics of the exposure-response relationships for safety?

The most common systemic organ class (SOC) associated with the reported treatment emergent adverse events (TEAEs) were gastrointestinal disorders (93 patients [60.0%]), nervous system disorders (67 patients [43.2%]), musculoskeletal and connective tissue disorders (61 patients [39.4%]), and infections and infestations (61 patients [39.4%]), consistent with the known safety profile of octreotide and the disease burden of acromegaly. Dose-response was not evident for adverse events by octreotide dose in the phase three trial. Refer to the clinical review by Dr. Smita Abraham for a comprehensive analysis of the adverse events in the phase 3 trial.

2.3.4 Does this drug prolong QT/QTc interval?

One of the reasons for increased mortality observed in acromegalic patients is the underlying cardiovascular disease. An established risk factor for potentially fatal cardiac arrhythmias is the prolongation of the QT interval. Octreotide, one of the somatostatin analogues (SSA) currently used for the medical treatment acromegaly is listed among the drugs able to prolong the QT interval.

A plot of the data from study CH-ACM-01 showed that change in baseline for QTcF (Δ QTcF) as a function of octreotide concentrations showed a slight trend toward a positive increase in Δ QTcF as octreotide plasma concentration increased (Figure 4), independent of dose. However, the slope is not statistically significant ($p = 0.0621$). There does not appear to be an effect of octreotide on Δ QTcF over the range of concentrations observed in this study.

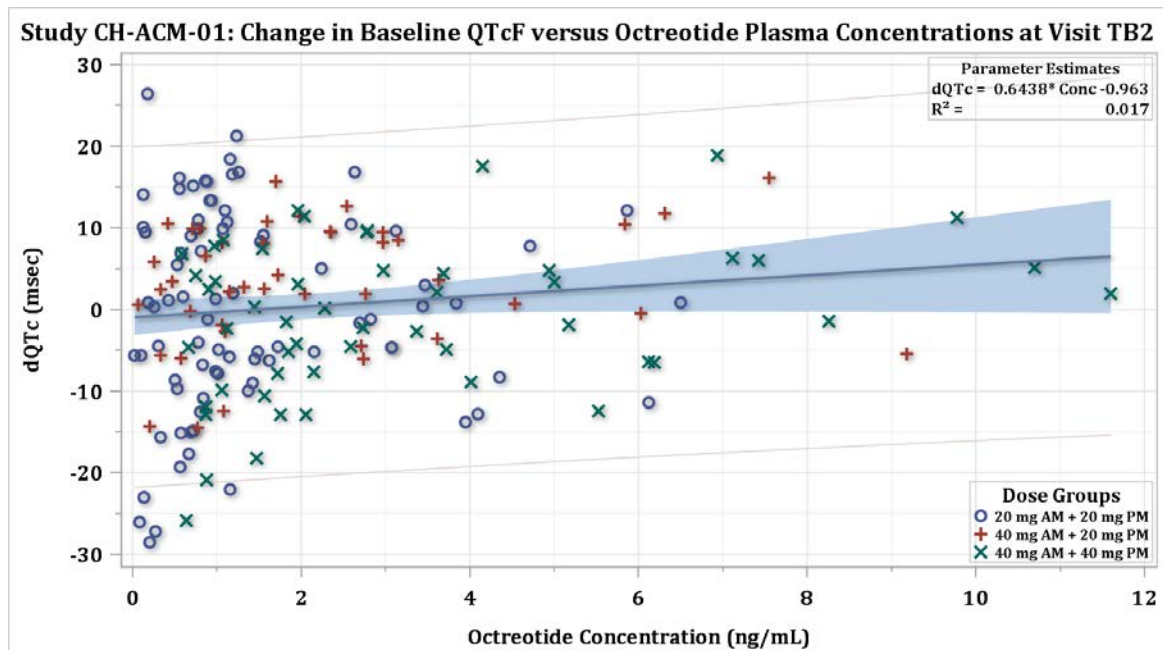


Figure 4. Individual subject change from baseline QTcF versus octreotide plasma concentration at Visit TB2 after Mycapssa administration of 40 mg as 20 mg BID, 60 mg as 40 mg AM & 20 mg PM, or 80 mg as 40 mg BID to patients with acromegaly — PK sub-study population.

2.4 How does the pharmacokinetics of oral octreotide (Mycapssa) compare to that of the listed product, Sandostatin s.c.?

Pharmacokinetic comparison of oral octreotide and the listed drug, subcutaneously administered Sandostatin, were carried out in 2 single-dose studies. A dose range of 3 mg to 20 mg Mycapssa administered orally compared to a dose of 0.1 mg Sandostatin administered subcutaneously were investigated in study CHI-001, and an oral dose of 20 mg Mycapssa under fed and fasting conditions compared to a subcutaneous dose of 0.1 mg Sandostatin under fasting conditions in study CHI-002. Findings from the individual studies are discussed below:

2.4.1 Single-Dose Study CHI-001:

This was an exploratory relative bioavailability study comparing 3 mg, 10 mg and 20 mg oral dose of octreotide (Mycapssa capsules) to 0.1 mg of Sandostatin administered subcutaneously. The study was conducted in 12 male Caucasian subjects between the ages of 18 – 36 years. An initial dose of 3 mg was chosen by the sponsor based on results of the oral toxicology study in cynomolgus monkeys. The no observed adverse effect level (NOAEL) in the monkey was the highest dose tested, which was 9.75 mg given twice daily for 28 days. Based on an average human body weight of 70 kg, the human equivalent dose (HED) of the monkey NOAEL is approximately 111 mg. The starting dose, Mycapssa 3 mg, was approximately 33 times lower than the HED of the NOAEL. After safety with 3 mg was established, the 10 mg dose was initiated. Similarly after safety was established with the 10 mg dose, the 20 mg dose was initiated.

On Day 1 and Day 7, the subjects received either one 3 mg octreotide capsule orally or 0.1 mg Sandostatin subcutaneously in a cross-over fashion. On Day 28, all subjects received an oral dose of 10 mg Mycapssa. On Day 55, subjects who consented to participate further, received an oral dose of 20 mg Mycapssa. All treatments were administered after a 10-hour overnight fast.

The mean plasma concentrations of octreotide increased in a dose-related manner following oral administration. The plasma concentrations appeared to decay similarly after all three oral and the s.c. doses, demonstrating linear PK.

There was, however, considerable intra- and inter-subject variability in the plasma concentration-time profile of octreotide following oral administration of Mycapssa. Mycapssa capsules are formulated with an enteric coating which could have contributed to this variability. In addition, octreotide being a peptide, could also have been subjected to variability in absorption.

Representative mean plasma concentration-time profiles of Mycapssa following oral single-dose, and Sandostatin following s.c. administrations are illustrated in [Figure 5](#) below for normal healthy volunteers.

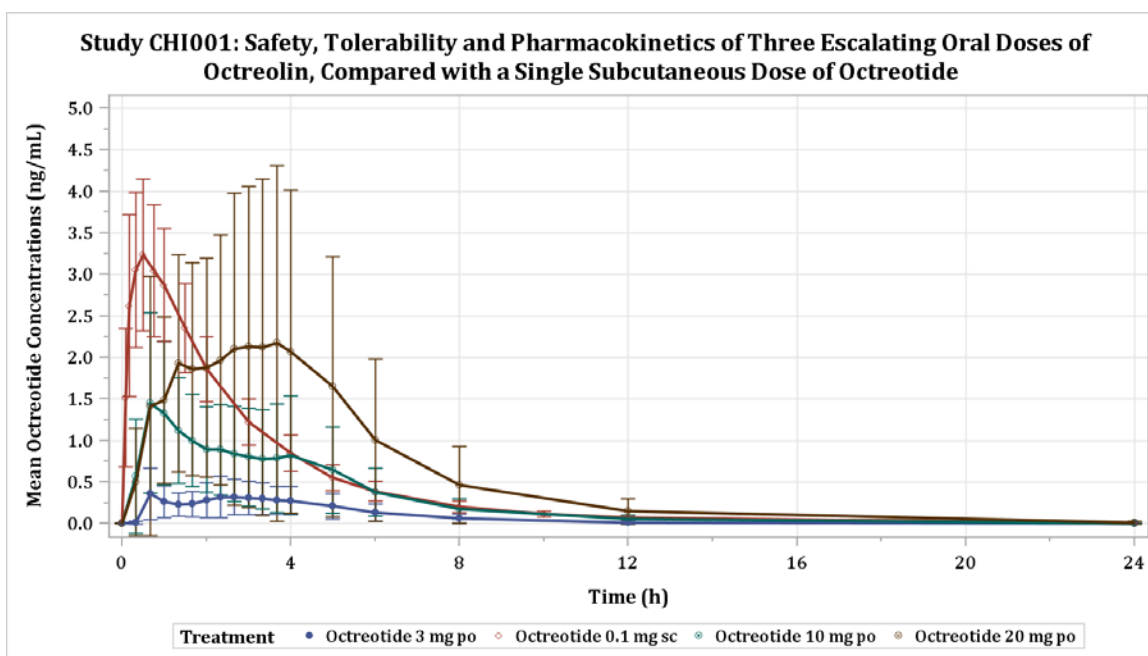


Figure 5 Mean serum concentration-time profile of octreotide following single-dose administration of Mycapssa and Sandostatin

Comparison of PK parameters following the three oral doses of octreotide and 0.1 mg Sandostatin s.c. showed that the 20 mg dose of Mycapssa had an exposure closely matching that of Sandostatin s.c.. The geometric mean ratios (Mycapssa/Sandostatin) for AUC_{0-t} and $AUC_{0-\infty}$ were 95.1% and 95.4%, respectively. The C_{max} ratio was 66.7%.

Based on $AUC_{(inf)}$ ratios, the relative systemic exposures to octreotide following the 3 mg and 10 mg oral doses of Mycapssa relative to the 0.1 mg s.c. dose of octreotide were 15.2% and 53.6%, ,

respectively. This indicates to obtain a comparable systemic exposure to a 0.1 mg s.c. dose of Sandostatin, a 20 mg oral dose of Mycapssa is needed.

After correcting for dose, the relative bioavailability of octreotide from oral Mycapssa relative to Sandostatin is 0.52%, 0.59%, and 0.52% for the 3 mg, 10 mg, and 20 mg doses, respectively.

The mean and SD of pharmacokinetic parameters for octreotide across the three oral doses and one sub-cutaneous dose are presented in [Table 7](#) below.

Table 7: Statistical Comparison of Pharmacokinetic Parameters for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Mycapssa 3 mg, 10 mg, and 20 mg to Healthy Volunteers under Fasted Conditions

Parameter	Geometric Mean Ratio (%)*				Within Subject
	Estimate	90% Confidence Interval			CV (%)
Oral 3 mg vs. SC 0.1 mg					
Cmax	12.00	8.48	→	16.99	53.41
AUC(0-t)	14.19	9.93	→	20.27	55.10
AUC(inf)	15.15	10.66	→	21.55	54.20
Oral 10 mg vs. SC 0.1 mg					
Cmax	47.53	33.59	→	67.25	53.41
AUC(0-t)	52.64	36.84	→	75.21	55.10
AUC(inf)	53.64	37.32	→	77.08	54.20
Oral 20 mg vs. SC 0.1 mg					
Cmax	66.74	45.47	→	97.95	53.41
AUC(0-t)	95.17	64.15	→	141.20	55.10
AUC(inf)	95.39	64.63	→	140.80	54.20
Oral 10 mg vs. Oral 3 mg					
Cmax	395.92	279.80	→	560.23	53.41
AUC(0-t)	370.96	259.65	→	530.00	55.10
AUC(inf)	353.99	246.33	→	508.72	54.20
Oral 20 mg vs. Oral 3 mg					
Cmax	555.91	378.73	→	815.96	53.41
AUC(0-t)	670.70	452.10	→	995.01	55.10
AUC(inf)	629.57	426.54	→	929.25	54.20
Oral 20 mg vs. Oral 10 mg					
Cmax	140.41	95.66	→	206.09	53.41
AUC(0-t)	180.80	121.87	→	268.23	55.10
AUC(inf)	177.85	119.10	→	265.58	54.20

*Based on analysis of natural log-transformed pharmacokinetic parameters, *uncorrected for dose*.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCHI-001, Table 7, Page 43)

2.4.2 Single-Dose Study CHI-002

Study CHI-002 evaluated the single-dose PK of octreotide following a 20 mg Mycapssa dose under fasting and fed conditions and 0.1 mg Sandostatin dose under fasting conditions. Discussions about the effect of food on the pharmacokinetics of oral octreotide are in [Section 2.8](#).

As seen in [Figure 6](#), the mean elimination half-life ($t_{1/2}$) was similar following oral administration of Mycapssa under fasted (2.66 ± 0.73 hour) and s.c. administration of Sandostatin (2.27 ± 0.25 hour).

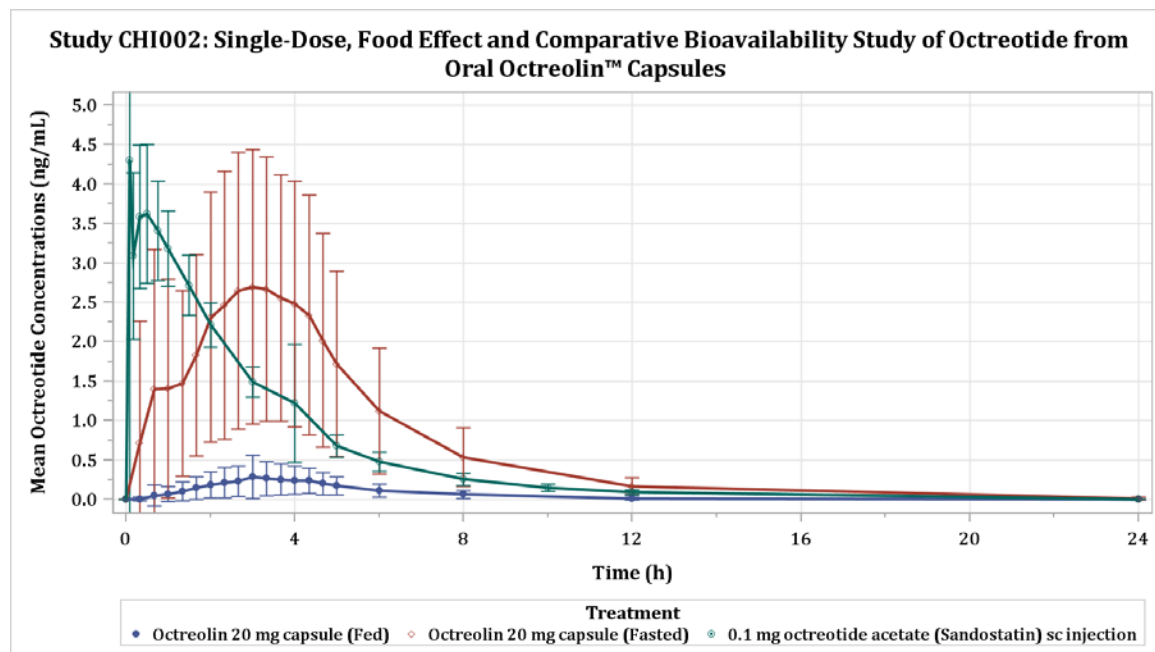


Figure 6 Mean serum concentration-time profile of octreotide following single-dose administration of Mycapssa and Sandostatin

The relative systemic exposure, based on the least squares means for AUC_{0-t} , to octreotide from the 20 mg fasted dose of Mycapssa relative to the 0.1 mg s.c. dose of octreotide was 97%, indicating that a comparable systemic exposure to a 0.1 mg s.c. dose of octreotide was obtained following single 20 mg oral dose of Mycapssa ([Table 8](#)). These results are in agreement with the findings from Study CHI-001. However, similar to study CHI-001, large intra-subject variability was observed in this study leading to the very wide confidence intervals of 73% – 128% for AUC_{0-t} .

Table 8: Statistical Comparison of Pharmacokinetic Parameters for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Mycapssa 20 mg to Healthy Volunteers under Fasted Conditions

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	96.83	73.03 - 128.37
Cmax for Octreotide	ng/mL	63.77	45.29 - 89.78

Mean pharmacokinetic parameters for octreotide following the two Mycapssa oral treatments and Sandostatin subcutaneous administration are shown in [Table 9](#).

Table 9: Pharmacokinetic Parameters for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Mycapssa 20 mg to Healthy Volunteers under Fasted Conditions

Parameter*	20 mg Oral		Subcutaneous 0.1 mg
	Fed	Fasted	
Tlag (h)†	1.00 (24) [0.33 – 3.67]	0.330 (24) [0.330 – 1.02]	—‡
Cmax (ng/mL)	0.377 ± 0.261 (24)	3.62 ± 1.93 (24)	3.83 ± 0.86 (14)
Tmax (h)	3.00 (24) [0.670 – 4.67]	2.50 (24) [0.330 – 4.33]	0.50 (14) [0.203 – 4.00]
AUC(0-t) (h×ng/mL)	1.29 ± 0.884 (24)	15.2 ± 8.73 (24)	12.0 ± 1.53 (14)
AUC(inf) (h×ng/mL)	1.45 ± 0.892 (23)	15.4 ± 8.74 (24)	12.3 ± 1.57 (14)
λz (1/h)	0.3309 ± 0.0892 (23)	0.2799 ± 0.0783 (24)	0.3083 ± 0.0331 (14)
t½ (h)	2.28 ± 0.78 (23)	2.66 ± 0.73 (24)	2.27 ± 0.25 (14)

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

‡There was no lag time after SC administration.

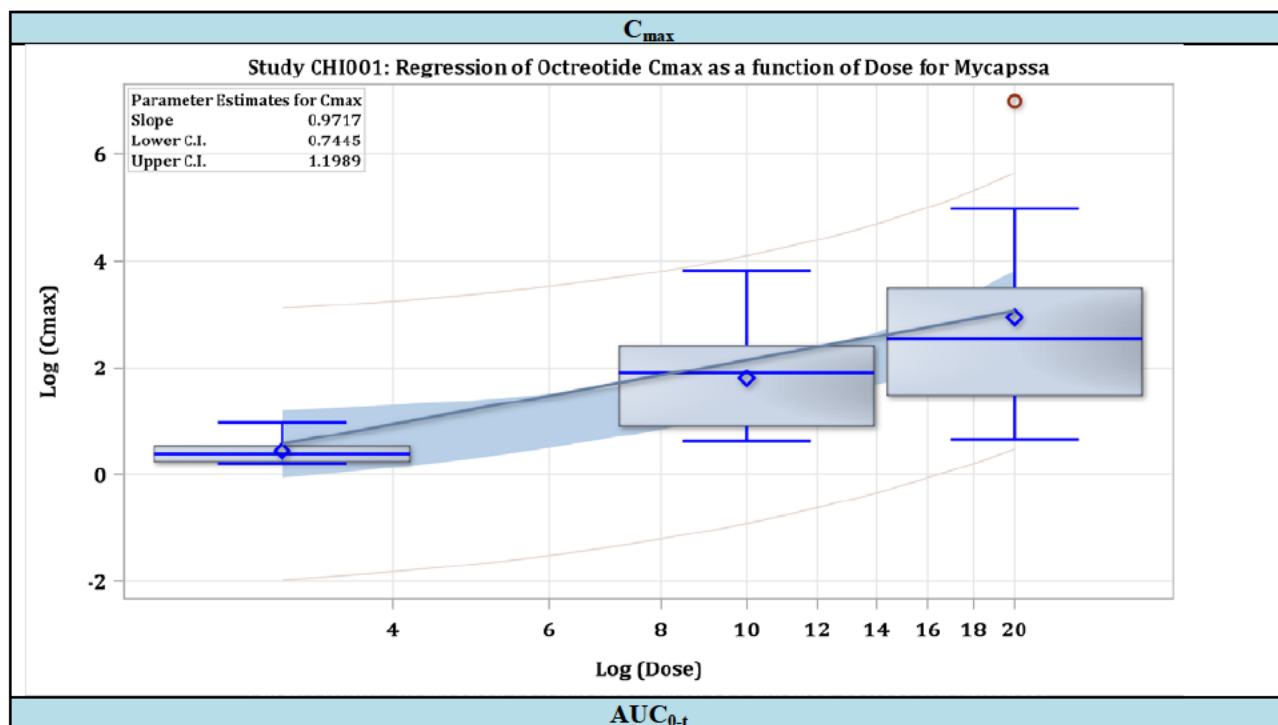
(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCHI-002, Table 8, Page 44)

2.4.3 Was dose-proportionality established for Mycapssa?

Dose proportionality in the Mycapssa treatment groups was assessed by using a power model $Y = \alpha \cdot \text{Dose}^\beta$, where Y , α , and β correspond to the PK parameter (AUC or $C_{\max}$), proportionality constant and an exponent, respectively. If the 90% CI for the exponent β contained “1”, the relationship between dose and the PK parameters was considered to be dose proportional.

Findings from the model showed that for the single-dose study CHI-001, the slopes for $C_{\max}$ and AUC_{0-t} included unity; the $C_{\max}$ and AUC_{0-t} point estimates of the slope (90% confidence interval) were 0.97 (0.74, 1.20) and 1.01 (0.77, 1.26), respectively, over a 6.67-fold range of doses (3 mg to 20 mg), indicating that octreotide plasma concentrations increased in a dose-proportional manner with increasing dose within the dose range (3 mg – 20 mg) evaluated in study CHI-001.

Regression plots to determine dose-linearity for study CHI-001 are shown in [Figure 7](#).



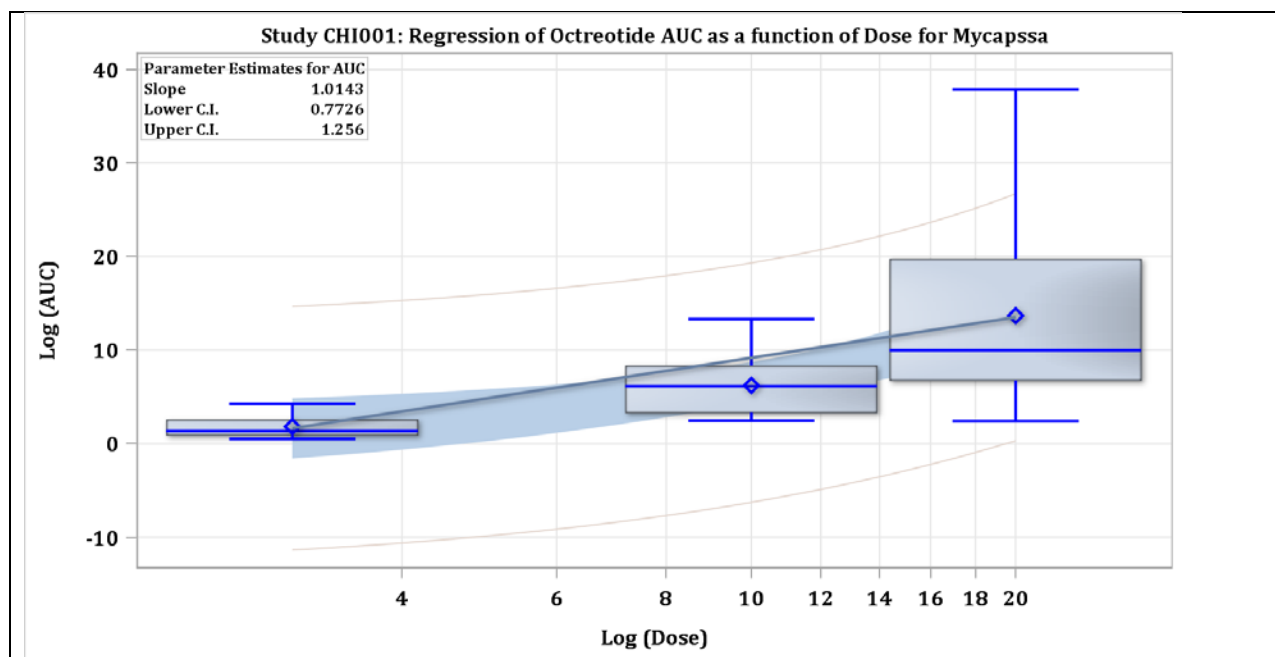


Figure 7 Regression of PK Parameters ($C_{\max}$ and AUC_{0-t}) over Dose following single-dose administration of Mycapssa

Dose linearity was also evaluated for the PK-sub study of the safety and efficacy study, CH-ACM-001.

Findings from the model showed that for the PK-sub study, the slopes for $C_{\max}$ and AUC_{0-t} also included unity; the $C_{\max}$ and AUC_{0-inf} point estimates of the slope (90% confidence interval) were 1.11 (0.43, 1.78) and 1.29 (0.59, 1.99), respectively, over a 2-fold range of doses (40 mg to 80 mg), indicating that octreotide plasma concentrations increased in a dose-proportional manner with increasing dose within the dose range (40 mg – 80 mg) evaluated in study CH-ACM-001.

Regression plots to determine dose-linearity for study CH-ACM-001 shown in [Figure 8](#).

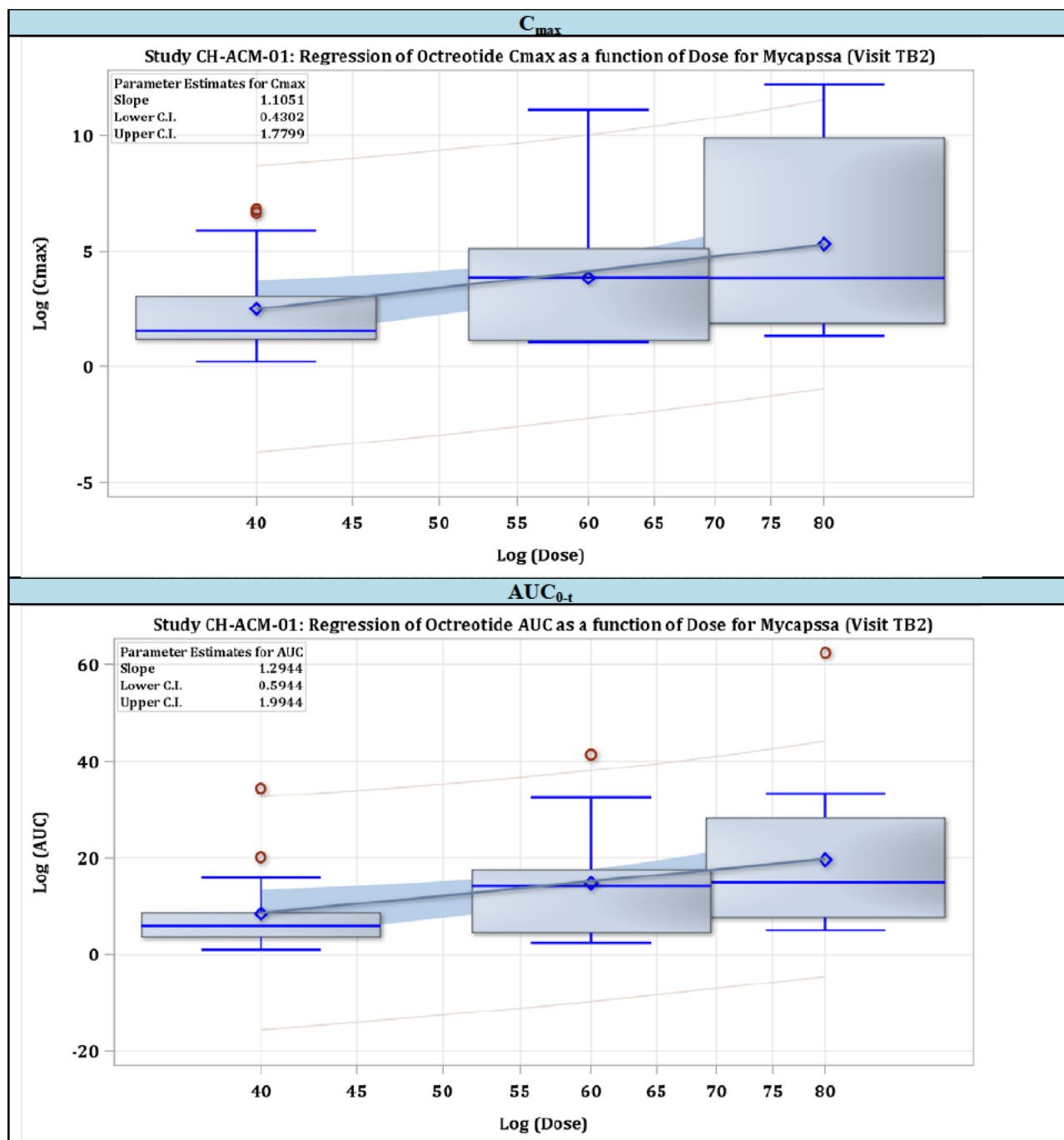
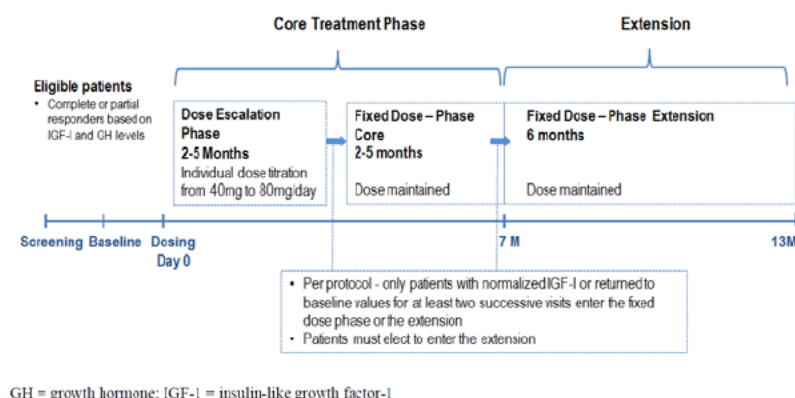


Figure 8 Regression of PK Parameters (C_{max} and AUC_{0-t}) over Dose following single-dose administration of Mycapssa

Overall, dose proportionality was observed between the Mycapssa doses evaluated, 3 mg – 80 mg.

2.4.4 What were the pharmacokinetics and Pharmacodynamics of oral octreotide following multiple daily oral doses?

Multiple-dose pharmacokinetics of oral octreotide are available from a PK sub-study of the pivotal Phase 3 study. The Phase 3 study was a multi-center, international, open-label dose-titration, study in subjects diagnosed with acromegaly. The study consisted of a Core Treatment Period comprising of a dose escalation phase (> 2 months) during which a therapeutic dosage regimen of oral octreotide for each individual subject was defined based on the control of IGF-1 and symptoms of acromegaly and a fixed dose phase (2-5 months) during which patients were treated with the established therapeutic regimen of oral octreotide. The core treatment period was followed by an optional open-label extension period of 6 months, as shown in the design below:



The primary objective of the study was to determine the effect of Mycapssa therapy on IGF-1 levels and GH levels, as measures of response. Evaluation of the PK profile of Mycapssa during chronic treatment was an exploratory objective.

Representative mean plasma concentration-time profiles of octreotide following multiple-dose oral administration of Mycapssa at the second monthly visit of the fixed-dose phase (Visit TB2) are illustrated in [Figure 9](#) below.

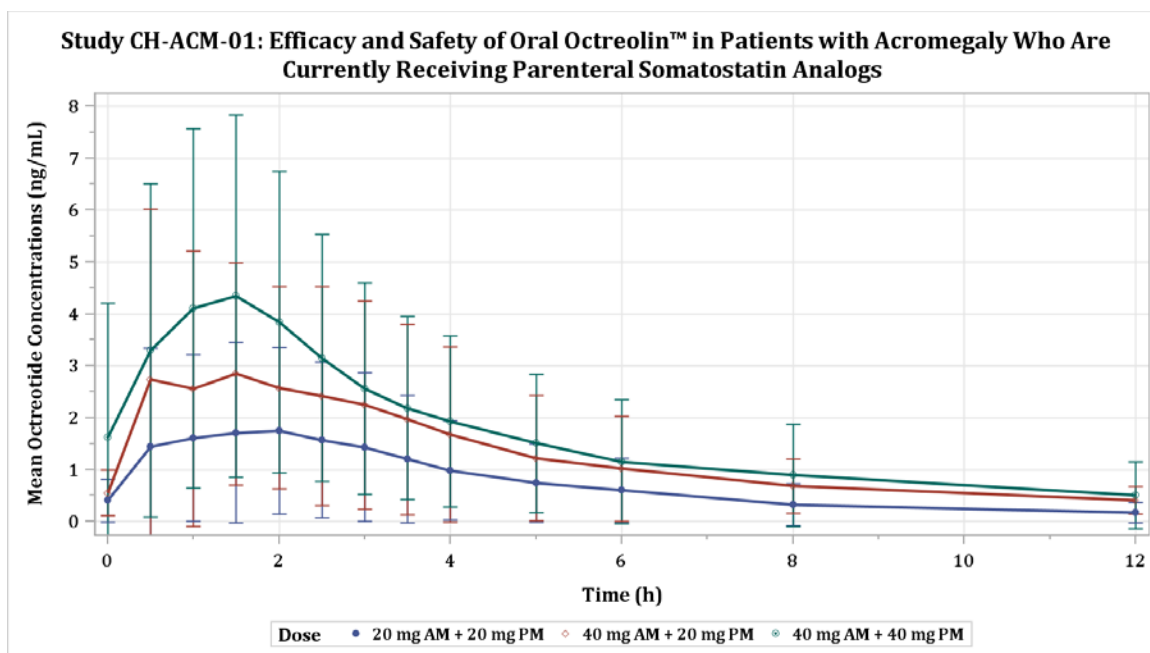


Figure 9 Mean plasma concentration time profile of Octreotide after multiple-dose Oral administration of Mycapssa at Visit TB2

Mean concentration-time profiles of octreotide and growth hormone at the interval of 2-4 hours post dosing following multiple-dose oral administration of Mycapssa at the end of treatment (Visit TB6) are illustrated in [Figure 10](#) below.

The mean serum GH concentrations appeared to be reasonably constant over the measurement period of 2.5 to 4 hour period after dosing in all 3 cohorts with lower concentrations and mean values for C_{av} in the 40 mg cohort than in the 60 mg and 80 mg cohorts. This observation could have been due to a consequence of subjects with more severe disease up titrating to the 60 mg and 80 mg regimens, as required per protocol.

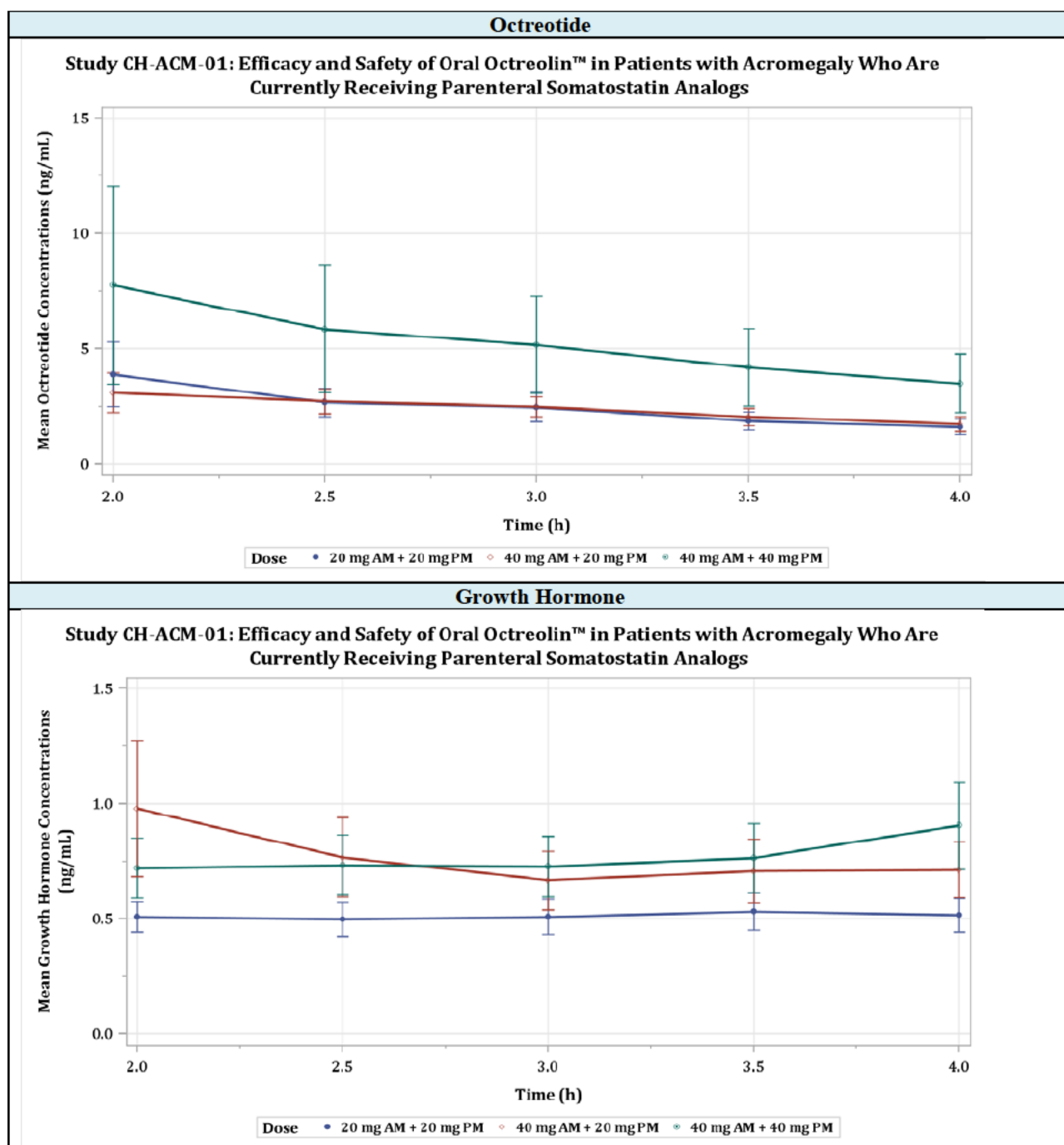


Figure 10 Mean plasma concentration time profile of Octreotide 2-4 hours post-dosing after multiple-dose Oral administration of Mycapssa at Visit TB6

A PK/PD correlation was attempted ([Figure 11](#)) to evaluate a possible correlation between the octreotideAUC₂₋₄ and growth hormone concentrations. As discussed earlier, no correlation was found.

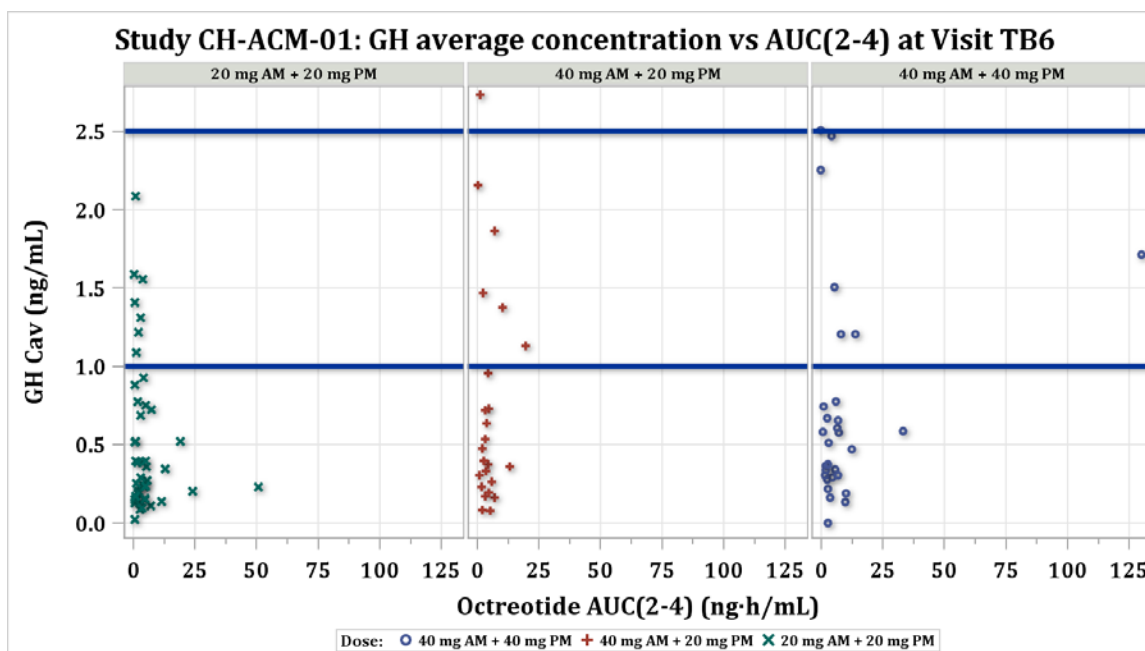


Figure 11 Exposure-Response relationship between growth hormone and octreotide AUC₂₋₄ at 2-4 hours post-dosing after multiple-dose Oral administration of Mycapssa at Visit TB6

2.4.5 Was bioequivalence established between oral Mycapssa and Sandostatin s.c.?

No, bioequivalence was not established between oral Mycapssa (test) and Sandostatin s.c. (ref). As seen from the findings of study CHI-002, the ratio of least squares means (test/ref) for AUC_{0-t} was 0.97 with 90% confidence intervals of 73.03% - 128.37%, which failed to meet the bioequivalence criteria. Similarly C_{max} with a point estimate of 0.64 and 90% confidence intervals of 45.29% - 89.78% failed to meet the bioequivalence criteria. The sample size selected for the study was very small. Only 14 subjects participated in the Sandostatin s.c. dosing phase, while data from 24 subjects was available for the oral Mycapssa treatment. Oral octreotide exhibits large intra-subject variability, and a properly designed bioequivalence study would have required in excess of 40 subjects for a bioequivalence determination.

Design of Study CHI-002: This study was designed as a single-dose comparison. Sandostatin s.c. is recommended to be given t.i.d., and Mycapssa is proposed to be given b.i.d. Ideally the entire dosing duration, i.e. Sandostatin t.i.d., vs. Mycapssa b.i.d should have been compared so that a measure of the comparative AUCs during the duration (t.i.d or b.i.d) would have been obtained.

Additional pharmacodynamic comparison of growth hormone and IGF-1 concentration, between the two products would have lent support to the safety and efficacy study. However, a PD comparison between the two products was not carried out.

Simulation of single-dose PK data for b.i.d/t.i.d comparison:

Single dose PK data from study CHI-002 was simulated to a bid regimen for Mycapssa and t.i.d regimen for Sandostatin, using the non-parametric superposition principle built into the PK/PD software, Phoenix. The simulated plasma curves are shown below in [Figure 12](#):

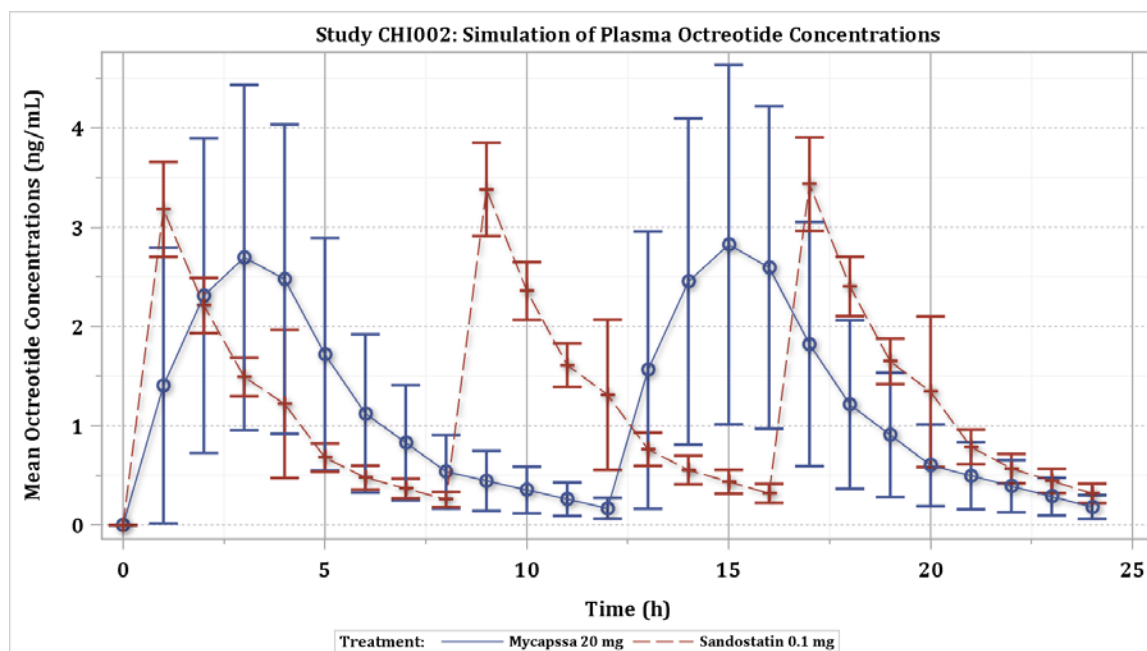


Figure 12 Simulated mean plasma concentration time profile of octreotide following oral Mycapssa bid and tid Sandostatin s.c.

The predicted octreotide C_{max} ratio (Mycapssa/Sandostatin) from the simulated data was 0.81 and predicted AUC_{0-24} ratio was 0.77. Statistical analysis of the simulated data indicated that bioequivalence was not achieved between Mycapssa and Sandostatin ([Table 10](#)):

Table 10: Statistical Comparison of Pharmacokinetic Parameters for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Mycapssa 20 mg to Healthy Volunteers under Fasted Conditions – Simulated Data

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

2.4.6 What other comparative information was provided for oral Mycapssa and Sandostatin?

Reducing circulating insulin-like growth factor I (IGF-I) levels to normal for age and sex and reducing serum GH concentrations to less than 1 µg/L after an oral glucose load are the biochemical goals of Acromegaly therapy.

According to Giustina et al.³, “Baseline biochemical parameters for the diagnosis of acromegaly include a fasting or random GH and IGF measurement. If a random GH level is less than 0.4 mg/L and IGF is in the age- and gender-matched normal range, the diagnosis of acromegaly is

³ Giustina A, Barkan A, Casanueva FF, et al.: Criteria for Cure of Acromegaly: A Consensus Statement. *J Clin Endocrinol Metab* 85: 526-529, 2000

excluded in a patient who has no other inter-current illness. If either of these levels is not achieved, a glucose tolerance test should be performed with 75 g oral glucose and subsequent measurements of glucose and GH every 30 min over 2 h. During this time, the GH level should fall to 1 µg/L or less for acromegaly to be excluded. Although mean integrated 24-h GH levels of less than 2.5 µg/L also exclude acromegaly, these values correlate tightly with results of the glucose suppression test”.

Duration of octreotide action on growth hormone :

According to the sponsor, a review by Chanson² showed that a plasma octreotide concentration between 0.5- 1 ng/mL was associated with a suppression of growth hormone concentration to <0.25 µg/mL, a concentration indicative of effect in patients with pituitary tumors. Based on this assumption, the sponsor calculated the duration of time for which octreotide concentrations were ≥ 0.5 ng/mL and 1 ng/mL to be 5.92 and 3.92 h, respectively, following 0.1 mg Sandostatin s.c., and 7.33 and 4.17 h, respectively, following Mycapssa 20 mg administered orally.

A summary of the time above 0.5 ng/mL (the claimed minimum effective concentration) following Sandostatin and Mycapssa dosing from study CHI-001 is shown in [Table 11](#).

Table 11 Summary of the Time above 0.5 ng/mL for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Mycapssa 3 mg, 10 mg, and 20 mg to Healthy Volunteers under Fasted Conditions

Parameter*	Octreotide 0.1 mg SC	Octreolin 3 mg PO	Octreolin 10 mg PO	Octreolin 20 mg PO
Time $\geq$ 0.5 ng/mL (h)	5.92 (12) [4.92 – 7.92]	0.66 (3) [0.66 – 1.67]	3.34 (12) [0.34 – 7.67]	7.33 (9) [1.66 – 23.0]
Time $\geq$ 1 ng/mL (h)	3.92 (12) [2.92 – 4.92]	—†	1.34 (9) [0.33 – 5.00]	4.17 (8) [0.33 – 11.0]

*Median (N) [Range].

†There were no concentrations $\geq$ 1 ng/mL.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCHI-001, Table 9, Page 48)

Similarly in study CHI-002, the sponsor calculated the duration of time for which octreotide concentrations were $\geq$ 0.5 ng/mL and 1 ng/mL to be 4.92 and 3.42 h, respectively, following 0.1 mg Sandostatin s.c., 4.00 h and 5.67 h following Mycapssa 20 mg administered orally under fasting conditions, and 0.00 and 0.67 h, respectively, following Mycapssa 20 mg administered orally under fed conditions. Administration of octreotide under fed conditions drastically reduces the of time during which octreotide concentrations are above $\geq$ 0.5 ng/mL.

A summary of the time above minimum effective concentration following Sandostatin and Mycapssa dosing is shown in [Table 12](#).

Table 12 Summary of the Time above 0.5 ng/mL for Octreotide after Oral Administration of Mycapssa 20 mg under Fed and Fasted Conditions and Subcutaneous Administration of 0.1 mg.

Parameter*	20 mg Oral		Subcutaneous 0.1 mg
	Fed	Fasted	
Time $\geq$ 0.5 ng/mL (h)	0.67 (7) [0.00 – 2.00]	5.67 (23) [1.66 – 7.67]	4.92 (14) [3.92 – 5.92]
Time $\geq$ 1 ng/mL (h)	0.00 (1)	4.00 (22) [0.33 – 7.67]	3.42 (14) [2.92 – 3.92]

*Median (N) [Range].

Based on these comparisons the sponsor concluded that oral octreotide has similar duration of action as Sandostatin injection.

2.5 Intrinsic Factors

2.5.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Information on the intrinsic factors affecting the pharmacokinetics of octreotide was pooled from several 7 Phase 1, studies. Only data from the 20 mg Mycapssa administered under fasting conditions and 0.1 mg

Sandostatin administered subcutaneously were pooled due to similarity in total exposure. The data from phase 3 sub-study was also explored to determine if there were any factors affecting the PK of octreotide. Based on pooled analysis and phase 3 sub-study data, no notable differences in octreotide exposure were observed across age groups, between sexes, across race groups, or by body weight.

2.5.1.1 Age

Data pooled from 7 Phase 1 studies indicated that there appears to be no relationship between age and total or peak octreotide exposure in subjects 18 – 73 years of age ([Figure 13](#))

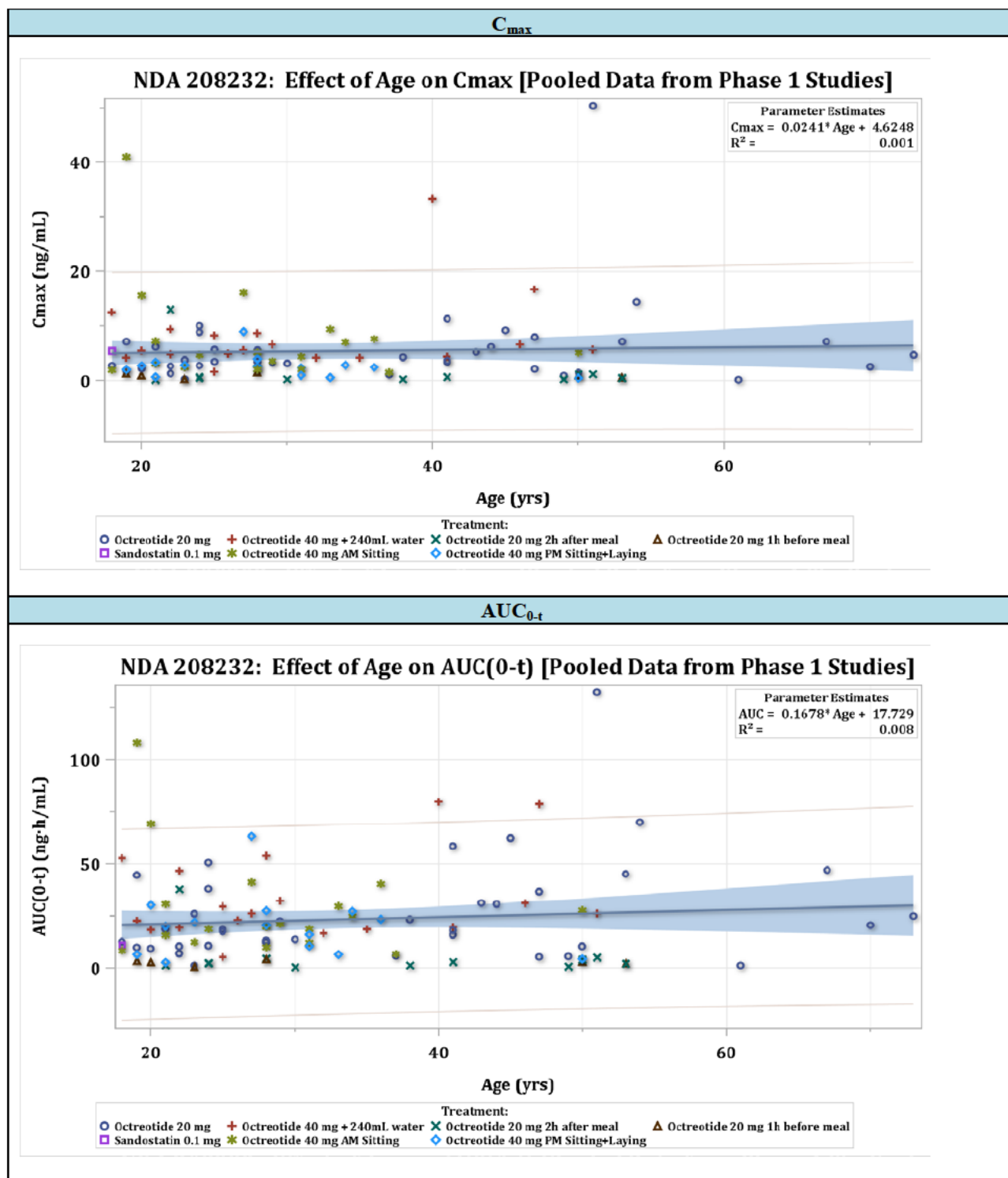


Figure 13 Scatter Plot for Octreotide PK Parameters vs. Age in Healthy Volunteers

Similarly, no relationship could be established between age and total or peak octreotide exposure in acromegaly patients in the PK sub-study (age range 22-73 years) of the Phase 3 trial ([Figure 14](#)).

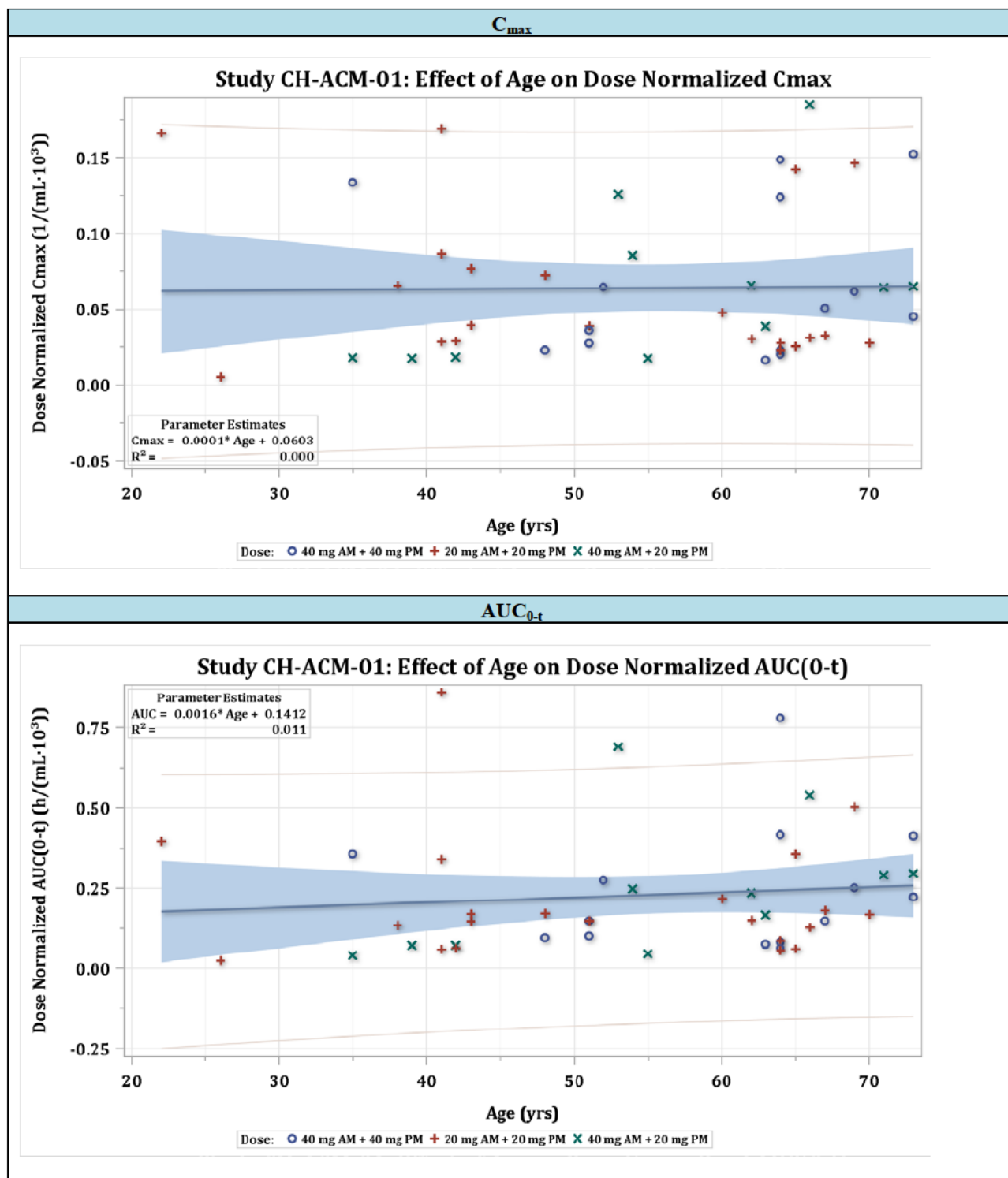


Figure 14 Scatter Plot for Octreotide PK Parameters vs. Age in Acromegaly Patients

2.5.1.2 Gender and Race

Gender:

No gender differences were noted in the pharmacokinetics of octreotide from the pooled Phase 1 data in healthy volunteers (M=52 n; F=54) (Figure 15), or PK sub-study of the Phase 3 trial in acromegaly patients (M=22; F=24) (Figure 16).

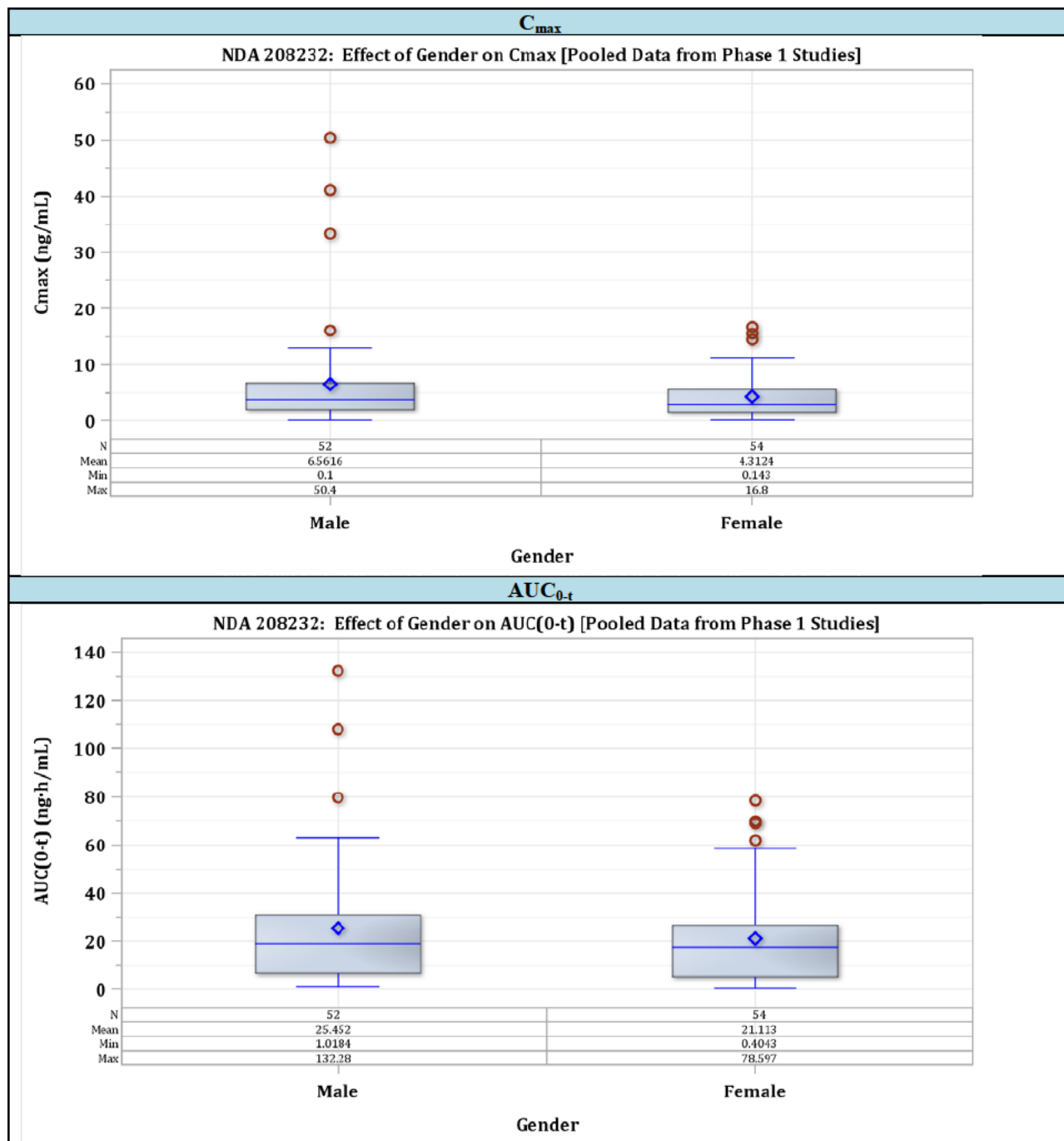


Figure 15 Boxplot of Octreotide PK Parameters vs. Gender in Healthy Volunteers

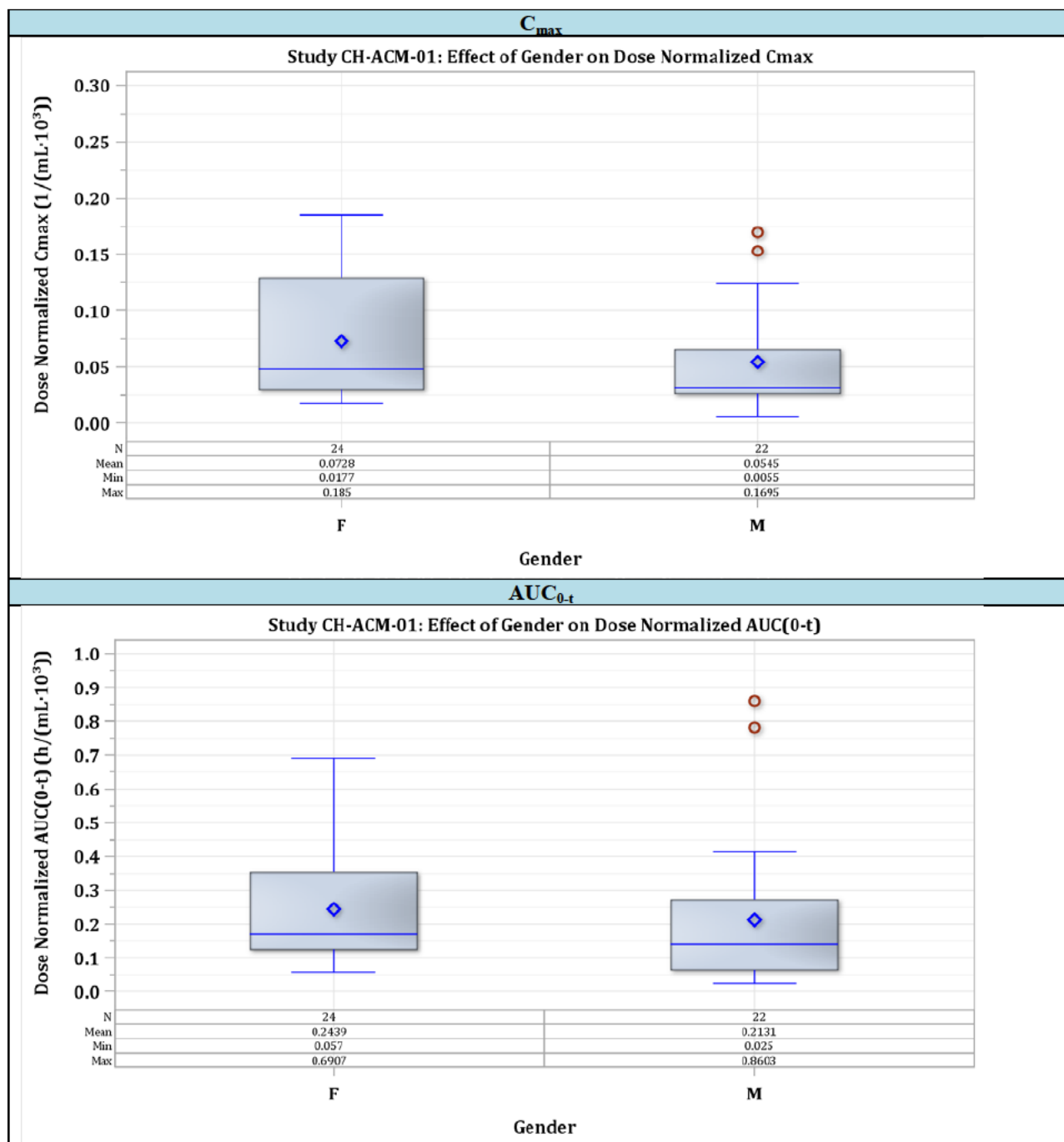


Figure 16 Boxplot of Octreotide PK Parameters vs. Gender in Acromegaly Patients

Race:

Though the majority of the subjects in the Phase 1 trials were Caucasians, race does not have a substantial effect on the pharmacokinetic profiles of octreotide in healthy volunteers ([Figure 17](#)). In the PK sub-study of the Phase 3 trial in acromegaly patients, all the subjects were Caucasians, except for one subject of “other” race ([Figure 18](#)).

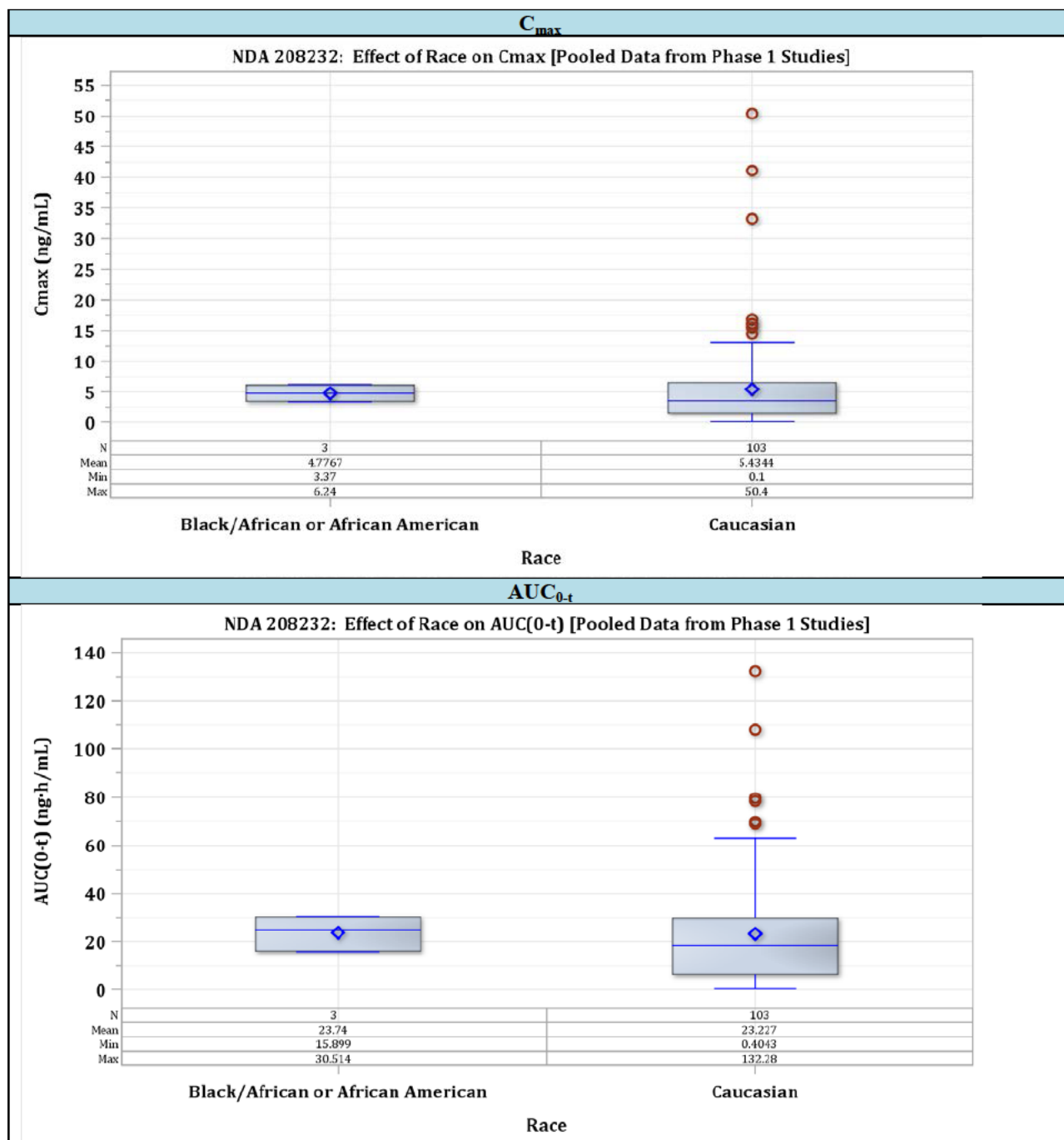


Figure 17 Boxplot of Octreotide PK Parameters vs. Race in Healthy Volunteers

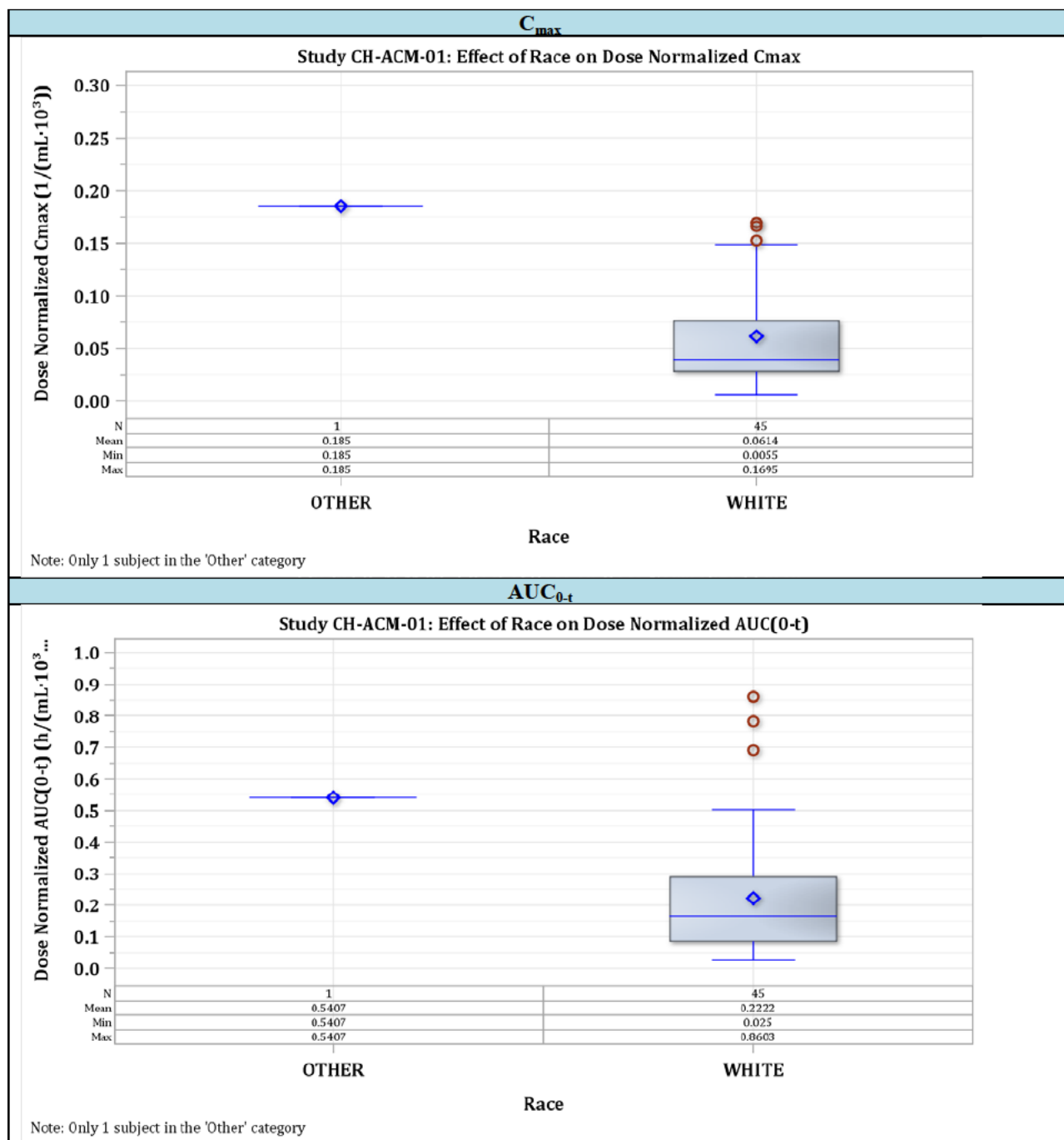


Figure 18 Boxplot of Octreotide PK Parameters vs. Race in acromegaly Patients

2.5.1.3 Body Weight

Pooled analysis of the phase 1 studies indicated that there was no correlation between body weight and octreotide C_{max} or AUC_{0-t} . (Figure 19). Similarly, there was no correlation between body weight and octreotide C_{max} or AUC_{0-t} in acromegaly patients (Figure 20).

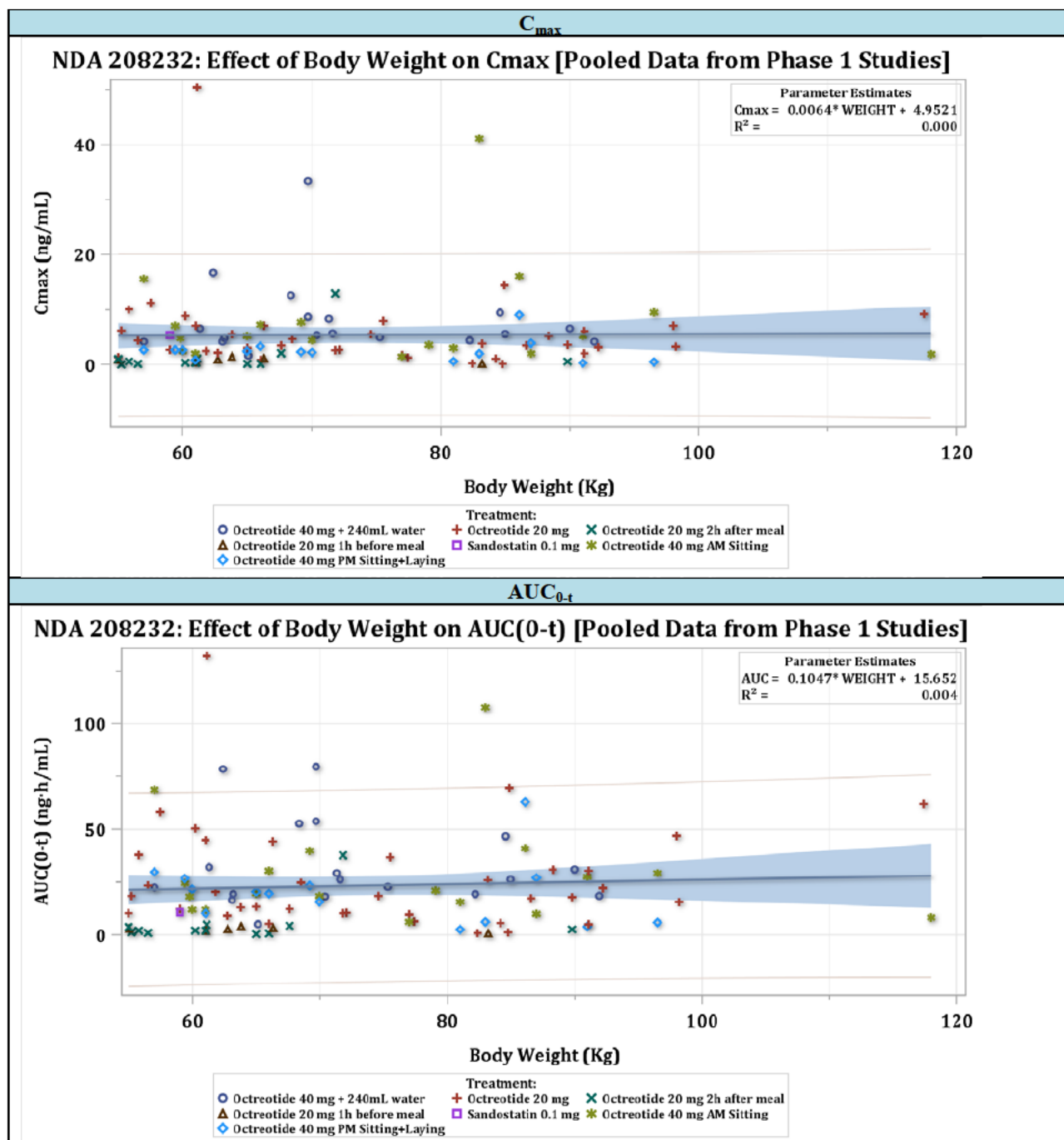


Figure 19 Scatter Plot for Octreotide PK Parameters vs. Body Weight in Healthy Volunteers

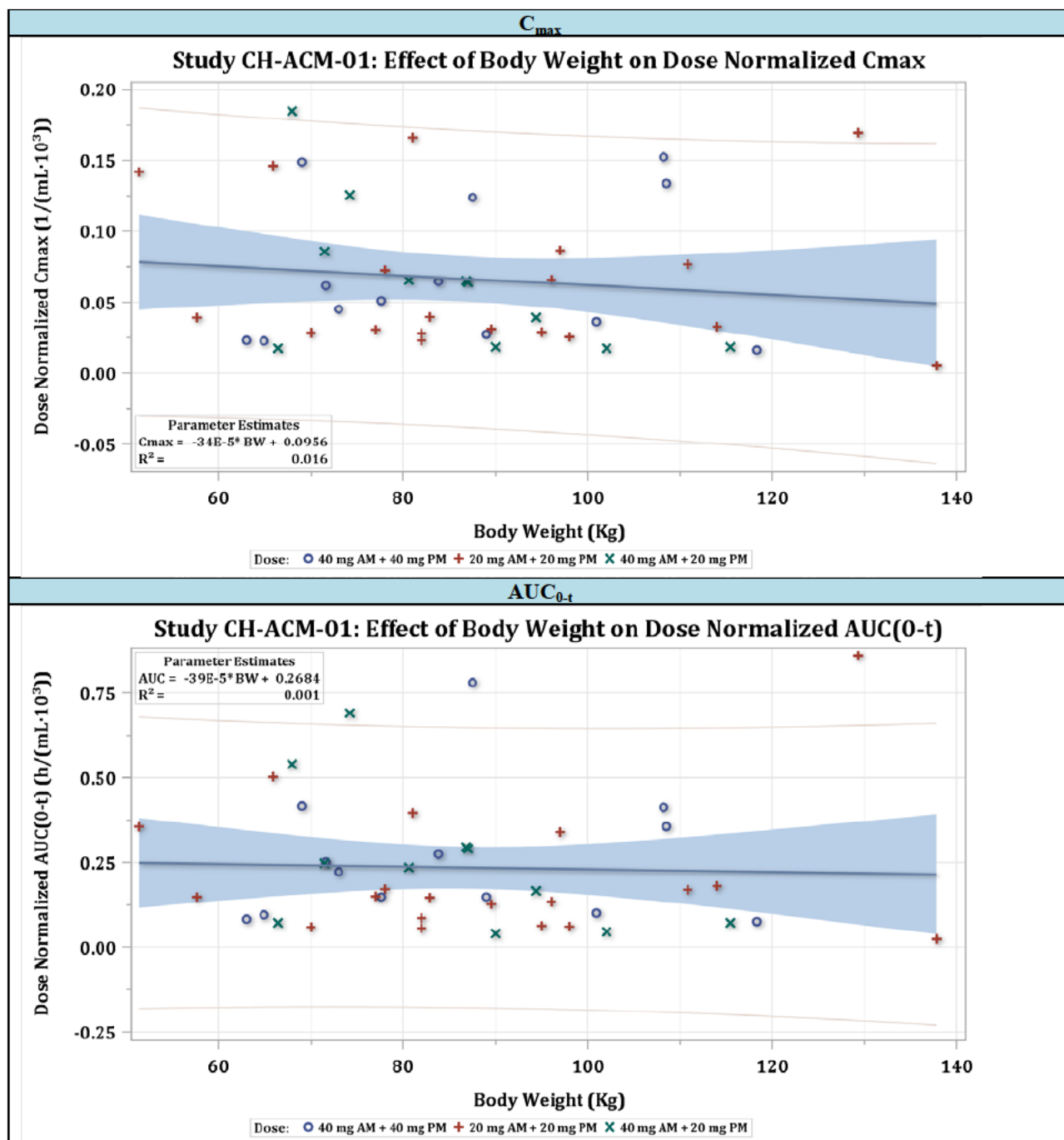


Figure 20 Scatter Plot for Octreotide PK Parameters vs. Body Weight in Acromegaly Patients

Reviewer's Comments: Based on pooled data analysis, no dose adjustments based on age, race, gender, and body weight are recommended.

2.5.2 Does renal function affect octreotide pharmacokinetics?

The pharmacokinetics of oral octreotide was evaluated in study CHI-007 in subjects with severe renal impairment (SRI) or end stage renal disease (ESRD). The primary objective of the study was to evaluate the PK of a single dose of 40 mg oral octreotide acetate in both severe renal impairment (defined as estimated glomerular filtration rate [eGFR] between 15 and 29 mL/min/1.73 m²) and of ESRD (Stage 5 dosed with study medication on their off dialysis day), and to compare it with that in a control group of normal healthy subjects (defined as eGFR $\geq$ 90 mL/min/1.73 m²) matched to each of the renally impaired subjects by gender, age, and weight. Subjects with ESRD on dialysis had higher mean plasma octreotide concentrations than did those with severe renal impairment ([Figure 21](#)). Comparison of pharmacokinetic parameters showed that subjects with ESRD on dialysis had with higher mean values for C_{max} , AUC_{0-t} , AUC_{inf} , and $t_{1/2}$ ([Table 13](#)), consistent with an effect of renal impairment on octreotide exposure. The median values for T_{max} were similar in both ESRD and SRI subjects and the difference was not statistically significant ($p = 0.7374$). The median value for T_{max} increased from 2 h in healthy subjects to 4 h in subjects with SRI and the difference was statistically significant ($p = 0.0416$).

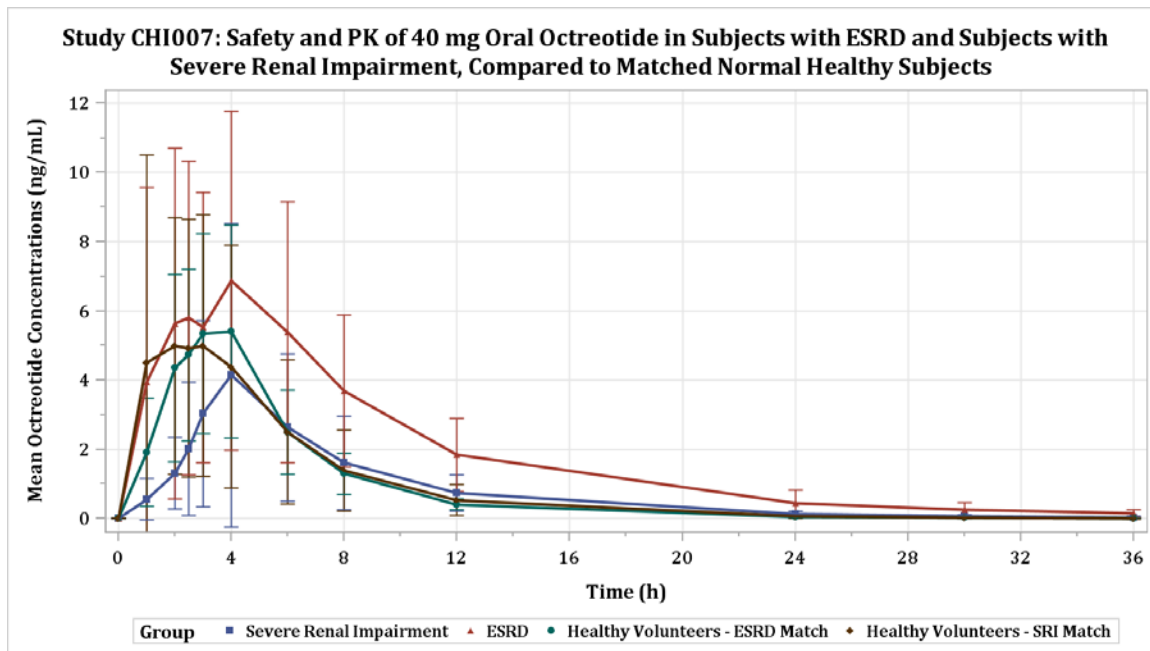


Figure 21 Mean plasma Octreotide concentrations in ESRD and SRI subjects following 20 mg Mycapssa

Table 13 Summary of Pharmacokinetic Parameters for Octreotide After Oral Administration of a Single 40 mg Dose of Oral Octreotide Acetate to Subjects With ESRD on Dialysis, Severe Renal Impairment, and Matched Healthy Subjects

Parameter*	ESRD on Dialysis		Severe Renal Impairment	
	Subjects	Matched Healthy Volunteers	Subjects	Matched Healthy Volunteers
C _{max} (ng/mL)	9.30 ± 5.47 (6)	6.13 ± 3.19 (6)	4.40 ± 4.17 (6)	6.33 ± 5.16 (6)
T _{max} (h)	3.00 (6) [1.00 – 8.00]	3.50 (6) [2.00 – 4.00]	4.00 (6) [1.00 – 6.00]	2.00 (6) [1.00 – 3.00]
AUC(0-t) (h×ng/mL)	68.0 ± 37.9 (6)	32.2 ± 15.0 (6)	28.5 ± 23.8 (6)	35.1 ± 29.1 (6)
AUC(inf) (h×ng/mL)	69.5 ± 38.8 (6)	32.4 ± 15.0 (6)	29.0 ± 23.9 (6)	35.4 ± 29.1 (6)
λ _z (1/h)	0.0999 ± 0.0171 (6)	0.1853 ± 0.0333 (6)	0.1264 ± 0.0303 (6)	0.1521 ± 0.0421 (6)
t _{1/2} (h)	7.09 ± 1.07 (6)	3.84 ± 0.67 (6)	5.90 ± 2.10 (6)	4.95 ± 1.78 (6)
CL/F (L/h)	980 ± 912 (6)	1,460 ± 647 (6)	2,542 ± 2,163 (6)	6,341 ± 10,546 (6)
V _z /F (L)	9,905 ± 9,095 (6)	8,159 ± 4,004 (6)	19,713 ± 14,465 (6)	37,752 ± 63,539 (6)

*Mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

AUC(0-t) = area under the plasma concentration-time curve from 0 to the final time with a concentration ≥ LOQ;

AUC(inf) = area under the plasma concentration-time curve from 0 to infinity; CL/F = apparent oral clearance;

C_{max} = maximum plasma concentration; ESRD = end-stage renal disease; LOQ = limit of quantitation; t_{1/2} = elimination half-

life; T_{max} = time of maximum plasma concentration; V_z/F = apparent oral volume of distribution

The rank order of exposure, in renally impaired subjects (ESRD on dialysis > SRI), after administration of oral octreotide is consistent with that known for Sandostatin. SRI subjects had a longer mean t_{1/2} of 5.90 hours for oral octreotide acetate compared to 3.1 hours for Sandostatin. It is not clear if this difference would lead to any significant accumulation differences of octreotide between oral octreotide and Sandostatin in SRI patients at steady-state.

2.5.3 Does hepatic dysfunction affect octreotide pharmacokinetics?

The safety and tolerability of oral octreotide acetate in subjects with cirrhosis and portal hypertension were investigated in study CH-PHT-01. This study also evaluated the effect of oral octreotide acetate on the hepatic venous pressure gradient (HVPG) in subjects with cirrhosis and portal hypertension. In Stage 1 of the study, eligible subjects received single oral dose of 10 mg oral octreotide acetate. Based on a Safety Monitoring Committee assessment of hemodynamic, safety and tolerability results of Group 1, a single oral dose of 20 mg oral octreotide acetate¹ was administered in Stage 2. Mean plasma octreotide concentrations following a single dose of 10 mg or 20 mg Mycapssa administered orally are shown in [Figure 22](#).

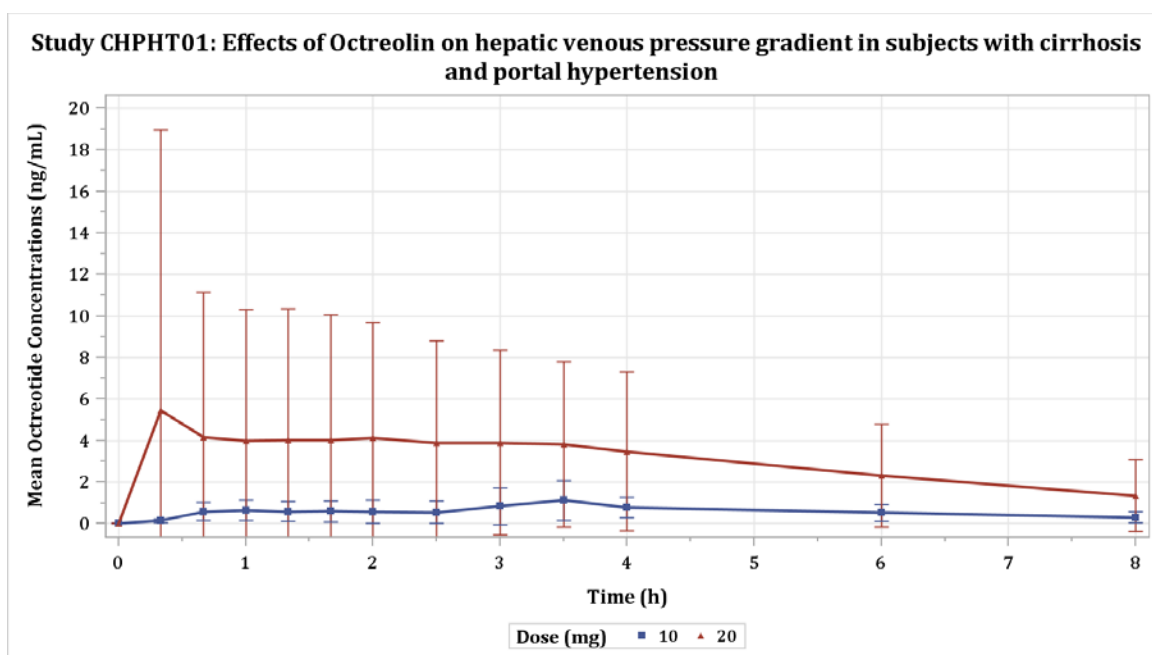


Figure 22 Mean plasma octreotide concentrations after oral administration of single 10 mg and 20 mg doses of oral octreotide acetate to patients with cirrhosis and portal hypertension

There was a dose-related but greater than dose-proportional increase in the mean plasma octreotide concentrations after administration of 10 mg and 20 mg. This is also apparent from examination of the arithmetic or geometric mean values for C_{max} , $AUC_{(0-t)}$, and AUC_{inf} (Table 14). The geometric mean ratios for C_{max} and AUC_{inf} were 3.4 and 5.1, respectively, greater than the 2 fold increase in dose. The mean elimination half-life ($t_{1/2}$) was comparable for both dose groups.

Table 14 Summary of Pharmacokinetic Parameters for Octreotide after oral administration of single 10 mg and 20 mg doses of oral octreotide acetate to patients with cirrhosis and portal hypertension

Parameter*	Dose	
	10 mg	20 mg
C _{max} (ng/mL)	1.33 ± 0.78 (6) [1.17; 60.0]	7.59 ± 12.9 (12) [3.99; 142]
T _{max} (h)	3.27 (6) [0.667 – 4.00]	2.33 (12) [0.333 – 6.00]
AUC(0-2) (h×ng/mL)†	1.12 ± 0.64 (5) [1.00; 55.0]	7.91 ± 13.8 (12) [3.61; 183]
AUC(0-t) (h×ng/mL)	4.67 ± 3.08 (6) [3.97; 68.3]	25.0 ± 32.5 (12) [15.5; 125]
AUC(inf) (h×ng/mL)	3.99 ± 1.86 (4) [3.62; 57.2]	32.9 ± 45.6 (10) [18.3; 154]
λ _z (1/h)	0.3524 ± 0.0657 (4)	0.2902 ± 0.0665 (10)
t _{1/2} (h)	2.02 ± 0.38 (4)	2.51 ± 0.60 (10)
Tlag (h)‡	3.02 (1) [3.02 – 3.02]	0.83 (2) [0.67 – 1.00]

*Mean ± standard deviation (N) [geometric mean, geometric %CV] except T_{lag} and T_{max} for which the median (N) [Range] is reported.

†AUC₀₋₂ was calculated for use in the pharmacokinetic/pharmacodynamic analyses.

‡A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCH-PHT-01, Table 11.2-2, Page 49)

An evaluation of the relationship between percent change from baseline to the minimal hepatic venous pressure gradient (HPVG) post-baseline and octreotide exposure as measured by either C_{max} or AUC₍₀₋₂₎ did not show any relationship (Figure 23).

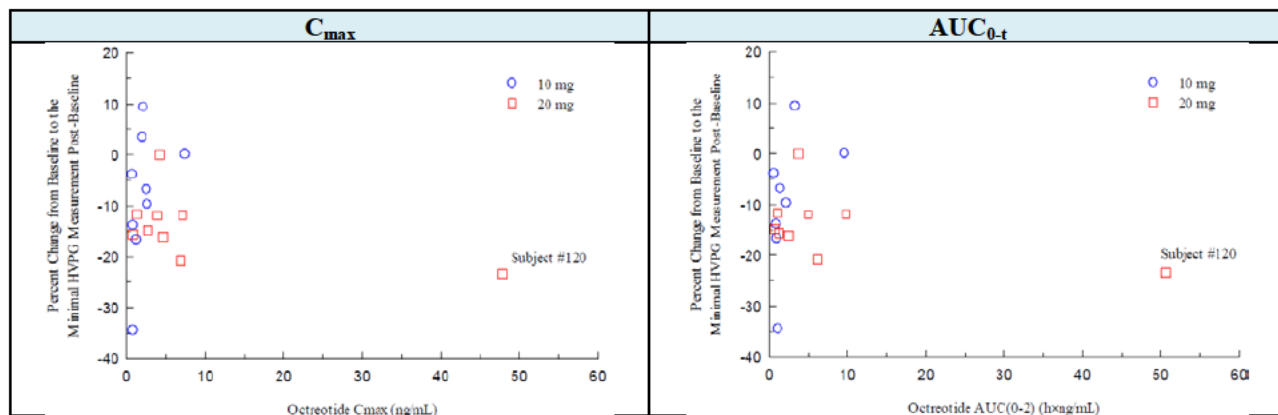


Figure 23 Relationship between the percent change from baseline to the minimal HPVG measurement post-baseline and octreotide C_{max} or AUC₀₋₂

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCH-PHT-01, Figures 11-5 and 11-6, Page 51)

Classification of the subjects who participated in the trial showed that of the 6 subjects that received 10 mg, 3 each were Child-Pugh Class A and Class B, and for the 20 mg group, 7 were Child-Pugh Class A

and 4 were Class B. There did not appear to be major differences in C_{max} , $AUC_{(0-t)}$, $AUC_{(inf)}$, or $t_{1/2}$ (Table 15) between Child-Pugh classes, however, the sample size within each dose level was small. Further, there was no control group in this study.

Table 15 Summary of pharmacokinetic parameters for octreotide after oral administration of single 10 mg and 20 mg doses of oral octreotide acetate to patients with cirrhosis and portal hypertension by Child-Pugh Class — Subject (b) (6) excluded.

Parameter*	Dose			
	10 mg		20 mg	
	Child-Pugh A	Child-Pugh B	Child-Pugh A	Child-Pugh B
C_{max} (ng/mL)	1.31 ± 0.60 (3) [1.22; 49.0]	1.35 ± 1.08 (3) [1.11; 85.3]	4.24 ± 2.13 (7) [3.81; 52.6]	3.41 ± 2.99 (4) [2.33; 145]
T_{max} (h)	3.53 (3) [1.00 – 4.00]	3.00 (3) [0.67 – 4.00]	4.00 (7) [0.33 – 6.00]	1.50 (4) [0.67 – 3.00]
$AUC_{(0-2)}$ (h×ng/mL)†	1.00 ± 0.13 (2) [1.00; 12.9]	1.20 ± 0.89 (3) [1.00; 82.6]	4.25 ± 3.04 (7) [3.15; 118]	3.63 ± 4.15 (4) [2.36; 135]
$AUC_{(0-t)}$ (h×ng/mL)	4.13 ± 1.16 (3) [4.00; 32.1]	5.21 ± 4.63 (3) [3.94; 117]	16.8 ± 7.80 (7) [15.19; 51.8]	14.8 ± 14.7 (4) [9.65; 156]
$AUC_{(inf)}$ (h×ng/mL)	4.70 ± 1.46 (3) [4.53; 36.0]	1.85 (1) [1.85; –]	19.6 ± 9.39 (6) [17.7; 53.4]	18.1 ± 23.3 (3) [9.54; 238]
λ_z (1/h)	0.3782 ± 0.0499 (3)	0.2750 (1)	0.3024 ± 0.0650 (6)	0.2986 ± 0.0628 (3)
$t_{1/2}$ (h)	1.85 ± 0.23 (3)	2.52 (1)	2.38 ± 0.51 (6)	2.40 ± 0.55 (3)
T_{lag} (h)‡	3.02 (1) [3.02 – 3.02]	—§	1.00 (1) [1.00 – 1.00]	0.67 (1) [0.67 – 0.67]

Source: PK Report Amendment 1, January 2, 2014

*Mean ± standard deviation (N) [geometric mean, geometric %CV] except T_{lag} and T_{max} for which the median (N) [Range] is reported.

† $AUC_{(0-2)}$ was calculated for use in the pharmacokinetic/pharmacodynamic analyses.

‡A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

§No subject exhibited a lag time.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCH-PHT-01, Table 11.5-2, Page 54)

A post-hoc analysis conducted by the sponsor showed that the PK of octreotide after administration of 10 mg or 20 mg of oral octreotide acetate in subjects with stable cirrhosis and portal hypertension appeared to be comparable to the PK in healthy volunteers.

Pharmacokinetics and safety in subjects with severe hepatic impairment (Child-Pugh Class C) were not evaluated.

2.5.4 What is the incidence of formation of antibodies to octreotide during and after the treatment? What is the impact of antibodies on PK, efficacy and safety?

According to the sponsor, to date, even though there have been reports of detection of treatment-emergent antibodies that are reactive with octreotide and lanreotide, there have been no reports of anti-octreotide antibodies reactive with native somatostatin.

2.6 Extrinsic Factors

2.6.1 Drug-Drug Interactions

The sponsor did not conduct any *in vitro* permeability, *in vitro* metabolism, or *in vitro* metabolic drug-drug interaction studies that used human biomaterials for this NDA.

The sponsor used permeation enhancers in the formulation to facilitate octreotide absorption across the intestinal membrane. These inactive ingredients are called collectively as “Transient Permeability Enhancer (TPE)”, and their activity is based on transient increased paracellular small intestinal absorption. The Lactulose/Mannitol (L/M) assay is a standard diagnostic test that measures paracellular and transcellular absorption. Mannitol is easily absorbed and serves as a marker of transcellular uptake, while lactulose is only slightly absorbed and serves as a marker for paracellular absorption. In a dedicated study (CHI-004) designed to assess the duration of Mycapssa-induced intestinal permeability after a single dose of Mycapssa 20 mg, the L/M assay was used serially under different test conditions to assess the duration of TPE-induced changes in intestinal permeability following Mycapssa administration. Intestinal permeability was characterized by lactulose percent recovery, mannitol percent recovery, and the ratio of L to M. Maximal L/M ratio was recorded 2 hours after Mycapssa treatment, indicating increased intestinal permeability. Within 5.5 hours of Mycapssa administration the L/M ratio was back to basal levels recorded in non-treated subjects. This basal ratio was also maintained at 10 hours post Mycapssa administration.

Mycapssa capsule has a pH-sensitive enteric coating designed to withstand the acid environment of the stomach and deliver octreotide acetate to the small intestine for absorption. Drugs that elevate gastric pH, such as Proton pump inhibitors (PPI) have the potential of disrupting the capsule’s ability to stay intact in the stomach until it reaches the small intestine for absorption. Similarly motility inducers or inhibitors may affect the absorption pattern by changing the residence time of the capsule in the stomach. In order to address these issues, the sponsor conducted various drug-drug interaction (DDI) studies.

According to the Sandostatin package insert “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 growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution”. The sponsor has evaluated the effect of Mycapssa on drugs such as digoxin, lisinopril, oral contraceptives, metformin, warfarin, hydrochlorothiazide and cyclosporine.

(A) Effect of Other Drugs on Oral Octreotide:

2.6.1.1 What is the effect of a proton pump inhibitor (PPI) co-administration on the pharmacokinetics of oral octreotide?

The sponsor conducted study CHI-005 to evaluate the influence of concomitant PPI administration on the PK and bioavailability of octreotide after oral administration of Mycapssa in healthy male and female subjects, to evaluate the effect of change in gastric pH on the bioavailability of Mycapssa.

The rationale was that the bioavailability of Mycapssa may be potentially influenced by increase in gastric pH because the enteric-coating of the capsules, which is pH sensitive, might open prematurely in the stomach where Mycapssa may be inactivated. Therefore, PPIs such as Nexium (esomeprazole) that cause a significant and long-lasting elevation of gastric pH, may affect the absorption of Mycapssa.

The PK of Mycapssa was assessed before and after a 5-day administration of the selected PPI (esomeprazole, Nexium®). Oral octreotide was administered on Day 1 after a 10-hour overnight fast, followed by esomeprazole on Days 2-6 at least one hour before a meal. On Day 7, one Mycapssa 20 mg capsule and one Nexium 40 mg tablet were administered after a 10-hour overnight fast. The dose and duration of Nexium administration was sufficient to assure sustained reduction of gastric acidity.

As seen from [Figure 24](#), the mean plasma concentrations of octreotide were reduced when Mycapssa was administered after six days of dosing with esomeprazole 40 mg as compared to Mycapssa alone.

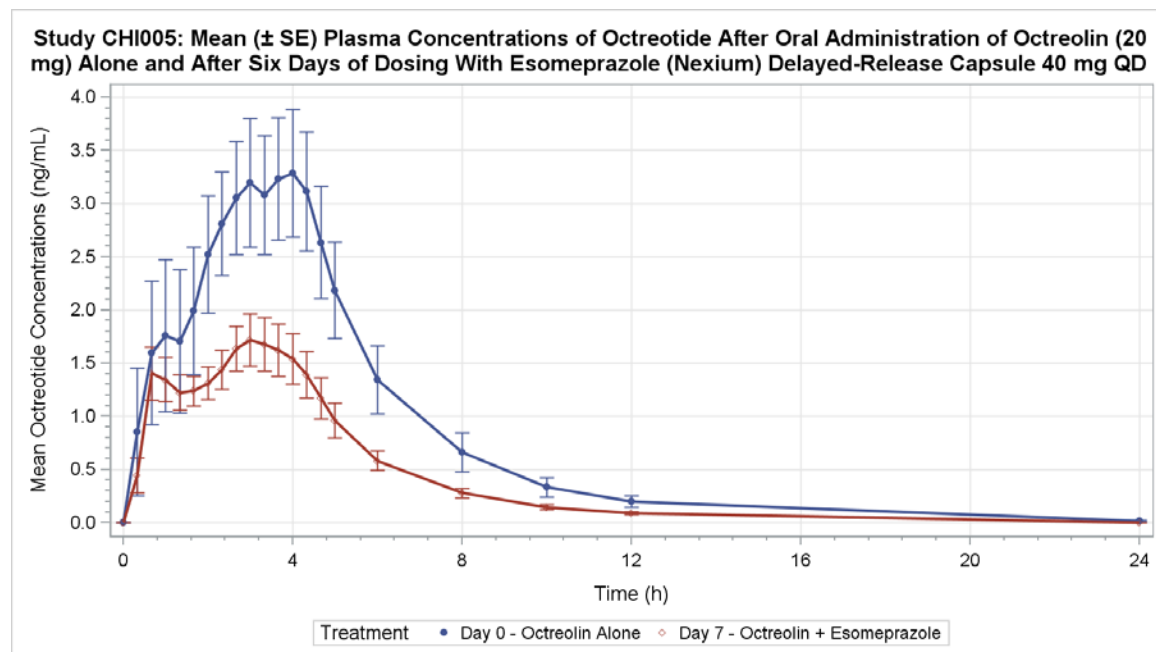


Figure 24 Mean plasma octreotide concentrations after oral administration of Mycapssa 20 mg alone and after six days of dosing with esomeprazole (Nexium) delayed-release capsule 40 mg QD

The geometric mean ratios of C_{max} , AUC_{0-t} , and AUC_{0-inf} for Mycapssa plus esomeprazole to Mycapssa alone, ranged from 54.80% to 59.14% demonstrating a significant reduction in the extent of absorption when Mycapssa is administered with a PPI ([Table 16](#)).

Therefore, co-administration of Mycapssa with PPIs antacids may require higher dosing of Mycapssa to achieve therapeutic levels.

Table 16 Statistical comparison of pharmacokinetic parameters for octreotide after oral administration of Mycapssa 20 mg alone and after six days of dosing with esomeprazole (Nexium) delayed-release capsule 40 mg QD

Parameter	Geometric Mean Ratio (%) [*]	
	Estimate	90% Confidence Interval
Day 0 vs. Day 7		
C _{max}	54.80	40.07 → 74.95
AUC(0-t)	59.04	39.78 → 87.63
AUC(inf)	59.14	40.11 → 87.20

^{*}Based on analysis of natural log-transformed pharmacokinetic parameters.

[†]Lower confidence limits that are < 80.00% and upper confidence limits that are > 125.00% are shown in red.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCHI-005, Panel 10.5-2, Page 39)

The median duration during which plasma octreotide concentrations were ≥ 0.5 ng/mL and 1 ng/mL were 5.33 h and 4.00 h, respectively following Mycapssa alone, and 5.00 h and 3.33 h following co-administration of Mycapssa and esomeprazole.

2.6.1.2 What is the effect of co-administration of Drugs that affect gastrointestinal motility on the pharmacokinetics of oral octreotide?

Study OCT-03, conducted by the sponsor had multiple objectives:

- To evaluate the effects of concomitantly administered metoclopramide on the absorption, pharmacokinetics (PK) and bioavailability of octreotide from oral octreotide acetate
- To evaluate the effects of concomitantly administered loperamide on the absorption, PK and bioavailability of octreotide from oral octreotide acetate
- To evaluate the effects of body posture (sitting or standing) on the absorption, PK and bioavailability of octreotide from oral octreotide acetate
- To evaluate the absorption of octreotide from oral octreotide acetate when administered at night, prior to going to bed.

The sponsor's rationale for this study was that gastrointestinal motility follows a circadian rhythm, with reduced activity during sleep⁴, which may alter the length of oral octreotide acetate exposure to the intestinal lumen. Oral octreotide acetate administration time (morning vs. night time) may have an impact on its pharmacokinetics due to differences in GI motility and posture changes in GI blood flow. This study assessed the PK of octreotide when administered concomitantly with drugs affecting the GI motility, in two body postures, and after morning and night dosing. Metoclopramide is a prokinetic agent commonly used to relieve symptoms caused by slow stomach emptying including nausea and vomiting and to relieve heartburn. Loperamide is an opiate receptor agonist used to control diarrhea. Metoclopramide was chosen in this study because it is one of the most commonly used gastrointestinal

⁴ Furukawa Y, Cook IJ, Panagopoulos V, et al. Relationship between sleep patterns and human colonic motor patterns. *Gastroenterology* 1994; **107**(5):1372-1381.

prokinetic drugs. Oral loperamide was chosen because of its known effects on reducing gastrointestinal motility and in delaying gastric emptying⁵.

Effect of posture on the absorption of octreotide will be discussed in a subsequent section.

(a) Effect of Metoclopramide on absorption, pharmacokinetics (PK) and bioavailability of octreotide

During this part of the study, metoclopramide 20 mg oral, was administered 2 hours prior to the administration of 40 mg oral octreotide acetate in the morning in a sitting posture.

Metoclopramide being a gastroprokinetic agent, increases gastric motility. Administration of oral octreotide acetate 2 hours after a 20 mg oral dose of metoclopramide resulted in a slight decrease in the mean plasma concentrations of octreotide ([Figure 25](#)).

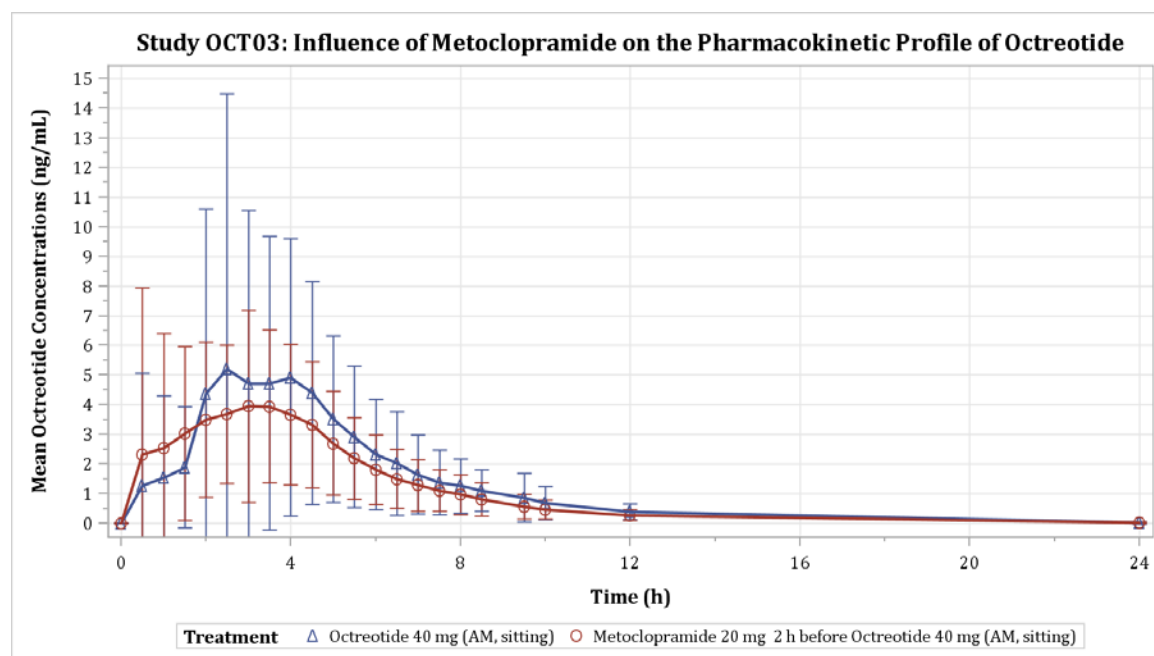


Figure 25 Mean plasma octreotide concentrations after oral administration of Mycapssa 40 mg alone and 2 Hours After a 20-mg Dose of Metoclopramide to Healthy Volunteers Under Fasted Conditions

Mean pharmacokinetic parameters for octreotide following both treatments is presented in Table 15. The least squares mean ratio for C_{max} , AUC_{0-t} , and AUC_{inf} were 95.02%, 87.45%, and 76.98%, respectively ([Table 17](#)), indicating that when oral octreotide acetate was administered 2 hours after a 20 mg oral dose of metoclopramide, there is a decrease of about 13% - 23 % in the extent of absorption ([Table 18](#)). Median T_{max} was unchanged between the two treatments. Mycapssa dose is titrated based on clinical response and therefore these changes in the extent of absorption do not necessitate any dosage adjustment when co-administering with Metoclopramide.

⁵ Sninsky CA, Davis RH, Clench MH, et al. Effect of lidamidine hydrochloride and loperamide on gastric emptying and transit of the small intestine. A double-blind study. *Gastroenterology* 1986; **90**(1):68-73

Table 17 Summary of Pharmacokinetic Parameters for Octreotide After Oral Administration of Single 40-mg (2 × 20 mg) Doses Alone and 2 Hours After a 20-mg Dose of Metoclopramide to Healthy Volunteers Under Fasted Conditions

Parameter*	Oral Octreotide Acetate Alone	Oral Octreotide Acetate with Metoclopramide
Tlag (h)†	1.24 (4) [0.95 – 1.50]	1.50 (1) [1.50 – 1.50]
Cmax (ng/mL)	7.81 ± 9.35 (18)	6.36 ± 5.45 (18)
Tmax (h)	3.00 (18) [0.50 – 9.50]	3.00 (18) [0.52 – 4.52]
AUC(0-t) (h×ng/mL)	28.5 ± 24.9 (18)	24.4 ± 14.9 (18)
AUC(inf) (h×ng/mL)	29.1 ± 24.9 (18)	24.6 ± 14.9 (18)
λz (1/h)	0.2979 ± 0.0938 (18)	0.2498 ± 0.0745 (18)
t½ (h)	2.60 ± 0.95 (18)	2.99 ± 0.77 (18)

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

AUC(0-t) = area under the concentration-time curve to the final sample with a concentration ≥ the limit of quantitation; AUC(inf) = area under the concentration-time curve from 0 extrapolated to infinity; Cmax = maximum plasma concentration; λz = elimination rate constant; LOQ = limit of quantitation; t½ = half-life; Tlag = absorption lag time; Tmax = time of maximum plasma concentration

Table 18 Statistical Comparison of Pharmacokinetic Parameters for Octreotide After Oral Administration of Single 40-mg (2 × 20 mg) Doses Alone and 2 Hours After a 20-mg Dose of Metoclopramide to Healthy Volunteers Under Fasted Conditions

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	87.45	58.55 - 130.63
AUC(0-inf) for Octreotide	ng·h/mL	76.98	50.57 - 117.17
Cmax for Octreotide	ng/mL	95.02	62.44 - 144.61

The time octreotide plasma concentrations were ≥ 0.5 ng/mL and 1 ng/mL were 9.00 hours and 6.00 hours, respectively following octreotide alone treatment, and 11.0 hours and 7.25 hours, respectively, following administration of octreotide 2-hours following metoclopramide administration. The ranges were comparable and neither increase was statistically significant.

(b) Effect of Loperamide on absorption, pharmacokinetics (PK) and bioavailability of octreotide

During this part of the study, loperamide 4 mg oral, was administered 2 hours prior to the administration of 40 mg oral octreotide acetate in the morning in a sitting posture.

Loperamide is a synthetic antidiarrheal that works, in part, by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. Administration of oral octreotide acetate 2 hours

after a 4 mg oral dose of loperamide resulted in similar mean plasma octreotide concentrations ([Figure 26](#)).

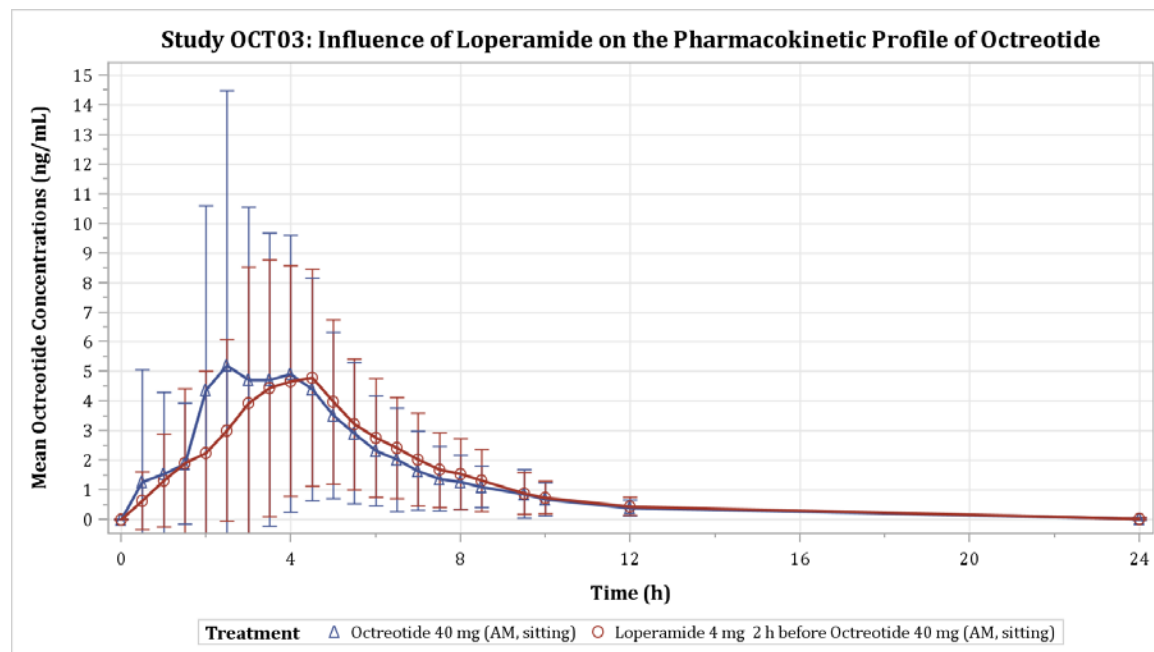


Figure 26 Mean plasma octreotide concentrations after oral administration of Mycapssa 40 mg alone and 2 Hours After a 4 mg Dose of Loperamide to Healthy Volunteers Under Fasted Conditions

Mean pharmacokinetic parameters for octreotide following both treatments is presented in [Table 19](#). The least squares mean ratio for C_{max} , AUC_{0-t} , and AUC_{inf} were 90.55%, 95.21%, and 91.21%, respectively ([Table 19](#)), indicating that when oral octreotide acetate was administered 2 hours after a 20 mg oral dose of metoclopramide, there is a small decrease of about 5% - 9 %in the extent of absorption, and about 10% decrease in the rate of absorption ([Table 20](#)).

Table 19 Summary of Pharmacokinetic Parameters for Octreotide After Oral Administration of Single 40-mg (2 × 20 mg) Doses Alone and 2 Hours After a 4-mg Dose of Loperamide to Healthy Volunteers Under Fasted Conditions

Parameter*	Oral Octreotide Acetate Alone	Oral Octreotide Acetate with Loperamide
Tlag (h)†	1.24 (4) [0.95 – 1.50]	1.00 (6) [1.00 – 2.50]
Cmax (ng/mL)	7.81 ± 9.35 (18)	5.80 ± 4.34 (18)
Tmax (h)	3.00 (18) [0.50 – 9.50]	3.98 (18) [2.00 – 4.98]
AUC(0-t) (h×ng/mL)	28.5 ± 24.9 (18)	27.7 ± 20.6 (18)
AUC(inf) (h×ng/mL)	29.1 ± 24.9 (18)	29.1 ± 20.7 (17)
λz (1/h)	0.2979 ± 0.0938 (18)	0.2477 ± 0.0651 (17)
t½ (h)	2.60 ± 0.95 (18)	2.99 ± 0.80 (17)

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

AUC(0-t) = area under the concentration-time curve to the final sample with a concentration ≥ the limit of quantitation; AUC(inf) = area under the concentration-time curve from 0 extrapolated to infinity; Cmax = maximum plasma concentration; λz = elimination rate constant; LOQ = limit of quantitation; t½ = half-life; Tlag = absorption lag time; Tmax = time of maximum plasma concentration

Table 20 Statistical Comparison of Pharmacokinetic Parameters for Octreotide After Oral Administration of Single 40-mg (2 × 20 mg) Doses Alone and 2 Hours After a 4-mg Dose of Loperamide to Healthy Volunteers Under Fasted Conditions

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	95.21	66.25 - 136.84
AUC(0-inf) for Octreotide	ng·h/mL	91.23	60.35 - 137.91
Cmax for Octreotide	ng/mL	90.55	61.02 - 134.39

The median T_{max} increased from 3.00 h when oral octreotide acetate was administered alone to 3.98 h after administration after loperamide ([Figure 27](#)), but the difference was not significant.

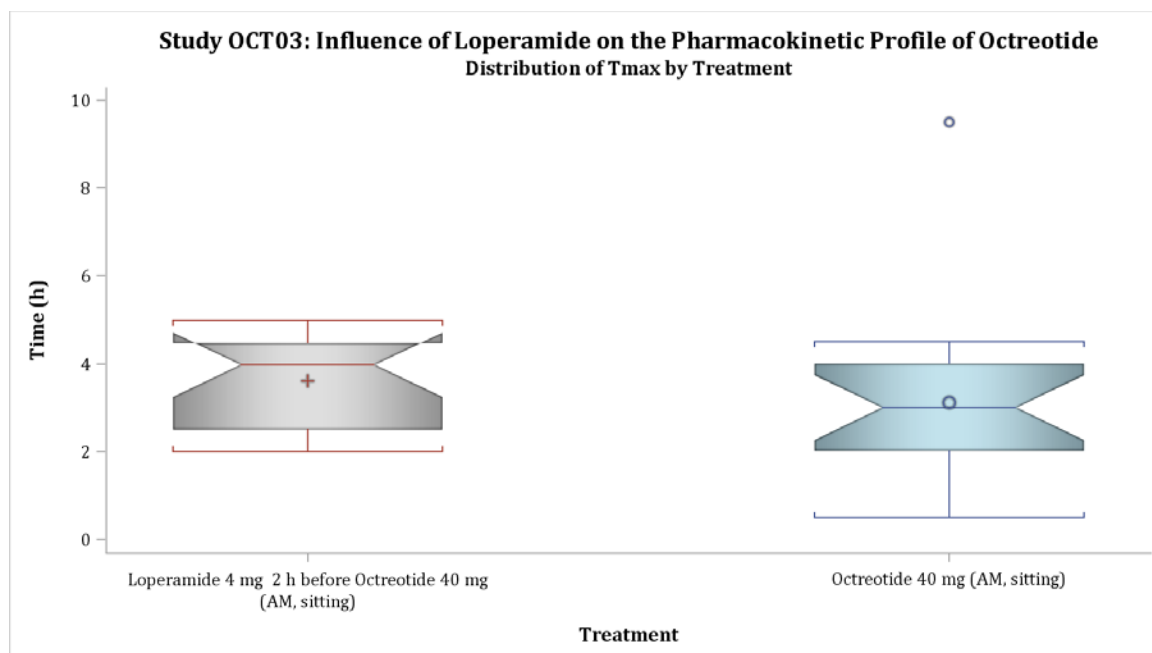


Figure 27 Distribution of T_{max} after oral administration of Mycapssa 40 mg alone and 2 Hours After a 4 mg Dose of Loperamide to Healthy Volunteers Under Fasted Conditions

The time plasma concentrations were ≥ 0.5 ng/mL and 1 ng/mL were 9.00 hours and 6.00 hours, respectively following octreotide alone treatment, and 11.5 hours and 5.75 hours, respectively, following administration of octreotide 2-hours following metoclopramide administration. The ranges were comparable and neither increase was statistically significant.

As Mycapssa dose is titrated based on clinical response, the 9-10% decrease in bioavailability does not necessitate any dosage adjustment when co-administering with Loperamide.

(B) Effect of Oral Octreotide on Other Drugs:

Mycapssa is formulated with TPE which can affect intestinal permeability. Therefore, sponsor evaluated the effect of oral octreotide on the absorption of other drugs (lisinopril, digoxin, metformin, warfarin, hydrochlorothiazide, and oral contraceptive). The DDI results are described below. All these studies utilized the “cocktail” design approach. However, the sponsor had limited PK sampling in these studies for a period of only 0-5 h post-dose. Hence the study results do not completely characterize the PK of the other drugs. However, the goal here was to evaluate the impact of oral octreotide on the other drugs absorption, which was captured in the 0-5 h sampling period. Hence these studies were found to be acceptable.

2.6.1.3 What is the effect of oral octreotide co-administration on the pharmacokinetics of Lisinopril and Digoxin

The PK of digoxin and lisinopril when administered concomitantly with oral octreotide acetate was investigated in Study OCT-02. The rationale for the study was that the TPE formulation in oral octreotide acetate might affect bioavailability of other orally administered representative probe drugs commonly used by acromegaly patients. The potential for drug-drug interaction (DDI) of oral octreotide acetate with

oral drugs was evaluated in this study. The sponsor chose Lisinopril as a drug with low permeability, and digoxin as a drug with a narrow therapeutic window.

(a) Influence of Octreotide on Lisinopril:

Administration of lisinopril concomitant with oral octreotide acetate resulted in an increase in lisinopril plasma concentrations compared to Lisinopril alone (Figure 28). C_{max} increased 50%, and AUC_{0-12} increased 40% (Table 21). The median T_{max} values were comparable when lisinopril was administered alone or with oral octreotide acetate. Hence, the dose of Lisinopril may need to be adjusted when administered concomitantly with Mycapssa.

Statistical comparisons of the two treatments are shown in Table 22.

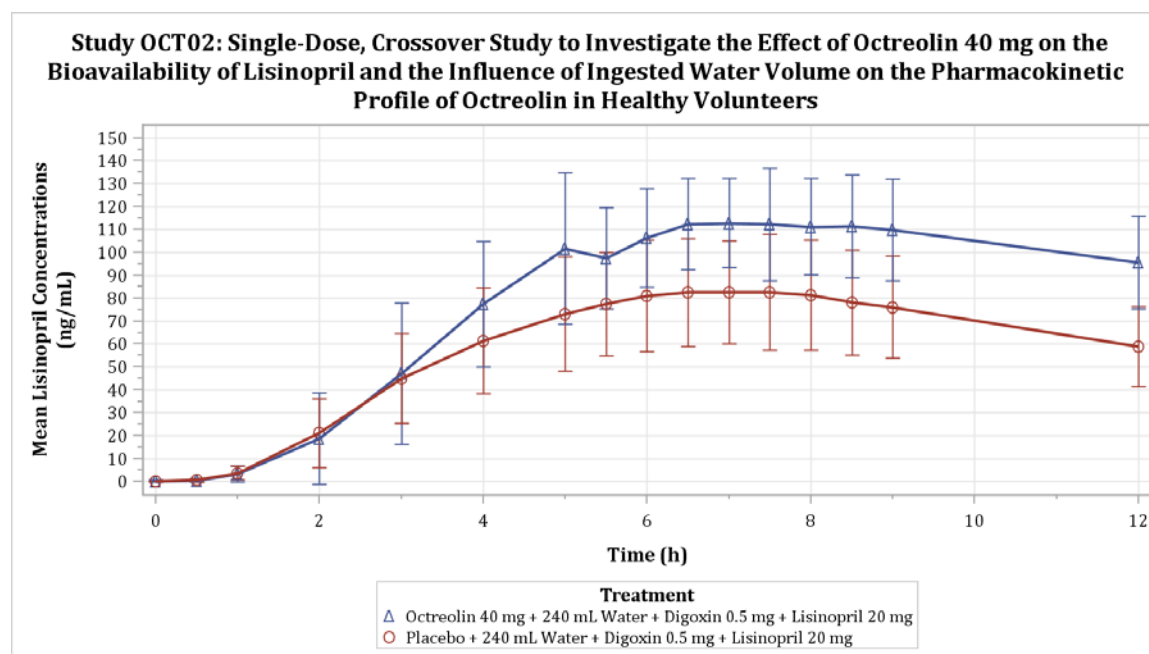


Figure 28 Mean Plasma Concentrations of Lisinopril After Oral Administration of Single 20 mg Doses to Healthy Volunteers With and Without a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate

Table 21: Summary of Lisinopril Pharmacokinetic Parameters After Oral Administration of Single 20 mg Doses to Healthy Volunteers With and Without a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate

Parameter*	Lisinopril† With Octreolin	Lisinopril† Alone
C _{max} (ng/mL)	128 ± 27.9 (17)	87.0 ± 24.2 (17)
T _{max} (h)	7.00 (17) [5.00 – 9.00]	7.50 (17) [6.50 – 9.00]
AUC(0-12) (h×ng/mL)	939 ± 189 (17)	690 ± 207 (17)

*Mean ± standard deviation (N) except T_{lag} and T_{max} for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

Table 22: Statistical Comparison of Pharmacokinetic Parameters for Lisinopril After Oral Administration of Single 20 mg Doses to Healthy Volunteers With and Without a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Lisinopril	ng·h/mL	139.74	121.84 - 160.26
C _{max} for Lisinopril	ng/mL	150.01	132.23 - 170.18

(b) Influence of Octreotide on Digoxin:

Administration of digoxin concomitant with oral octreotide acetate resulted in a decrease in digoxin plasma concentrations compared to digoxin alone ([Figure 29](#)). C_{max} decreased 37%, while AUC₀₋₁₂ was unchanged ([Table 23](#)), indicating that only the rate of absorption of digoxin was affected when administered concomitantly with oral octreotide.

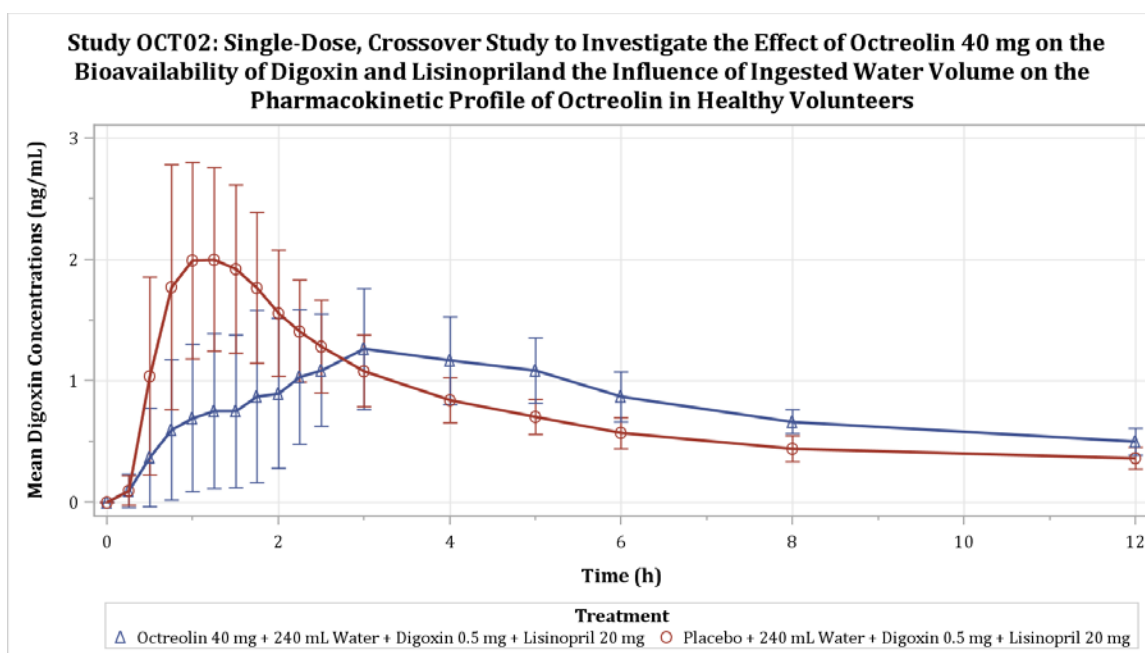


Figure 29 Mean Plasma Concentrations of Digoxin After Oral Administration of Single 20 mg Doses to Healthy Volunteers With and Without a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate

Table 23: Summary of Digoxin Pharmacokinetic Parameters After Oral Administration of Single 0.5 mg Doses to Healthy Volunteers With and Without a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate

Parameter*	Digoxin† With Octreolin	Digoxin† Alone
C _{max} (ng/mL)	1.55 ± 0.46 (17)	2.50 ± 0.71 (17)
T _{max} (h)	3.00 (17) [0.75 – 5.00]	1.00 (17) [0.75 – 2.50]
AUC(0-12) (h×ng/mL)	9.42 ± 2.09 (17)	9.14 ± 2.03 (17)

*Mean ± standard deviation (N) except T_{lag} and T_{max} for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

(Source: eCTD Module 5.3.1.2, Clinical Trial Report for StudyOCT-02, Table 13 Page 47)

The median T_{max} values for digoxin increased from 1 hour to 3 hours when digoxin was administered with oral octreotide acetate, compared to digoxin alone ([Figure 30](#)). Statistical comparisons of the two treatments are shown in [Table 24](#).

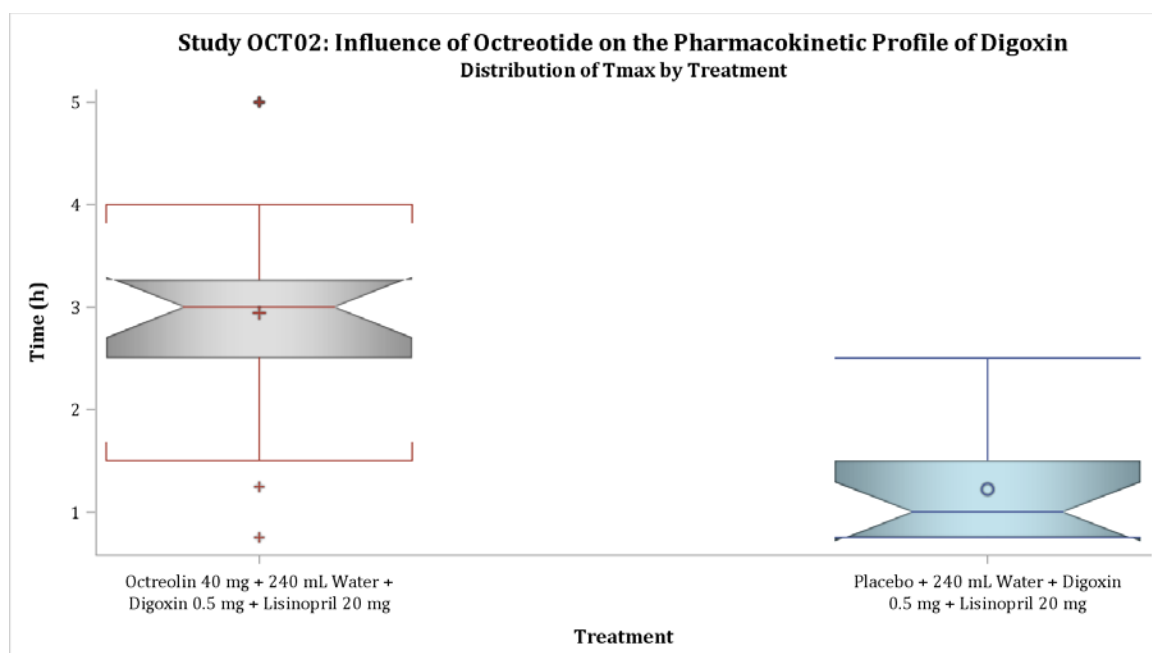


Figure 30 Median T_{max} Values of Digoxin After Oral Administration of Single 20 mg Doses to Healthy Volunteers With and Without a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate

Table 24: Statistical Comparison of Pharmacokinetic Parameters for Digoxin After Oral Administration of Single 0.5 mg Doses to Healthy Volunteers With and Without a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Digoxin	ng·h/mL	103.24	94.64 - 112.62
Cmax for Octreotide		62.59	54.89 - 71.38

Digoxin is a narrow therapeutic index drug and is monitored in patients. As concomitant administration of Mycapssa with digoxin results in decreased blood levels of digoxin, patients taking these drugs concomitantly should follow instructions in the product monograph for digoxin for appropriate monitoring of digoxin levels and dose adjustment, if necessary.

2.6.1.4 What is the effect of oral octreotide co-administration on the pharmacokinetics of Warfarin?

According to the sponsor, the TPE formulation in oral octreotide acetate might affect bioavailability of other orally administered representative probe drugs commonly used by acromegaly patients. Probe drugs with the following specific characterizations were included for the evaluation of potential drug-drug interaction: (i) drugs with low permeability such as metformin and hydrochlorothiazide (HCTZ), and (ii) drugs with a narrow therapeutic window such as warfarin and oral contraceptives.

R-Warfarin:

Administration of warfarin concomitant with oral octreotide acetate resulted in no change in R-warfarin plasma concentrations compared to warfarin administration with placebo (Figure 31). C_{max} and AUC_{0-5} were unchanged (Table 25), and the 90% confidence intervals were contained within the 80.00% - 125.00% limits. The median T_{max} values for R-warfarin increased from 1 hour to 2 hours when warfarin was administered with oral octreotide acetate, compared to warfarin administration with placebo. Statistical comparisons of the two treatments are shown in Table 26.

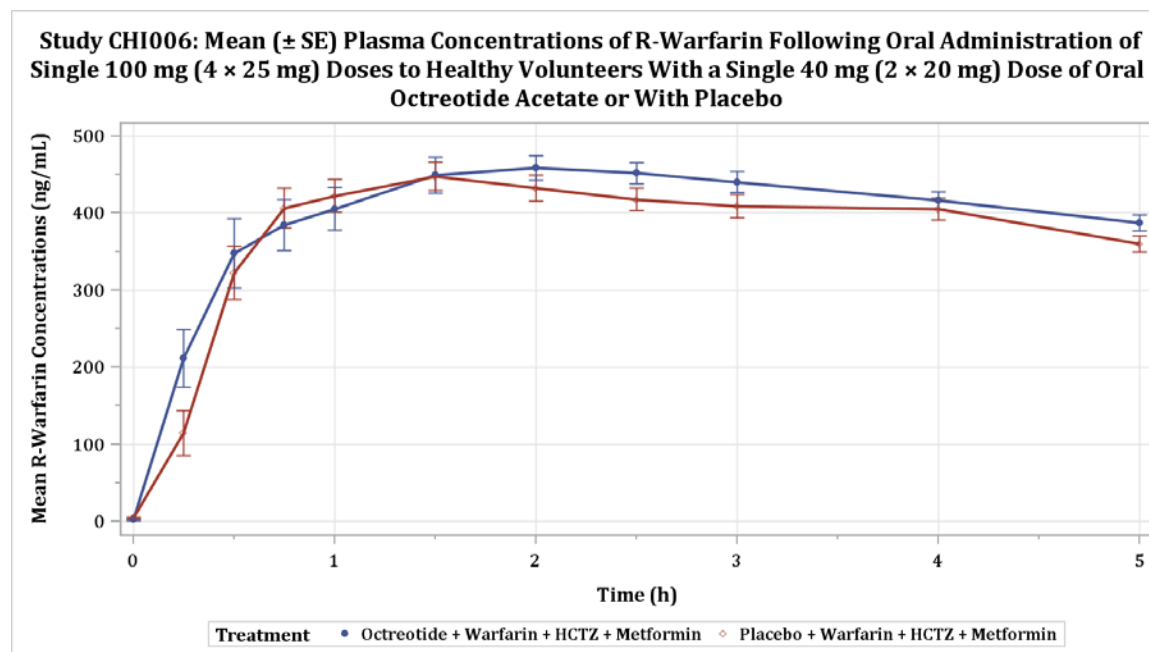


Figure 31 Mean Plasma Concentrations of R-Warfarin After Oral Administration of Single 7.5 mg Doses of Racemic Warfarin to Healthy Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Table 25 Summary of Pharmacokinetic Parameters for R-Warfarin after Oral Administration of Single 7.5 mg Doses of Racemic Warfarin to Healthy Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter*	Oral Octreotide Acetate	
	With	Without
C_{max} (ng/mL)	508 ± 97.0 (18)	498 ± 82.0 (18)
T_{max} (h)	2.00 (18) [0.50 – 5.00]	1.00 (18) [0.50 – 4.00]
$AUC(0-5)$ (h $\times$ ng/mL)	$2,012 \pm 348$ (18)	$1,907 \pm 280$ (18)

*Mean $\pm$ standard deviation (N) except T_{max} for which the median (N) [Range] is reported.
(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 9 Page 46)

Table 26 Statistical Comparison of Pharmacokinetic Parameters for R-Warfarin After Oral Administration of Single 7.5 mg Doses of Racemic Warfarin to Healthy Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter	Geometric Mean*		Geometric Mean Ratio (%)†	
	Test	Reference	Estimate	90% Confidence Interval
R-Warfarin with Octreolin vs. R-Warfarin with Placebo				
C _{max}	500.10	491.04	101.84	93.91 → 110.45
AUC(0-5)	1,984.36	1,886.85	105.17	99.62 → 111.02

*Least squares geometric means. Based on analysis of natural log-transformed pharmacokinetic parameters.

†Lower confidence interval limits < 80.00% and upper confidence interval limits > 125.00% are shown in red.

Warfarin was coadministered with HCTZ and metformin.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 10 Page 47)

S-Warfarin:

Administration of warfarin concomitant with oral octreotide acetate resulted in no change in S-warfarin plasma concentrations compared to warfarin administration with placebo (Figure 32). C_{max} and AUC₀₋₅ were unchanged (Table 27), and the 90% confidence intervals were contained within the 80.00% - 125.00% limits. The median T_{max} values for S-warfarin increased from 1 hour to 1.5 hours when warfarin was administered with oral octreotide acetate, compared to warfarin administration with placebo. Statistical comparisons of the two treatments are shown in Table 28.

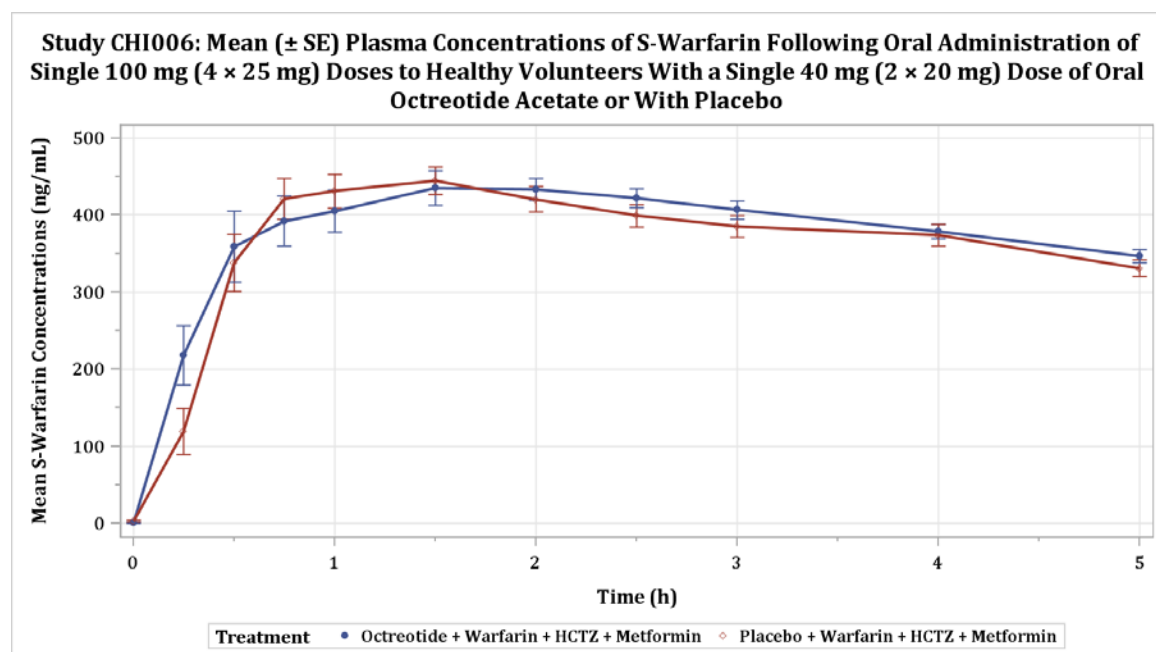


Figure 32 Mean Plasma Concentrations of S-Warfarin After Oral Administration of Single 7.5 mg Doses of Racemic Warfarin to Healthy Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Table 27: Summary of Pharmacokinetic Parameters for S-Warfarin After Oral Administration of Single 7.5 mg Doses of Racemic Warfarin to Healthy Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter*	Oral Octreotide Acetate	
	With	Without
C _{max} (ng/mL)	492 ± 114.2 (18)	503 ± 91.2 (18)
T _{max} (h)	1.50 (18) [0.30 – 5.00]	1.00 (18) [0.50 – 4.00]
AUC(0-5) (h×ng/mL)	1,894 ± 330 (18)	1,846 ± 286 (18)

*Mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 11 Page 48)

Table 28 Statistical Comparison of Pharmacokinetic Parameters for S-Warfarin After Oral Administration of Single 7.5 mg Doses of Racemic Warfarin to Healthy Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter	Geometric Mean*		Geometric Mean Ratio (%)†	
	Test	Reference	Estimate	90% Confidence Interval
S-Warfarin with Octreolin vs. S-Warfarin with Placebo				
C _{max}	480.09	494.64	97.06	88.49 → 106.46
AUC(0-5)	1,867.56	1,824.19	102.38	97.21 → 107.82

*Least squares geometric means. Based on analysis of natural log-transformed pharmacokinetic parameters.

†Lower confidence interval limits < 80.00% and upper confidence interval limits > 125.00% are shown in red.

Warfarin was coadministered with HCTZ and metformin.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 12 Page 49)

Though it appears that no recommendation for dosage adjustment for warfarin is needed when co-administering with Mycapssa, the data to base the recommendation on may be inadequate. Warfarin's reported half-life is 20-60 hours, and a sampling time of only 5 hours may not completely characterize the influence of Mycapssa on Warfarin's pharmacokinetics.

2.6.1.5 What is the effect of oral octreotide co-administration on the pharmacokinetics of Hydrochlorothiazide?

Administration of hydrochlorothiazide concomitant with oral octreotide acetate resulted in lower hydrochlorothiazide plasma concentrations compared to hydrochlorothiazide administration with placebo (Figure 33). C_{max} and AUC₀₋₅ were lower by 9% and 18%, respectively (Table 29), and the 90% confidence intervals were contained within the 80.00% - 125.00% limits only for C_{max}. The median T_{max} values for hydrochlorothiazide increased from 2.75 hour to 4.00 hours when hydrochlorothiazide was administered with oral octreotide acetate, compared to hydrochlorothiazide administration with placebo. Statistical comparisons of the two treatments are shown in Table 30.

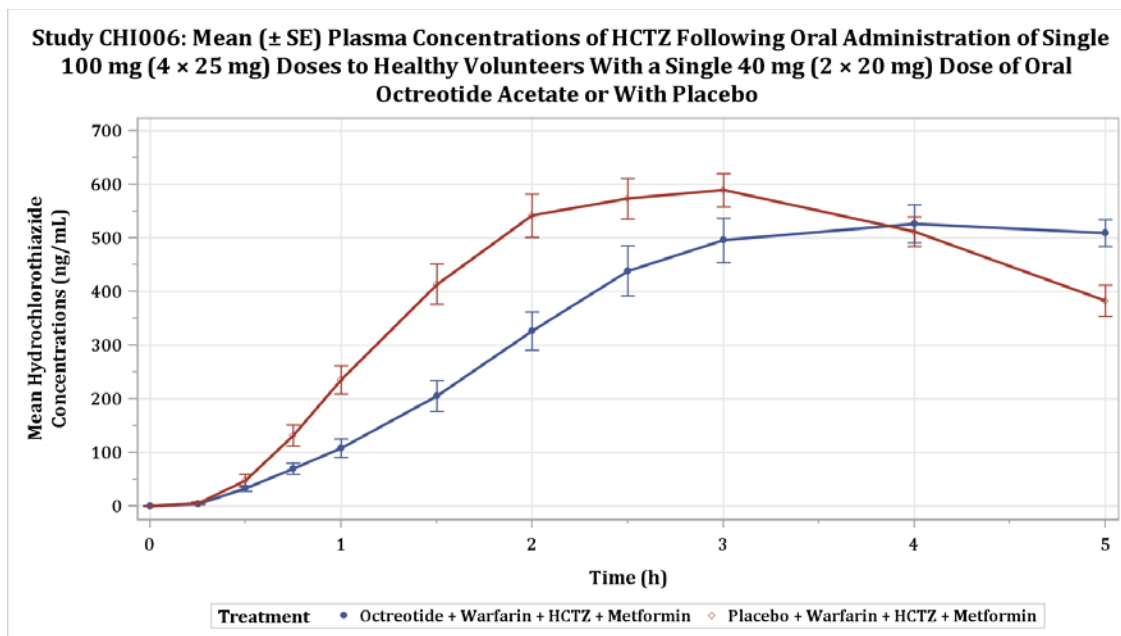


Figure 33 Mean Plasma Concentrations of HCTZ After Oral Administration of Single 100 mg (4×25 mg) Doses to Healthy Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Table 29 Summary of Pharmacokinetic Parameters for HCTZ After Oral Administration of Single 100 mg (4 × 25 mg) Doses to Healthy Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter*	Oral Octreotide Acetate	
	With	Without
C _{max} (ng/mL)	602 ± 141 (18)	655 ± 128 (18)
T _{max} (h)	4.00 (18) [2.50 – 5.05]	2.75 (18) [2.00 – 5.00]
AUC(0-5) (h×ng/mL)	1,722 ± 537 (18)	2,034 ± 392 (18)

*Mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 13 Page 50)

Table 30 Statistical Comparison of Pharmacokinetic Parameters for HCTZ After Oral Administration of Single 100 mg (4 × 25 mg) Doses to Healthy Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter	Geometric Mean*		Geometric Mean Ratio (%)†	
	Test	Reference	Estimate	90% Confidence Interval
HCTZ with Oral Octreotide Acetate vs. HCTZ with Placebo				
C _{max}	586.50	643.03	91.21	81.77 → 101.73
AUC(0-5)	1,633.38	1,996.30	81.82	70.97 → 94.33

*Least squares geometric means. Based on analysis of natural log-transformed pharmacokinetic parameters.

†Lower confidence interval limits < 80.00% and upper confidence interval limits > 125.00% are shown in red.

HCTZ was coadministered with warfarin and metformin.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 14 Page 51)

Though it appears that no recommendation for dosage adjustment for hydrochlorothiazide is needed when co-administering with Mycapssa, the data to base the recommendation on may be inadequate. When co-administered with Mycapssa, plasma profiles of hydrochlorothiazide at 5 hours did not yet appear to be in the elimination phase. Hydrochlorothiazide's reported half-life is 5.6-15.8 hours, and a sampling time of only 5 hours may not completely characterize the influence of Mycapssa on hydrochlorothiazide's pharmacokinetics.

2.6.1.6 What is the effect of oral octreotide co-administration on the pharmacokinetics of Metformin?

Administration of metformin concomitant with oral octreotide acetate resulted in a slower rate of absorption when metformin was administered with oral octreotide compared to placebo (Figure 34). C_{max} was higher by 11% and AUC₀₋₅ was lower by 5% (Table 31), and the 90% confidence intervals were contained within the 80.00% - 125.00% limits for both parameters.

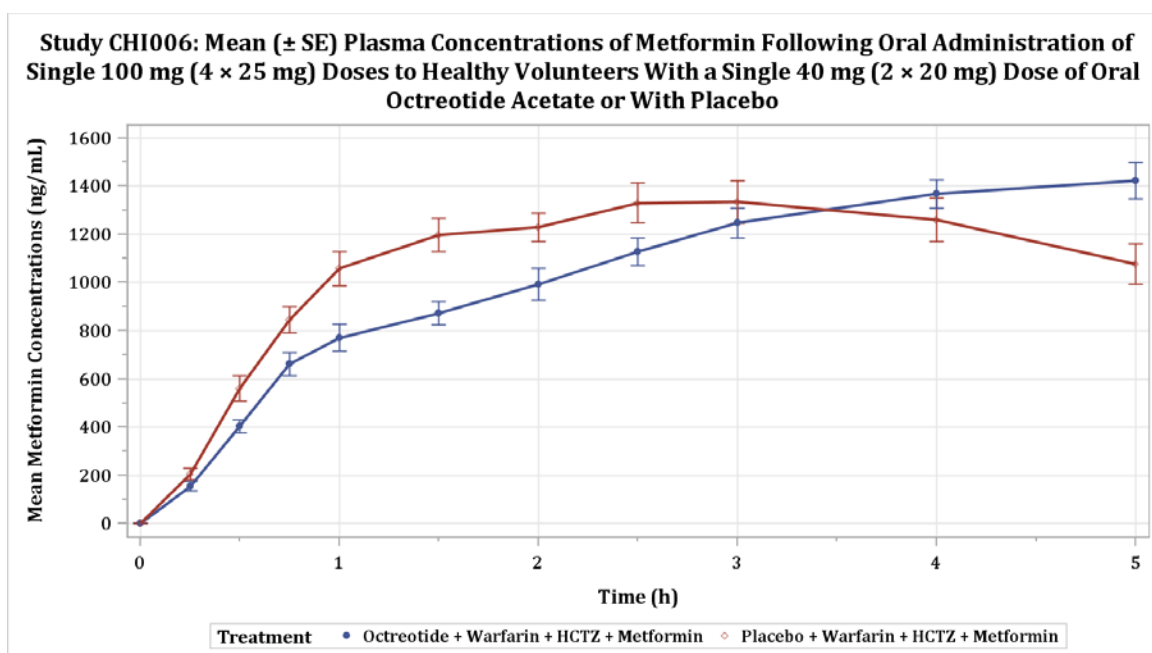


Figure 34 Mean Plasma Concentrations of Metformin After Oral Administration of Single 850 mg Doses to Healthy Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Table 31 Summary of Pharmacokinetic Parameters for Metformin After Oral Administration of Single 850 mg Doses to Healthy Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter*	Oral Octreotide Acetate	
	With	Without
C _{max} (ng/mL)	1,566 $\pm$ 242 (18)	1,450 $\pm$ 398 (18)
T _{max} (h)	5.00 (18) [1.00 – 5.05]	3.00 (18) [1.00 – 5.00]
AUC(0-5) (h $\times$ ng/mL)	5,165 $\pm$ 840 (18)	5,502 $\pm$ 1,276 (18)

*Mean $\pm$ standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 15 Page 52)

The median T_{max} values for metformin increased to 5.00 hours from 3.00 hours when metformin was administered with oral octreotide acetate, compared to metformin administration with placebo. Statistical comparisons of the two treatments are shown in [Table 32](#).

Table 32 Statistical Comparison of Pharmacokinetic Parameters for Metformin After Oral Administration of Single 850 mg Doses to Healthy Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter	Geometric Mean*		Geometric Mean Ratio (%)†	
	Test	Reference	Estimate	90% Confidence Interval
Metformin with Oral Octreotide Acetate vs. Metformin with Placebo				
C _{max}	1,547.78	1,399.01	110.63	100.21 → 122.15
AUC(0-5)	5,102.97	5,355.76	95.28	87.33 → 103.96

*Least squares geometric means. Based on analysis of natural log-transformed pharmacokinetic parameters.

†Lower confidence interval limits < 80.00% and upper confidence interval limits > 125.00% are shown in red.

Metformin was coadministered with HCTZ and warfarin.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 16 Page 52)

Though it appears that no recommendation for dosage adjustment for metformin is needed when co-administering with Mycapssa, the data to base the recommendation on may be inadequate. When co-administered with Mycapssa, plasma profiles of metformin at 5 hours did not yet appear to be in the elimination phase. Metformin's reported half-life is 4-9 hours, and a sampling time of only 5 hours may not completely characterize the influence of Mycapssa on metformin's pharmacokinetics.

2.6.1.7 What is the effect of oral octreotide co-administration on the pharmacokinetics of Ethinyl Estradiol and levonorgestrel?

Administration of ethinyl estradiol and levonorgestrel concomitant with oral octreotide acetate resulted in similar plasma concentrations of ethinyl estradiol whether ethinyl estradiol was co-administered with oral octreotide or with placebo ([Figure 35](#)). C_{max} and AUC₀₋₅ for ethinyl estradiol were comparable between the two administrations ([Table 33](#)), and the 90% confidence intervals were contained within the 80.00% - 125.00% limits for both parameters. The median T_{max} values for ethinyl estradiol increased slightly from 1.79 hours to 2.75 hours when ethinyl estradiol was administered with oral octreotide acetate, compared to ethinyl estradiol administration with placebo. Statistical comparisons of the two treatments are shown in [Table 34](#).

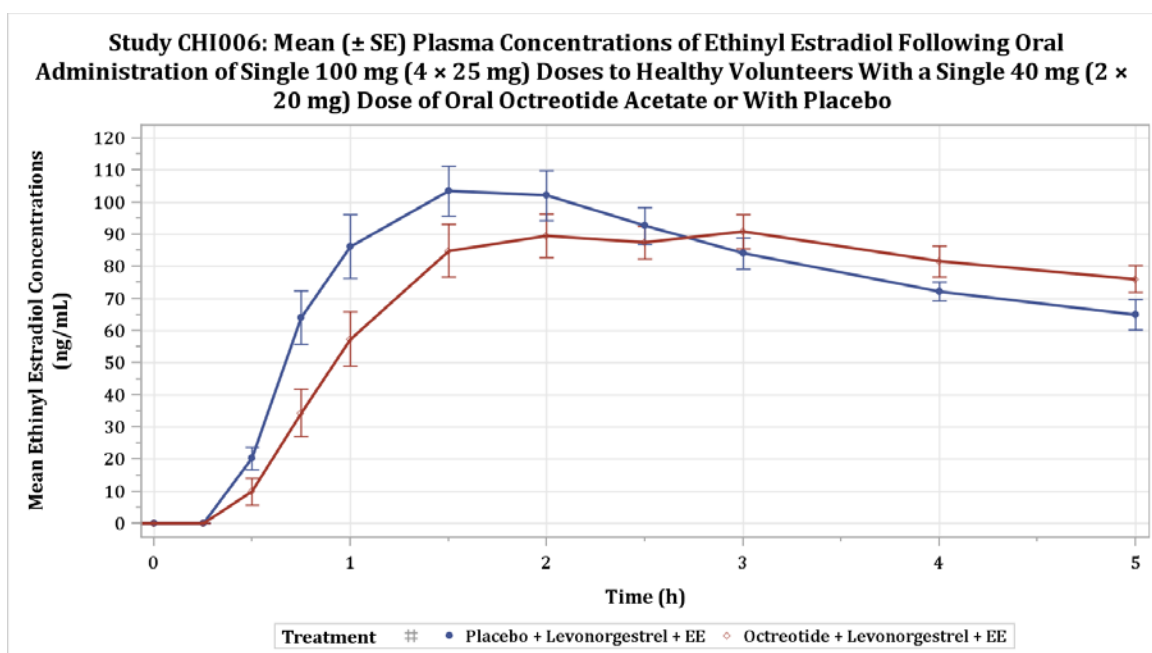


Figure 35 Mean Plasma Concentrations of Ethinyl Estradiol After Oral Administration of Single 0.06 mg Doses (2×0.03 mg) of Ethinyl Estradiol (with Levonorgestrel) to Healthy Female Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Table 33 Summary of Pharmacokinetic Parameters for Ethinyl Estradiol After Oral Administration of Single 0.06 mg Doses (2×0.03 mg) of Ethinyl Estradiol (with Levonorgestrel) to Healthy Female Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter*	Oral Octreotide Acetate	
	With	Without
C _{max} (pg/mL)	103 $\pm$ 21.2 (14)	113 $\pm$ 28.7 (14)
T _{max} (h)	2.75 (14) [1.50 – 5.00]	1.79 (14) [1.00 – 2.00]
AUC(0-5) (h $\times$ pg/mL)	351 $\pm$ 83.5 (14)	370 $\pm$ 80.2 (14)

*Mean $\pm$ standard deviation (N) except T_{max} for which the median (N) [Range] is reported.
(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 17 Page 53)

Table 34 Statistical Comparison of Pharmacokinetic Parameters for Ethinyl Estradiol After Oral Administration of Single 0.06 mg Doses (2×0.03 mg) of Ethinyl Estradiol (with Levonorgestrel) to Healthy Female Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter	Geometric Mean*		Geometric Mean Ratio (%)†		
	Test	Reference	Estimate	90% Confidence Interval	
Ethinyl Estradiol with Oral Octreotide Acetate vs. Ethinyl Estradiol with Placebo					
C _{max}	100.61	109.30	92.05	83.48 →	101.49
AUC(0-5)	341.52	361.96	94.35	86.19 →	103.29

*Least squares geometric means. Based on analysis of natural log-transformed pharmacokinetic parameters.

†Lower confidence interval limits < 80.00% and upper confidence interval limits > 125.00% are shown in red. Ethinyl estradiol was coadministered with levonorgestrel.

(Source: eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 18 Page 54)

Administration of ethinyl estradiol and levonorgestrel concomitant with oral octreotide acetate, however, resulted in lower plasma concentrations of norgestrel when levonorgestrel was co-administered with oral octreotide compared to co-administration with placebo (Figure 36). C_{max} and AUC₀₋₅ of norgestrel were 38% and 24% lower when co-administered with octreotide compared to co-administration with placebo (Table 35), and the 90% confidence intervals were outside the 80.00% - 125.00% limits for both parameters. The median T_{max} values for norgestrel increased from 1.03 hours to 2.00 hours when levonorgestrel was administered with oral octreotide acetate, compared to co-administration with placebo. Statistical comparisons of the two treatments are shown in Table 36.

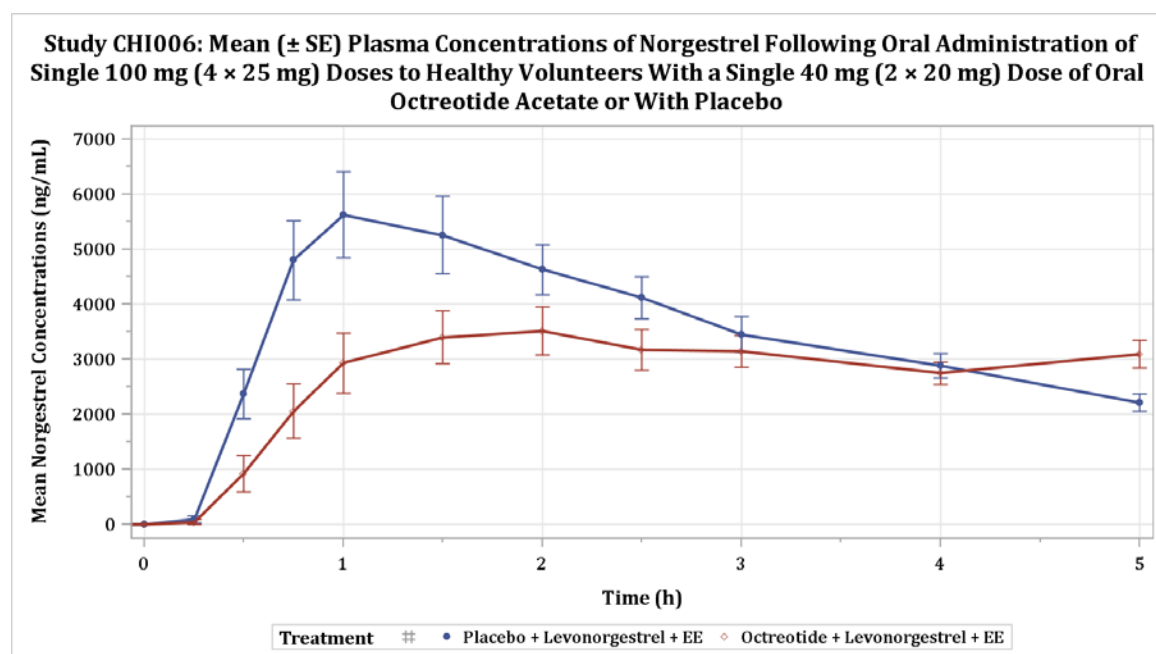


Figure 36 Mean Plasma Concentrations of Norgestrel After Oral Administration of Single 0.30 mg Doses (2×0.150 mg) of Levonorgestrel (with Ethinyl Estradiol) to Healthy Female Volunteers With a Single 40 mg (2×20 mg) Dose of Oral Octreotide Acetate or With Placebo

Table 35 Summary of Pharmacokinetic Parameters for Norgestrel After Oral Administration of Single 0.30 mg Doses (2 × 0.150 mg) of Levonorgestrel (with Ethinyl Estradiol) to Healthy Female Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter*	Oral Octreotide Acetate	
	With	Without
C _{max} (pg/mL)	4,192 ± 1,737 (14)	6,584 ± 2,108 (14)
T _{max} (h)	2.00 (14) [1.00 – 5.00]	1.03 (14) [0.75 – 4.00]
AUC(0-5) (h×pg/mL)	13,542 ± 5,124 (14)	17,528 ± 5,543 (14)

*Mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 19 Page 55)

Table 36 Statistical Comparison of Pharmacokinetic Parameters for Norgestrel After Oral Administration of Single 0.30 mg Doses (2 × 0.150 mg) of Levonorgestrel (with Ethinyl Estradiol) to Healthy Female Volunteers With a Single 40 mg (2 × 20 mg) Dose of Oral Octreotide Acetate or With Placebo

Parameter	Geometric Mean*		Geometric Mean Ratio (%)†	
	Test	Reference	Estimate	90% Confidence Interval
Norgestrel with Oral Octreotide Acetate vs. Norgestrel with Placebo				
C _{max}	3,831.65	6,177.76	62.02	53.98 → 71.26
AUC(0-5)	12,584.37	16,535.56	76.10	67.04 → 86.40

*Least squares geometric means. Based on analysis of natural log-transformed pharmacokinetic parameters.

†Lower confidence interval limits < 80.00% and upper confidence interval limits > 125.00% are shown in red.
Levonorgestrel was coadministered with ethinyl estradiol.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study CHI-006, Table 20 Page 56)

When co-administered with Mycapssa, plasma profiles of both ethinyl estradiol and levonorgestrel at 5 hours did not yet appear to be in the elimination phase. Administration of ethinyl estradiol and levonorgestrel concomitantly with oral octreotide acetate resulted in similar plasma concentrations of ethinyl estradiol whether ethinyl estradiol was co-administered with oral octreotide or with placebo. However, norgestrel concentrations were reduced. Levonorgestrel/Ethinyl estradiol's reported half-life is 19-24 hours, and a sampling time of only 5 hours may not completely characterize the influence of Mycapssa on the pharmacokinetics of Levonorgestrel and Ethinyl estradiol. Based on these results, patients using oral contraceptives containing levonorgestrel should be advised to use an alternative contraceptive method

2.6.1.8 What is the effect of oral octreotide co-administration on the pharmacokinetics of Cyclosporine?

Administration of cyclosporine concomitant with oral octreotide acetate resulted in lower plasma concentrations of cyclosporine when cyclosporine was co-administered with oral octreotide compared to co-administration with placebo (Figure 37). C_{max} and AUC_{0-t} of cyclosporine were 71% and 62% lower when co-administered with octreotide compared to co-administration with placebo (Table 37), and the 90% confidence intervals were well outside the 80.00% - 125.00% limits for both parameters. The median T_{max} values for cyclosporine increased from 1.50 hours to 3.03 hours when cyclosporine was administered with oral octreotide acetate, compared to co-administration with placebo (Figure 38). Statistical comparisons of the two treatments are shown in Table 38.

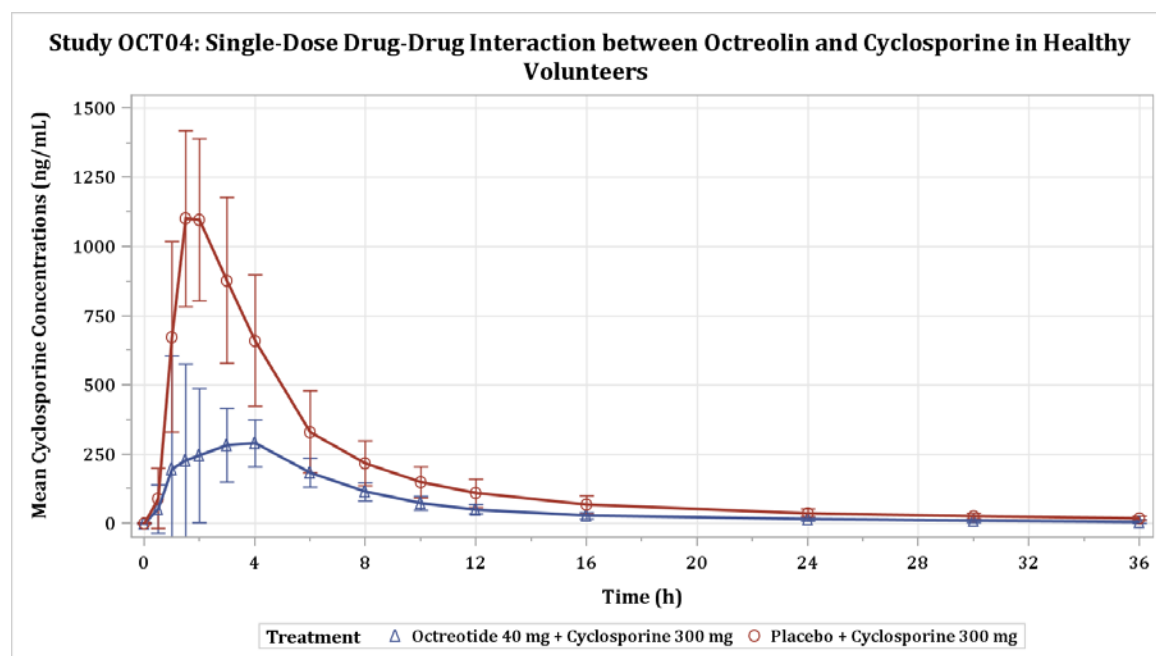


Figure 37 Mean Whole Blood Concentrations of Cyclosporine After Oral Administration of Single 300 mg Doses with Concomitant Oral Octreotide Acetate and Placebo to Healthy Volunteers Under Fasting Conditions

Table 37 Summary of Pharmacokinetic Parameters for Cyclosporine After Oral Administration of Single 300 mg Doses with Concomitant Oral Octreotide Acetate and Placebo to Healthy Volunteers Under Fasting Conditions

Parameter*	Cyclosporine + Oral Octreotide Acetate	Cyclosporine + Placebo
C _{max} (ng/mL)	413 ± 361 (15)	1,247 ± 249 (15)
T _{max} (h)	3.03 (15) [1.15 – 6.00]	1.50 (15) [1.00 – 3.03]
AUC(0-t) (h×ng/mL)	2,424 ± 1,115 (15)	6,256 ± 1,888 (15)
AUC(inf) (h×ng/mL)	2,544 ± 1,240 (14)	6,583 ± 2,088 (14)
λ _z (1/h)	0.0722 ± 0.0173 (14)	0.0647 ± 0.0085 (14)
t _{1/2} (h)	10.0 ± 2.08 (14)	10.9 ± 1.25 (14)

*Mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

AUC(0 t) = area under the concentration-time curve to the final sample with a concentration $\square$ the limit of quantitation; AUC(inf) = area under the concentration-time curve from 0 extrapolated to infinity; C_{max} = maximum plasma concentration; $\square$ z = elimination rate constant; LOQ = limit of quantitation; t_{1/2} = half-life; Tlag = absorption lag time; T_{max} = time of maximum plasma concentration

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-04, Table 5 Page 43)

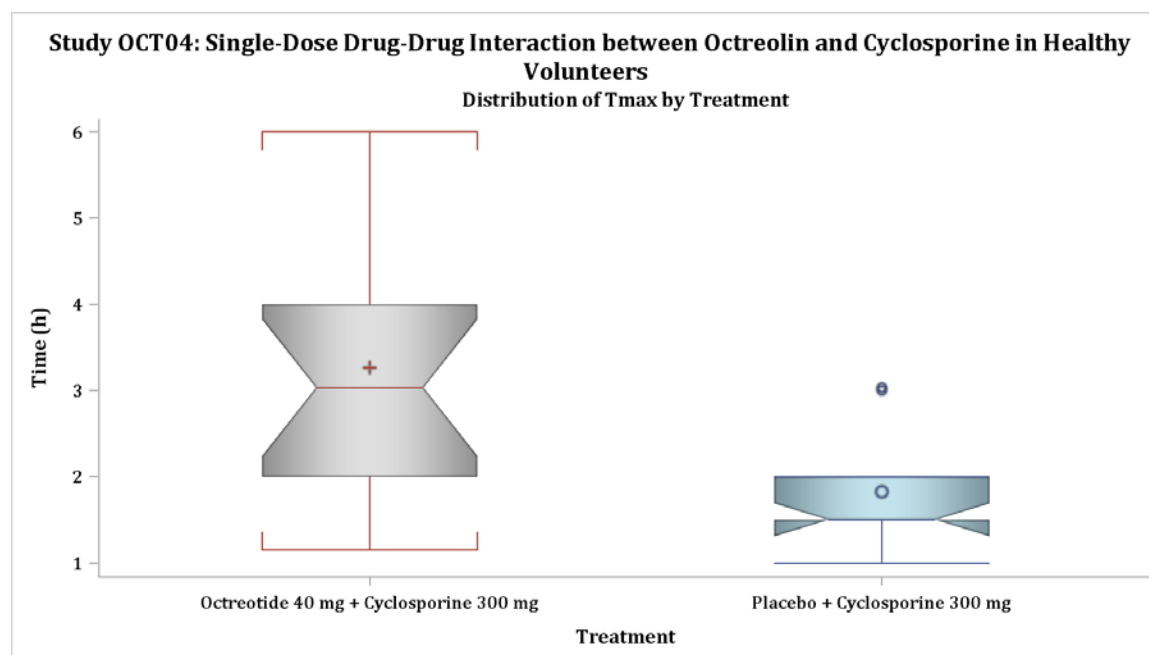


Figure 38 Median T_{max} Values of Cyclosporine After Oral Administration of Single 300 mg Dose with Concomitant Oral Octreotide Acetate and Placebo to Healthy Volunteers Under Fasting Conditions

Table 38 Statistical Comparison of Pharmacokinetic Parameters for Cyclosporine After Oral Administration of Single 300 mg Doses With Concomitant Oral Octreotide Acetate and Placebo to Healthy Volunteers Under Fasting Conditions

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	37.13	30.57 - 45.1
AUC(0-inf) for Octreotide	ng·h/mL	37.49	30.6 - 45.93
Cmax for Octreotide	ng/mL	28.55	22.44 - 36.32

In summary, concomitant administration of cyclosporine and oral octreotide acetate results in a 60% decrease in the extent of cyclosporine exposure and a decrease in the rate of cyclosporine absorption. This is consistent with the known effects of injectable somatostatin analogs. According to the Sandostatin label, “Concomitant administration of Sandostatin with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection”. Coadministration of cyclosporine with Mycapssa should be avoided.

2.6.2 Effect of Posture, and Water

2.6.2.1 What is the effect of Posture on Octreotide Absorption?

The influence of posture on the pharmacokinetics of oral octreotide was evaluated in study OCT-03. evaluated

(a) Morning Standing versus semi-sitting:

Compared to administration in the semi-sitting position, administration of oral octreotide acetate in the morning in a standing position resulted in a decrease in the mean plasma concentrations ([Figure 39](#)). However, the pattern varied among the individual subjects. The arithmetic mean values for C_{max} , AUC_{0-t} , and AUC_{inf} were also decreased when oral octreotide acetate was administered in a standing position compared to a sitting position ([Table 39](#)). The GMR for the 3 parameters were 71.34%, 61.23%, and 57.35% ([Table 40](#)). Although the associated 90% CIs were wide ([Table 39](#)), the GMRs suggest that, on average, there is a 40% decrease in the extent of absorption.

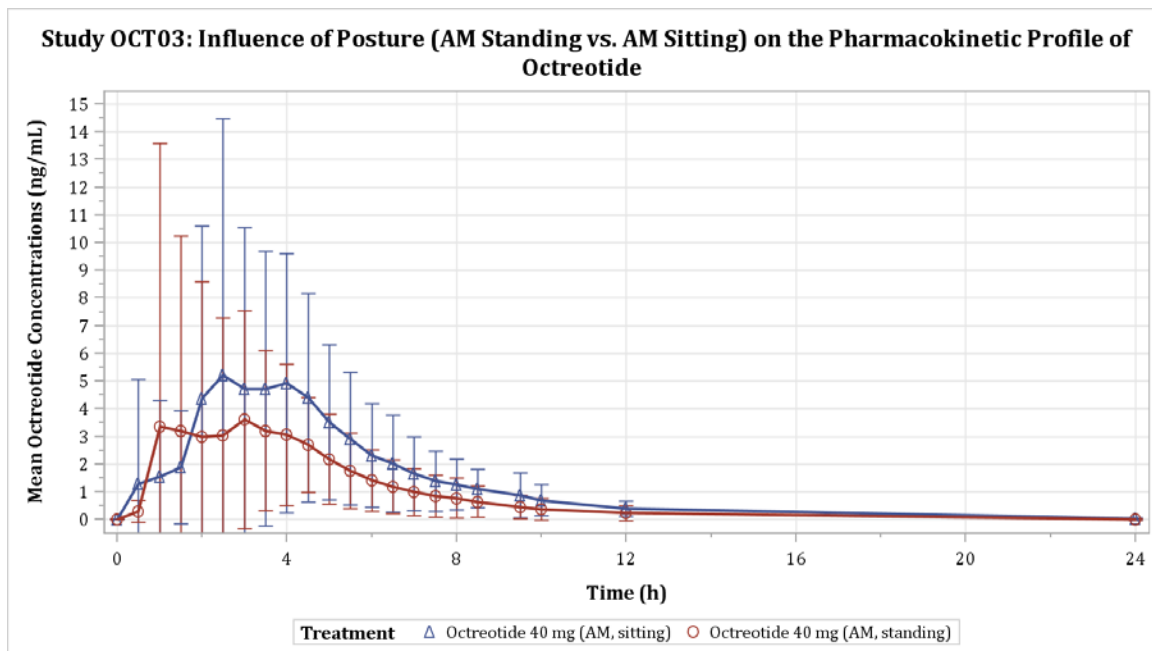


Figure 39 Mean plasma octreotide concentrations after oral administration of Mycapssa 40 mg in the Morning in Standing Position versus in the Morning in Sitting Position

Table 39 Summary of Pharmacokinetic Parameters for Octreotide After Oral Administration of Single 40-mg (2 × 20 mg) Doses in the Morning in Semi-Sitting Position and in the Morning in Standing Position to Healthy Volunteers Under Fasted Conditions

Parameter*	Morning Semi-Sitting	Morning Standing
T _{lag} (h)†	1.24 (4) [0.95 – 1.50]	1.50 (8) [0.97 – 3.05]
C _{max} (ng/mL)	7.81 ± 9.35 (18)	6.43 ± 10.0 (18)
T _{max} (h)	3.00 (18) [0.50 – 9.50]	3.00 (18) [1.00 – 4.50]
AUC(0-t) (h×ng/mL)	28.5 ± 24.9 (18)	19.5 ± 24.6 (18)
AUC(inf) (h×ng/mL)	29.1 ± 24.9 (18)	19.9 ± 24.7 (18)
λ _z (1/h)	0.2979 ± 0.0938 (18)	0.3183 ± 0.0679 (18)
t _{1/2} (h)	2.60 ± 0.95 (18)	2.32 ± 0.74 (18)

*Mean ± standard deviation (N) except T_{lag} and T_{max} for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

AUC(0-t) = area under the concentration-time curve to the final sample with a concentration ≥ the limit of quantitation; AUC(inf) = area under the concentration-time curve from 0 extrapolated to infinity; C_{max} = maximum plasma concentration; λ_z = elimination rate constant; LOQ = limit of quantitation; t_{1/2} = half-life; T_{lag} = absorption lag time; T_{max} = time of maximum plasma concentration

(Source: eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-03, Table 8 Page 41)

Table 40 Statistical Comparison of Pharmacokinetic Parameters for Mycapssa 40 mg in the Morning in Standing Position versus in the Morning in Sitting Position

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	61.23	40.77 - 91.94
AUC(0-inf) for Octreotide	ng·h/mL	57.35	37.37 - 88
C _{max} for Octreotide	ng/mL	71.34	42.85 - 118.79

Compared to administration in the semi-sitting position in the morning, administration of oral octreotide acetate in the semi sitting/laying position in the evening resulted in a decrease in the mean plasma concentrations ([Figure 40](#)). The arithmetic mean values for C_{max}, AUC_{0-t}, and AUC_{inf} were also decreased when oral octreotide acetate was administered in a standing position compared to a sitting position ([Table 41](#)). The GMR for the 3 parameters were 34.55%, 62.66%, and 58.29% ([Table 42](#)). Although the associated 90% CIs were wide, the GMRs suggest that, on average, there is a 40% decrease in the extent of absorption.

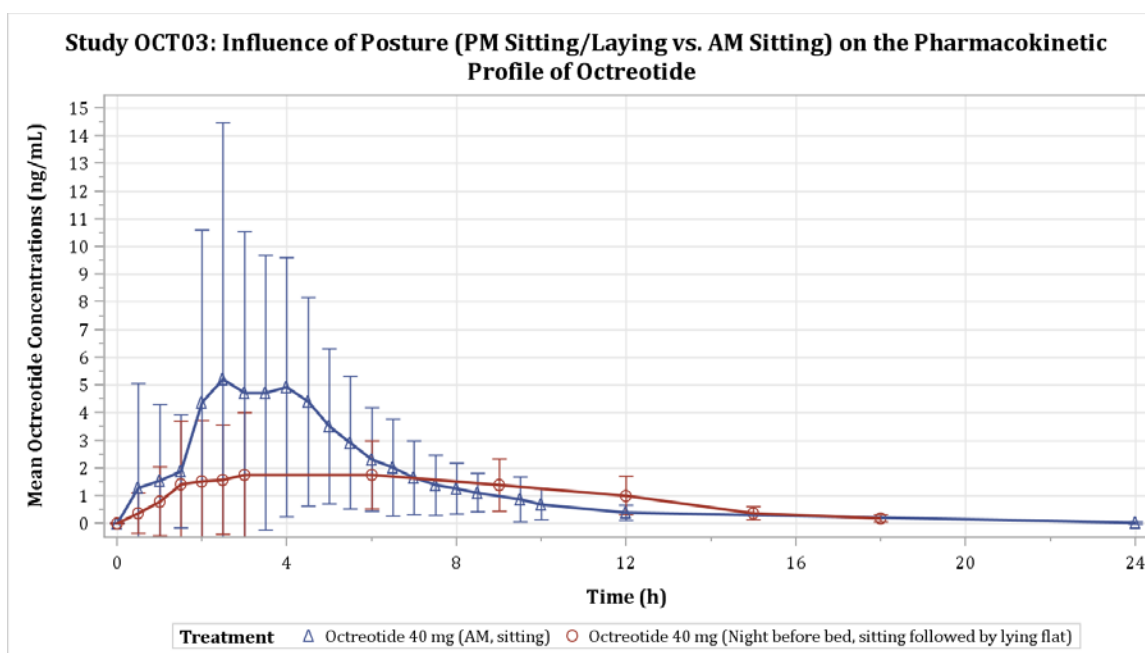


Figure 40 Mean plasma octreotide concentrations after oral administration of Mycapssa 40 mg in the Morning in Sitting Conditions versus Oral Administration in the Evening in the Sitting/Semi-Laying Position

Table 41 Summary of Pharmacokinetic Parameters for Octreotide After Oral Administration of Single 40-mg (2 × 20 mg) Doses in the Morning in Semi-sitting Position and at Night Prior to Going To Bed, Semi-sitting Followed by Lying, to Healthy Volunteers Under Fasted Conditions

Parameter*	Morning Semi-Sitting	Evening Semi-Sitting/Laying
Tlag (h)†	1.00 (3) [0.95 – 1.48]	0.98 (4) [0.93 – 2.00]
Cmax (ng/mL)	9.19 ± 10.2 (14)	2.56 ± 2.14 (14)
Tmax (h)	3.00 (14) [0.50 – 4.02]	4.48 (14) [0.93 – 12.0]
AUC(0-t) (h×ng/mL)	32.8 ± 26.7 (14)	19.9 ± 15.5 (14)
AUC(inf) (h×ng/mL)	33.3 ± 26.7 (14)	21.3 ± 16.2 (13)
λz (1/h)	0.2813 ± 0.0917 (14)	0.2828 ± 0.0422 (13)
t½ (h)	2.76 ± 1.00 (14)	2.50 ± 0.38 (13)

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

AUC(0-t) = area under the concentration-time curve to the final sample with a concentration ≥ the limit of quantitation; AUC(inf) = area under the concentration-time curve from 0 extrapolated to infinity; Cmax = maximum plasma concentration; λz = elimination rate constant; LOQ = limit of quantitation; t½ = half-life; Tlag = absorption lag time; Tmax = time of maximum plasma concentration

(Source: eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-03, Table 11 Page 44)

Table 42 Statistical Comparison of Pharmacokinetic Parameters for Mycapssa 40 mg in the Morning in Standing Position versus in the Evening in Sitting Position

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	62.66	38.43 - 102.16
AUC(0-inf) for Octreotide	ng·h/mL	58.29	31.79 - 106.88
Cmax for Octreotide	ng/mL	34.55	21.26 - 56.14

2.6.2.2 What is the effect of Volume of Water Administered on Octreotide Absorption?

In study OCT-02, administration of oral octreotide acetate with 75 mL rather than 240 mL of water resulted in a slight decrease in the mean plasma octreotide concentrations ([Figure 41](#)). C_{max} and AUC_{0-t} of octreotide were both about 12% lower when octreotide was administered with 75 mL of water rather than with 240 mL of water ([Table 43](#)), and the 90% confidence intervals were outside the 80.00% - 125.00% limits for both parameters.

The rationale for this study was that there is the potential effect of water on gastric emptying⁶ and possibly on octreotide absorption and octreotide bioavailability.

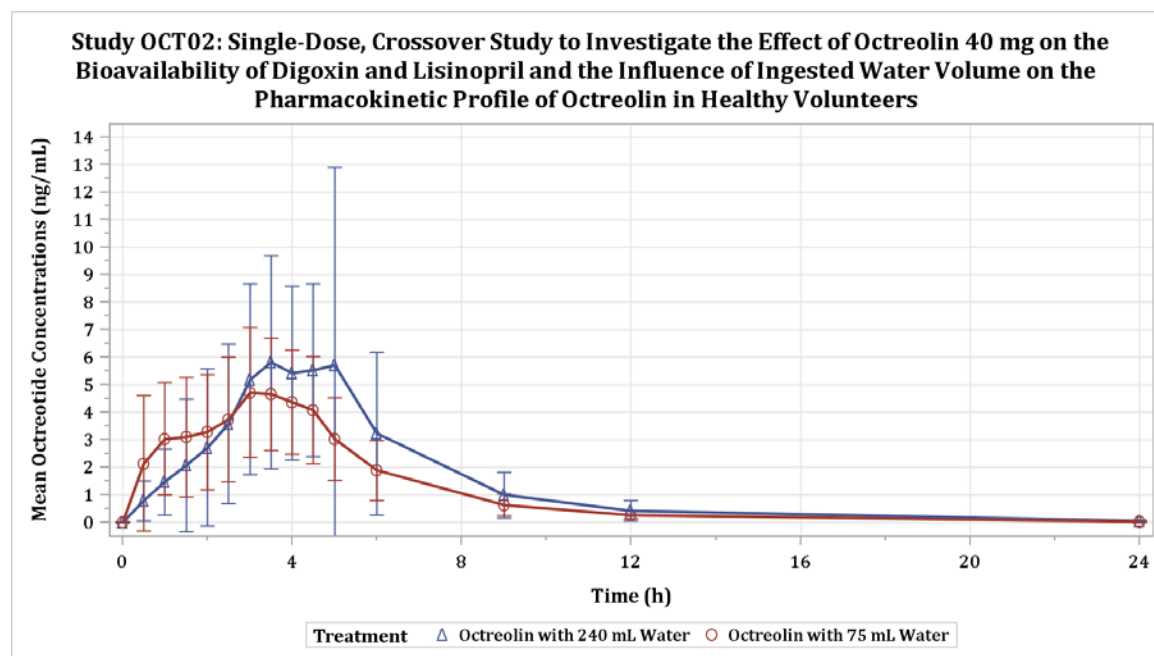


Figure 41 Mean Plasma Concentrations of Octreotide After Oral Administration of Single 40 mg (2 ×20 mg) Doses With 240 mL and 75 mL of Water to Healthy Volunteers Under Fasted Conditions

⁶ Karsdal MA, Henriksen K, Bay-Jensen AC, et al. Lessons learned from the development of oral calcitonin: the first tablet formulation of a protein in phase III clinical trials. *J Clin Pharmacol* 2011; **51**(4):460-471.

Table 43 Summary of Octreotide Pharmacokinetic Parameters After Oral Administration of Single 40 mg (2 ×20 mg) Doses With 240 mL and 75 mL of Water to Healthy Volunteers Under Fasted Conditions

Parameter*	Octreolin With 240 mL Water	Octreolin With 75 mL Water
Tlag (h)†	2.00 (1) [2.00 – 2.00]	2.00 (1) [2.00 – 2.00]
C _{max} (ng/mL)	8.21 ± 7.18 (18)	6.13 ± 2.11 (18)
T _{max} (h)	3.54 (18) [3.00 – 6.00]	3.00 (18) [0.50 – 4.53]
AUC(0-t) (h×ng/mL)	33.4 ± 20.9 (18)	26.5 ± 11.1 (18)
AUC(∞) (h×ng/mL)	35.3 ± 20.4 (17)	26.8 ± 11.1 (18)
λ _z (1/h)	0.2120 ± 0.0736 (17)	0.2496 ± 0.0843 (18)
t _{1/2} (h)	3.54 ± 0.88 (17)	3.05 ± 0.90 (18)

*Mean ± standard deviation (N) except Tlag and T_{max} for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-02, Table 10 Page 45)

The median T_{max} value was reduced from 3.54 hours to 3.00 hours following administration with 75 mL of water compared to administration with 240 mL of water ([Figure 42](#)). Statistical comparisons of the two treatments are shown in [Table 44](#).

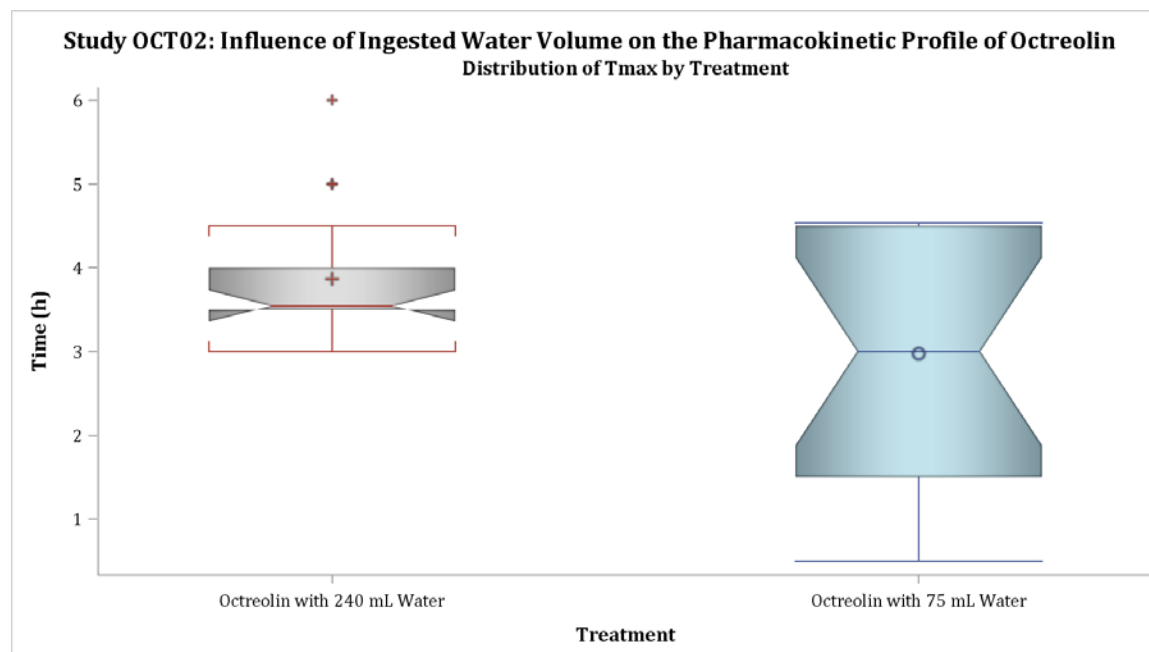


Figure 42 Median T_{max} Values of Octreotide After Oral Administration of Mycapssa 40 mg with Either 240 mL or 75 mL Water

Table 44 Statistical Comparison of Octreotide Pharmacokinetic Parameters After Oral Administration of Single 40 mg (2 ×20 mg) Doses With 240 mL and 75 mL of Water to Healthy Volunteers Under Fasted Conditions

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	88.52	66.51 - 117.81
AUC(0-inf) for Octreotide	ng·h/mL	78.2	61.73 - 99.07
Cmax for Octreotide	ng/mL	88.78	63.31 - 124.5

The study results indicate that patients should be advised to take Mycapssa with a full glass (8 oz) of water.

2.7 General Biopharmaceutics

2.7.1 What is the effect of food on the pharmacokinetics of oral octreotide?

The effect of administration of high-fat meal on the bioavailability of octreotide from Mycapssa 20 mg capsules following a single dose administration, was evaluated in study CHI-002.

As seen from [Figure 43](#), there appeared to be no effect on the elimination of octreotide by either the route of administration or diet (fed or fasted). The mean elimination half-life ($t_{1/2}$) was similar following oral administration of Mycapssa under fasted (2.66 ± 0.73 hour) and fed (2.28 ± 0.78 hour) conditions and s.c. administration of Sandostatin (2.27 ± 0.25 hour).

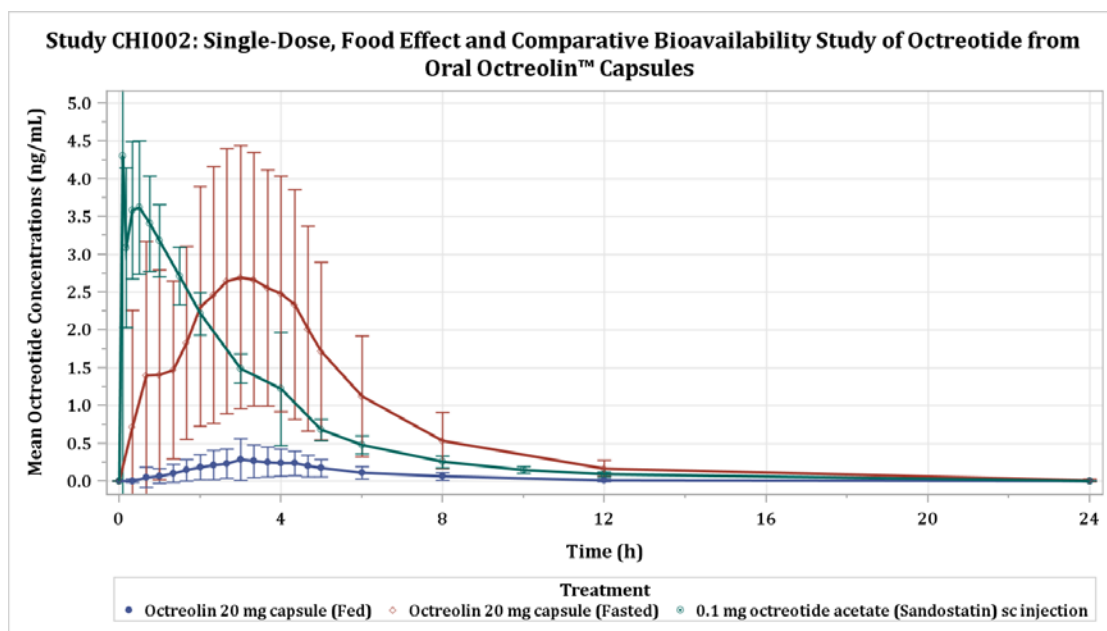


Figure 43 Mean serum concentration-time profile of octreotide following single-dose administration of Mycapssa and Sandostatin

A high-fat meal reduced the bioavailability of octreotide significantly, by approximately 90%. ([Table 45](#)).

Table 45: Pharmacokinetic Parameters for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Mycapssa 20 mg to Healthy Volunteers under Fasted Conditions

Parameter*	20 mg Oral		Subcutaneous 0.1 mg
	Fed	Fasted	
Tlag (h)†	1.00 (24) [0.33 – 3.67]	0.330 (24) [0.330 – 1.02]	—‡
C _{max} (ng/mL)	0.377 ± 0.261 (24)	3.62 ± 1.93 (24)	3.83 ± 0.86 (14)
T _{max} (h)	3.00 (24) [0.670 – 4.67]	2.50 (24) [0.330 – 4.33]	0.50 (14) [0.203 – 4.00]
AUC(0-t) (h×ng/mL)	1.29 ± 0.884 (24)	15.2 ± 8.73 (24)	12.0 ± 1.53 (14)
AUC(inf) (h×ng/mL)	1.45 ± 0.892 (23)	15.4 ± 8.74 (24)	12.3 ± 1.57 (14)
λ _z (1/h)	0.3309 ± 0.0892 (23)	0.2799 ± 0.0783 (24)	0.3083 ± 0.0331 (14)
t _{1/2} (h)	2.28 ± 0.78 (23)	2.66 ± 0.73 (24)	2.27 ± 0.25 (14)

*Mean ± standard deviation (N) except Tlag and T_{max} for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

‡There was no lag time after SC administration.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for StudyCHI-002, Table 8, Page 44)

The least-squares mean ratios, fed-to-fasted values for C_{max}, and AUC_(0-t), were 10.44%, and 9.45%, respectively ([Table 46](#)).

Table 46: Statistical Comparison of Pharmacokinetic Parameters for Octreotide after Mycapssa 20 mg to Healthy Volunteers under Fed Condition Compared to Fasted Conditions

PK Parameter	Units	Ratio(%)	90% CI
AUC(0-t) for Octreotide	ng·h/mL	9.45	7.13 - 12.53
C _{max} for Octreotide	ng/mL	10.44	7.86 - 13.86

The median value for T_{max} was slightly longer under fed (3.00 hours) compared to 2.50 hours under fasting conditions, however, the ranges were similar for both treatments ([Figure 44](#)).

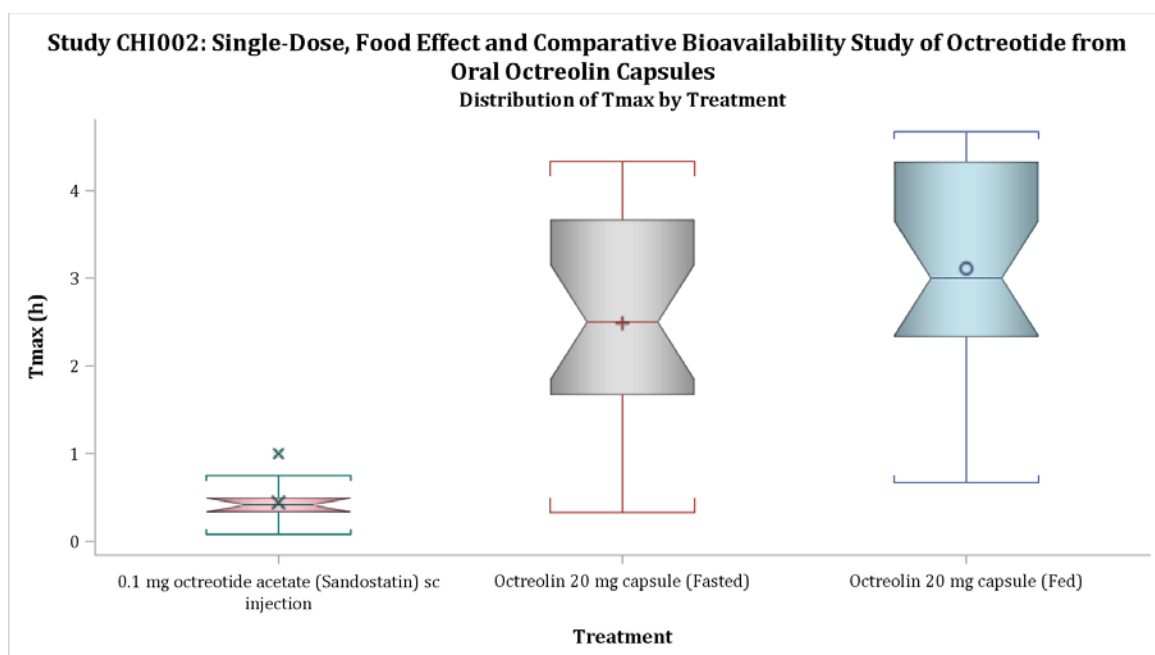


Figure 44 Distribution of octreotide T_{max} following single-dose administration of Mycapssa and Sandostatin

Based on the data above, patients will not benefit if Mycapssa is administered under fed (high-fat meal) conditions.

2.7.2 How does the size of the meals and timing of meals affect absorption of octreotide?

In study OCT-01, the sponsor evaluated the effect of meal timing and size on the absorption of octreotide from oral Mycapssa compared to a control fasting condition. Two types of meals were evaluated, a ‘full’ meal having the composition of a standard high-calorie/high-fat meal per FDA guidance, and a ‘light’ or reduced size high fat meal having one-third the total calorie content as the full meal. Both meals had the same relative percentage of protein, carbohydrate, and fat. Caloric compositions of the meals are summarized in [Table 47](#) below:

Table 47 Compositions of Full and Reduced Size (Light) Test Meals

Meal Type	Calories			
	Total	Protein	Carbohydrate	Fat
Full Meal*	800 → 1000	~150	~250	~500 → 600
Reduced size high fat meal	270 → 330	~50	~80	~270 → 200

Meal Type	Food Composition**			
	Total	Protein	Carbohydrate	Fat
Full Meal*		40.80	70.98	57.50
	169.28	(24.1%)	(41.9%)	(34.0%)
Reduced size high fat meal	51.07	12.58	20.72	17.77
		(24.6%)	(40.6%)	(34.8%)

* Standard high-calorie/high-fat meal per FDA guidance

** Grams (percent of total)

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-01, Panel 9-1 Page 20)

The following test conditions for oral Mycapssa administration were evaluated in the main study: (a) 1 hour prior to full test meal, (b) 1 hour after full test meal, (c) 30 minutes prior to light test meal, (d) 10-hour fast (Fasting condition). A cohort of 12 subjects who participated in the main study received two additional treatments: (e) 1 hour prior to a reduced size high fat meal and (f) 2 hours following a full meal.

Administration of oral Mycapssa 1 hour before a full high fat meal (Treatment A), 1 hour after a full high fat meal (Treatment B), or 0.5 hours before a reduced size high fat meal (Treatment C) resulted in a substantial decrease in plasma octreotide concentrations ([Figure 45](#)). The geometric mean ratios for AUC_{0-t} and C_{max} ranged from 14.88% to 21.17% (1 hour before a full high fat meal), 7.71% to 7.80% (1 hour after a full high fat meal), and 18.22% to 26.84% (0.5 hour before a reduced size high fat meal), respectively, versus fasted condition ([Table 48](#)). Statistical comparisons are shown in [Table 49](#).

Administration of oral Mycapssa 1 hour before a reduced size high fat meal (Treatment E) resulted in mean plasma concentrations that were higher compared to Treatments A-C, but more variable compared to fasted condition (treatment D). Administration of oral Mycapssa 2 hours after a full high fat meal (Treatment F) resulted in a substantial decrease in plasma octreotide concentrations ([Figure 46](#)). The geometric mean ratios for AUC_{0-t} and C_{max} ranged from 40.21% to 58.69% (1 hour before a reduced size high fat meal), and 11.14% to 12.18% (2 hours after full high fat meal), respectively, versus fasted condition ([Table 50](#)). Statistical comparisons are shown in [Table 51](#).

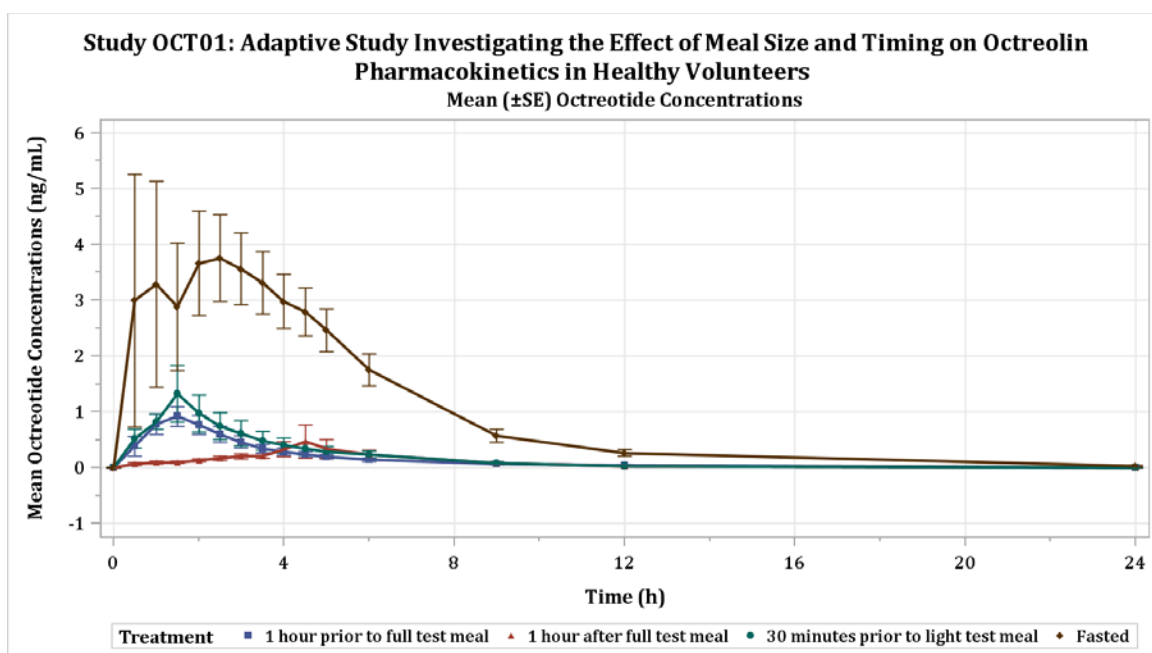


Figure 45 Mean Plasma Concentrations of Octreotide After Oral Administration of Mycapssa Under Test Conditions A-D

Table 48 Summary of pharmacokinetic parameters for octreotide by Test Condition A-D (Main Study)

Parameter*	1 Hour Before Full High Fat Meal	1 Hour After Full High Fat Meal	0.5 Hour Before Reduced Size High Fat Meal	Fasted
Tlag (h)†	1.25 (2) [1.00 – 1.50]	1.50 (14) [1.00 – 3.50]	1.50 (1) [1.50 – 1.50]	1.00 (3) [1.00 – 1.00]
Cmax (ng/mL)	1.19 $\pm$ 0.99 (20)	0.59 $\pm$ 1.41 (23)	1.55 $\pm$ 2.52 (24)	5.91 $\pm$ 9.82 (24)
Tmax (h)	1.50 (20) [0.50 – 4.50]	3.00 (23) [0.50 – 6.00]	1.50 (24) [0.50 – 6.00]	3.00 (24) [0.52 – 5.00]
AUC(0-t) (h $\times$ ng/mL)	3.54 $\pm$ 3.36 (20)	1.97 $\pm$ 3.10 (23)	4.17 $\pm$ 5.95 (24)	23.5 $\pm$ 26.8 (24)
AUC(inf) (h $\times$ ng/mL)	3.49 $\pm$ 3.14 (17)	1.91 $\pm$ 0.81 (10)	4.97 $\pm$ 6.55 (19)	24.4 $\pm$ 27.3 (23)
λ_z (1/h)	0.2747 $\pm$ 0.0551 (17)	0.2974 $\pm$ 0.0396 (10)	0.2948 $\pm$ 0.0560 (19)	0.2883 $\pm$ 0.0910 (23)
t _{1/2} (h)	2.62 $\pm$ 0.56 (17)	2.37 $\pm$ 0.35 (10)	2.44 $\pm$ 0.50 (19)	2.65 $\pm$ 0.85 (23)

*Mean $\pm$ standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration $\geq$ LOQ occurred at the first sample time.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-01, Panel 11-1 Page 37)

Table 49 Statistical comparison of pharmacokinetic parameters between fed and fasted Test Conditions (Main Study)

Parameter	Geometric Mean*		Geometric Mean Ratio (%)			
	Test	Reference	Estimate	90% Confidence Interval		
1 Hour Before Full High Fat Meal vs. Fasted						
Cmax	0.73	3.45	21.17	13.28	→	33.73
AUC(0-t)	2.31	15.53	14.88	9.79	→	22.62
AUC(inf)	2.48	16.21	15.32	9.94	→	23.61
1 Hour After Full High Fat Meal vs. Fasted						
Cmax	0.27	3.45	7.80	5.00	→	12.16
AUC(0-t)	1.20	15.53	7.71	5.17	→	11.48
AUC(inf)	1.33	16.21	8.22	4.85	→	13.95
0.5 Hour Before Reduced Size High Fat Meal vs. Fasted						
Cmax	0.93	3.45	26.84	17.34	→	41.56
AUC(0-t)	2.83	15.53	18.22	12.30	→	26.98
AUC(inf)	3.31	16.21	20.42	13.50	→	30.90

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-01, Panel 11-2 Page 37)

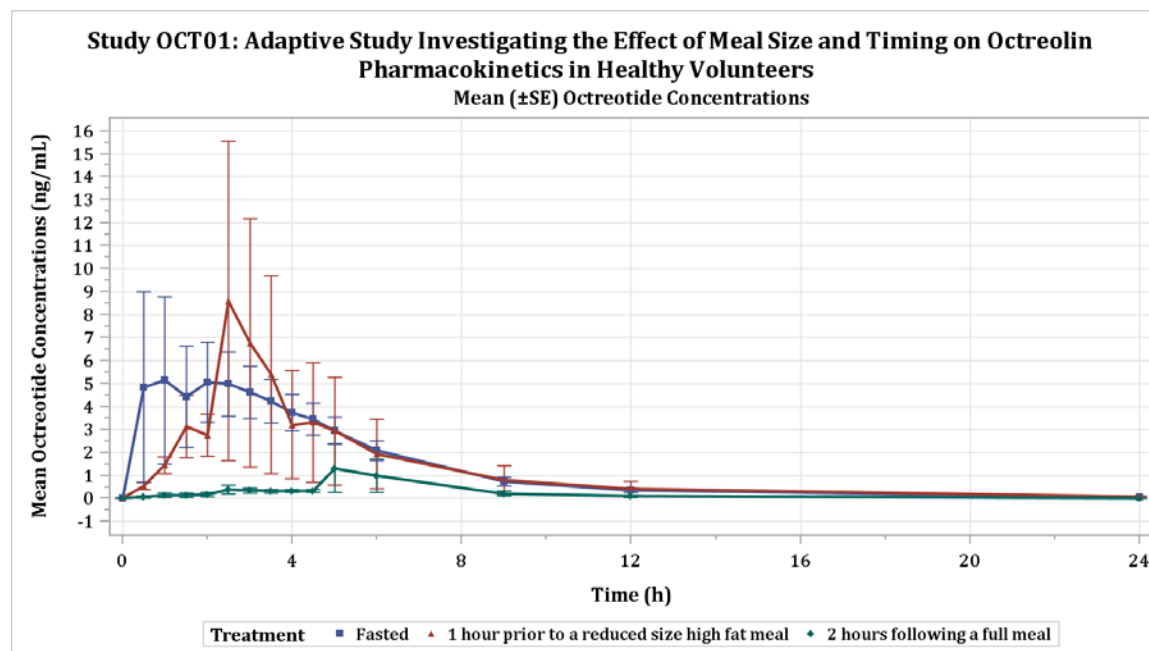


Figure 46 Mean Plasma Concentrations of Octreotide After Oral Administration of Mycapssa Under Test Conditions E-F

Table 50 Summary of pharmacokinetic parameters by Test Condition E-F (Adaptive Module) and Test Condition D§ (Fasted)

Parameter*	1 Hour Before Reduced Size High Fat Meal	2 Hours After Full High Fat Meal	Fasted§
Tlag (h)†	1.25 (2) [1.00 – 1.50]	2.00 (8) [1.02 – 6.00]	—‡
Cmax (ng/mL)	9.34 ± 23.9 (12)	1.68 ± 3.61 (12)	8.57 ± 13.5 (12)
Tmax (h)	1.50 (12) [0.50 – 3.00]	3.75 (12) [1.00 – 12.00]	2.50 (12) [0.52 – 4.00]
AUC(0-t) (h×ng/mL)	29.3 ± 73.7 (12)	5.31 ± 10.3 (12)	31.5 ± 34.9 (12)
AUC(inf) (h×ng/mL)	29.8 ± 74.8 (12)	7.31 ± 12.5 (08)	33.8 ± 36.1 (11)
λz (1/h)	0.2796 ± 0.0720 (12)	0.2892 ± 0.0410 (08)	0.2650 ± 0.0918 (11)
t½ (h)	2.69 ± 0.92 (12)	2.44 ± 0.37 (08)	2.90 ± 0.92 (11)

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

§ Only subjects in the adaptive study are included for the fasted treatment.

†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.

‡There was no lag time after drug administration for any subject.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-01, Panel 11-3 Page 38)

Table 51 Statistical comparison of pharmacokinetic parameters between fed and fasted Test Conditions (Adaptive Module)

Parameter	Geometric Mean*		Geometric Mean Ratio (%)			
	Test	Reference	Estimate	90% Confidence Interval		
1 Hour Before Reduced Size High Fat Meal vs. Fasted						
Cmax	2.80	4.77	58.69	26.11	→	131.91
AUC(0-t)	8.59	21.37	40.21	19.50	→	82.90
AUC(inf)	8.88	24.35	36.45	16.16	→	82.21
2 Hours After Full High Fat Meal vs. Fasted						
Cmax	0.58	4.77	12.18	5.42	→	27.38
AUC(0-t)	2.38	21.37	11.14	5.40	→	22.98
AUC(inf)	3.10	24.35	12.73	5.07	→	31.97

*Based on analysis of natural log-transformed pharmacokinetic parameters.

(Source eCTD Module 5.3.1.2, Clinical Trial Report for Study OCT-01, Panel 11-4 Page 39)

In summary, regardless of meal, meal size or timing, the oral bioavailability of oral octreotide is reduced significantly when administered with food. Except for a ~60% decrease in exposure following administration 1 hour before a reduced size high fat meal, there were higher magnitude of decreased exposure ranging from ~82% to ~92% following the other 4 meal size/timing treatments.

Based on this information, Mycapssa should be recommended to be taken with a full glass of water on an empty stomach (ie, at least 1 hour before a meal or at least 2 hours after a meal).

2.7.3 Does alcohol influence the release of octreotide from Mycapssa capsule?

The sponsor conducted an *in vitro* alcohol induced dose dumping study of octreotide from Mycapssa capsules. At the 40% (v/v) alcohol level, the drug started releasing around 30 minutes (in the acidic stage) and released more than 90% of the drug by 2 hours. In contrast, only ~5% of the drug was released at 2 hrs from the 20%(v/v) alcohol level media and practically no release from media containing 10%, and 5% alcohol (v/v) level at the 2-hour mark. For complete details, please see the Biopharm review by Dr. Vidula Kolhatkar in DARRTS.

The sponsor submitted a biowaiver request for In Vivo Alcohol-Induced Dose Dumping Testing. In the waiver request, the sponsor states the following:

“An *in vitro* alcohol dose dumping study (75-60-56) demonstrated premature release of octreotide acetate with alcohol at concentrations of $\geq 40\%$, although this release would not inherently lead to an increase in systemic exposure based on the pharmacokinetic studies in rats (75-30-05) which demonstrated that octreotide absorption was 50-fold higher when octreotide-TPE was administered to the rat jejunum compared to the rat stomach. In the cases of higher alcohol concentrations wherein alcohol compromises the enteric coating and induces premature release of the drug in the stomach, lower exposure is more likely. This would affect efficacy rather than safety of the product. While decreased efficacy could pose a safety concern in certain diseases or with drugs with a narrow therapeutic index where acute loss of pharmacologic effect would exacerbate the condition, this is not the case for this product for the treatment of a chronic and slowly progressing disease like acromegaly. Based on the formulation of MYCAPSSA, the release of capsule contents in the stomach does not pose a safety concern, as the formulation and its individual components will be broken down in the lumen of the stomach resulting in minimal or no systemic octreotide exposure. Additionally, based on the results of food effect studies with the oral octreotide capsules, the Sponsor intends to include clear instructions for use in the product label which will state that the drug product is to be taken 1 hour before a meal or at least 2 hours after a meal and to swallow capsules with water (Section 1.14.1). The avoidance of alcohol, or any other drink or food, with consumption of the drug is therefore inherent with these dose-administration restrictions. Additional details on the rationale are provided in Section 2.7.1.8.1.”

We agree with the sponsor that likely alcohol induced dose dump of octreotide will not pose a safety concern, due to the poor absorption characteristics of octreotide from the acidic environment.

2.8 Analytical

2.8.1 Are the analytical methods for octreotide appropriately validated?

An HPLC assay with MS/MS detection was developed to detect octreotide in human serum. The assay was validated serum samples in terms of recovery, linearity, accuracy, precision and sensitivity.

Octreotide:

The method is briefly described as follows:

A bioanalytical method was developed and validated for the analysis of octreotide in human plasma and serum, utilizing

(b) (4)

(b) (4)

(b) (4) The

peak area ratios of octreotide to internal standard were plotted versus concentration, and the unknown concentrations of quality controls and subject samples were interpolated from the reference standard curve. Plasma and serum octreotide concentrations were reported as ng/mL.

The sponsor reports that three versions of this method, LCMS 296 Version 2 (Validation in Human Tripotassium EDTA Plasma (K3EDTA), LCMS 296 Version 3 (Validation in Human Dipotassium EDTA (K2EDTA) Plasma), and LCMS 296.4 Version 1 (Validation in Human Serum) were independently validated and utilized for the quantitation of octreotide in human K3EDTA, K2EDTA plasma, and serum samples.

A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in [Table 52](#).

Three drug-drug interaction studies were conducted requiring the quantitation of digoxin, lisinopril, norgestrel, ethinyl estradiol, metformin, hydrochlorothiazide, (R, S)-warfarin, and cyclosporine utilizing previously validated analytical methods at the analytical CRO (PPD). A listing of these studies is presented in [Table 53](#). According to the sponsor, in all cases, analyte interference testing was conducted at the time of sample analysis to assure that the interactive drugs including octreotide did not interfere with the quantitation of any of the analytes being tested.

Table 52 Summary of Studies Supported by the Quantitation of Octreotide in Human Plasma and Serum via HPLC with MS/MS Detection

Clinical Protocol No.	PK Report Title	Date of PK Report	Sample Analysis Report Title	Date of Bioanalytical Report	Bioanalytical Method(s) (conducted by PPD)
CHI-001	A Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Oral Doses of Octreolin™ Compared to a Single Subcutaneous Injection of Octreotide in Healthy Volunteers Protocol CHI-001 Pharmacokinetic Report Amendment 1 (Appendix 16.2.6)	May 2013	Reissued Analytical Report Project REV Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	March 2013	LCMSC 296 V 2 (Appendix 16.1.10)
CHI-002	A Single-Dose, Two-Way Cross-Over Study to Evaluate the Effect of Food on the Bioavailability of Octreotide from Oral Octreolin™ Capsules in Healthy Volunteers Protocol CHI-002 Pharmacokinetic Report Amendment 1 (Appendix 16.2.6)	May 2013	Reissued Analytical Report Project GCW Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	March 2013	LCMSC 296 V 2 (Appendix 16.1.10)
CHI-004	A Phase 1 Single-Dose Cross-Over Study to Evaluate the Duration of Octreolin™ Induced Intestinal Permeability as Determined by the Lactulose/Mannitol Assay in Healthy Adult Volunteers Protocol CHI-004 Pharmacokinetic and Pharmacodynamic Report Amendment 1 (Appendix 16.2.6)	May 2013	Reissued Analytical Report Project GSW Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	March 2013	LCMSC 296 V 2 (Appendix 16.1.10)
CHI-005	A Single-Center, Open-Label Study to Investigate the Pharmacokinetic Interaction Between Octreolin™ and A Proton Pump Inhibitor in Healthy Volunteers Protocol CHI-005 Pharmacokinetic Report Amendment 1 (Appendix 16.2.6)	May 2013	Reissued Analytical Report Project MCX Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	March 2013	LCMSC 296 V 2 (Appendix 16.1.10)

Clinical Protocol No.	PK Report Title	Date of PK Report	Sample Analysis Report Title	Date of Bioanalytical Report	Bioanalytical Method(s) (PPD)
OCT-01	A Single-Center, Pilot, Partially-Randomized, Open-Label, Crossover, Adaptive Study Designed to Investigate the Effect of Meal Size and Timing on Octreolin™ Pharmacokinetics in Healthy Volunteers Protocol OCT-01 Pharmacokinetic Report (Appendix 16.2.6)	May 2013	Reissued Analytical Report Project LQY Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10) Analytical Report Project MQY Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection ^a (Appendix 16.1.10)	Jan 2013 April 2014	LCMSC 296 V 2 (Appendix 16.1.10)
CH-PHT-01	Proof of Concept Study Designed to Evaluate the Effects of Octreolin™ on Hepatic Venous Pressure Gradient in Subjects with Cirrhosis and Portal Hypertension Protocol CH-PHT-01 Pharmacokinetic and Pharmacodynamic Report Amendment 1 (Appendix 16.2.6)	Jan 2014	Analytical Report Project WUX Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	April 2013	LCMSC 296 V 2 (Appendix 16.1.10)
OCT-02	A Single-Dose, Crossover Study to Investigate the Effect of Octreolin™ 40 mg on the Bioavailability of Digoxin and Lisinopril and the Influence of Ingested Water Volume on the Pharmacokinetic Profile of Octreolin™ in Healthy Volunteers Protocol OCT-02 Pharmacokinetic Report (Appendix 16.2.6)	May 2013	Analytical Report Project HLZ Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	May 2013	LCMSC 296 V 2 (Appendix 16.1.10)
CHI-006	A Single-Dose, Crossover Study to Investigate the Drug-Drug Interaction Between Oral Octreotide Acetate and Four Probe Drugs, Warfarin, Hydrochlorothiazide, Metformin and Estradiol, in Healthy Volunteers Protocol CHI-006 Pharmacokinetic Report (Appendix 16.2.6)	May 2013	Analytical Report Project CLZ Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	July 2013	LCMSC 296 V 2 (Appendix 16.1.10)

^a Analysis of samples from the Adaptive portion of the study

Clinical Protocol No.	PK Report Title	Date of PK Report	Sample Analysis Report Title	Date of Bioanalytical Report	Bioanalytical Method(s) (PPD)
CH-ACM-01	Efficacy and Safety of Oral Octreolin® in Patients with Acromegaly Who Are Currently Receiving Parenteral Somatostatin Analogs, Pharmacokinetic/Pharmacodynamic Report (Appendix 16.2.13, page 287)		Analytical Report Projects XUX and XUX2 Quantitation of Octreotide in Human Plasma and Human Serum via HPLC with MS/MS Detection (Appendix 16.1.10)	April 2014	LCMSC 296 V 2 (CHI -004 16.1.10 page 935) LCMSC 296.4 V 1.00 (Section 5.3.1.4)
OCT-03	A Single-Center, Randomized, Open-Label, Single-Dose, Crossover Study to Investigate the Pharmacokinetic Interaction between Octreolin™ and Drugs that Affect Gastrointestinal Mobility and the Effect of Body Posture on Absorption of Octreotide from Octreolin™ in Healthy Volunteers Protocol OCT-03 Pharmacokinetic Report Amendment I (Appendix 16.2.6)	March 2014	Analytical Report Project GVZ Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	March 2014	LCMSC 296 V 3 (Appendix 16.1.10 Report OCT -04 16.1.10 page 658)
OCT-04	A Single-Dose, Crossover Study to Investigate the Drug-Drug Interaction Between Octreolin™ and Cyclosporine in Healthy Volunteers Protocol OCT-04 Pharmacokinetic Report Amendment II (Appendix 16.2.6)	March 2014	Analytical Report Project RAFL Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	March 2014	LCMSC 296 V 3 (Appendix 16.1.10)
CHI-007	A Phase 1, Open-Label Study to Evaluate the Safety and Pharmacokinetics of 40 mg Oral Octreotide Acetate in Subjects with End Stage Renal Disease (ESRD) and Subjects with Severe Renal Impairment, Compared to Matched Normal Healthy Subjects Protocol CHI-007 Pharmacokinetic Report Amendment I (Appendix 16.2.6)	June 2014	Analytical Report Project RBBI Quantitation of Octreotide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	March 2014	LCMSC 296 V 3 (Appendix 16.1.10)

(source: Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 2.7.1-3, pages 29-31)

Table 53 Summary of Drug-Drug Interaction Studies Supported by the Quantitation of Interactive Drugs in Human Plasma and Whole Blood via HPLC with MS/MS Detection

Clinical Protocol No.	PK Report Title	Date	Sample Analysis Report Title	Date	Bioanalytical Method(s)
OCT-02	A Single-Dose, Crossover Study to Investigate the Effect of Octreolin™ 40 mg on the Bioavailability of Digoxin and Lisinopril and the Influence of Ingested Water Volume on the Pharmacokinetic Profile of Octreolin in Healthy Volunteers Protocol OCT-02 Pharmacokinetic Report (Appendix 16.2.6)	May 2013	Analytical Report Project ILZ Quantitation of Digoxin in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	June 2013	LCMSD 455.2 (Appendix 16.1.10)
			Analytical report Project AGZH Quantitation of Lisinopril in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	June 2013	P1206 (Appendix 16.1.10)
CHI-006	A Single-Dose, Crossover Study to Investigate the Drug-Drug Interaction between Oral Octreotide Acetate and Four Probe Drugs, Warfarin, Hydrochlorothiazide, Metformin and Estradiol, in Healthy Volunteers Protocol CHI-006 Pharmacokinetic Report (Appendix 16.2.6)	May 2013	Analytical Report Project GLZ Quantitation of Ethinyl Estradiol and Norgestrel in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	July 2013	LCMSD 256.1 (Appendix 16.1.10)
			Analytical Report Project FLZ Quantitation of Metformin in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	June 2013	LCMS 153.5 V2 (Appendix 16.1.10)
			Analytical Report Project ELZ Quantitation of Hydrochlorothiazide in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	June 2013	LCMSD 205.5 (Appendix 16.1.10)
			Analytical Report Project DLZ Quantitation of Warfarin Enantiomers in Human Plasma via HPLC with MS/MS Detection (Appendix 16.1.10)	June 2013	LCMSB 194 V 2 (Appendix 16.1.10)
OCT-04	A Single-Dose, Crossover Study to Investigate the Drug-Drug Interaction Between Octreolin™ and Cyclosporine in Healthy Volunteers Protocol OCT-04 Pharmacokinetic Report Amendment II (Appendix 16.2.6)	March 2014	Analytical Report Project RAFM Quantitation of Cyclosporine in Human Whole Blood via HPLC with MS/MS Detection (Appendix 16.1.10)	April 2014	LCMSD 582 (Appendix 16.1.10)

(source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1-6, page 34)

(b) Human Growth Hormone (GH)

Human Growth Hormone (GH) was assayed by a IDS-iSYS hGH assay, which is a sandwich type immunoassay. The assay's detection principle is chemiluminescence. Growth hormone molecules are captured by a biotinylated monoclonal anti-GH antibody, which binds then to streptavidin-coated magnetic particles. After incubation and a washing step, an acridinium-labelled anti-GH antibody is added to give a directly proportional chemiluminescence signal, initiated by the triggers hydrogen peroxide and sodium hydroxide.

The specificity of the monoclonal anti-GH antibodies is shown [Table 54](#).

Table 54 Cross Reactivity of Anti-GH Monoclonal Antibodies

Analyte, MW (concentration)	Cross-Reactivity
GH, 22kDa	100%
GH, 20kDa (10 ng/mL)	None Detected
Placental GH (200 ng/mL)	None Detected
HPL (10,000 ng/mL)	None Detected
Prolactin (40,000 ng/mL)	None Detected
Pegvisomant (50,000 ng/mL)	None Detected

Source: Validation Report: Human Growth Hormone (GH) IDS-iSYS IS-3700 (CH-ACM-01 Appendix 16.1.10 page 989)

The lower limit of quantification (LOQ) set by the instrument software for the determination of GH is 0.05 ng/mL. Concentrations below the LOQ are reported as < 0.05 ng/mL by the iSYS Analyzer. To verify the reproducibility of the assay at concentrations below the lowest calibration standard of 0.17 ng/mL, 7 independent human serum samples were obtained with GH concentrations at or below the lowest calibration standard; only RLU (raw data) values are reported for those samples with concentrations below the LOQ. These samples were assayed in replicates of 10 in a single analytical run. The lower limit of quantitation was defined as the lowest concentration measurable with an acceptable intra-assay variability of < 15%.

Results demonstrating the lower limit of quantitation for GH was confirmed to be 0.05 ng/mL is shown in [Table 55](#).

Table 55 Summary of Results to Confirm LOQ of 0.05 ng/mL GH

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7
n	10	10	10	10	10	10	10
Mean (ng/mL)	0.20	0.08	0.11	0.09	0.06	1535.60 ^a	1722.40 ^a
SD	0.01	0.01	0.01	0.01	0.00	74.52	104.04
CV%	5.60	6.15	7.42	6.87	5.18	4.85	6.04

^a The iSYS Analyzer reports GH concentrations below the LOQ as <0.05 ng/mL. Results for Samples 6 and 7 were below the LOQ; therefore, for the purpose of this experiment, the counts RLU were reported in order to determine the %CV of the instrument output
Source: Validation Report: Human Growth Hormone (GH) IDS-iSYS IS-3700 (CH-ACM-01 Appendix 16.1.10 page 994)

(a) Insulin-like Growth Factor-1 (IGF-1):

IGF-1 was assayed by the IDS-iSYS IGF-1, which is a sandwich type immunoassay; the detection principle is chemiluminescence. The samples are acidified to dissociate IGF-1 from binding proteins. The free IGF-1 is captured by a biotinylated monoclonal anti-IGF-1 antibody, which binds then to streptavidin-coated magnetic particles. To generate a signal, an acridinium-labeled anti-IGF-1 antibody is added to give a directly proportional chemiluminescence signal, initiated by the triggers hydrogen peroxide and sodium hydroxide.

The specificity of the monoclonal anti-IGF-1 antibodies is shown [Table 56](#).

Table 56 Cross Reactivity of Anti-IGF-1 Monoclonal Antibodies

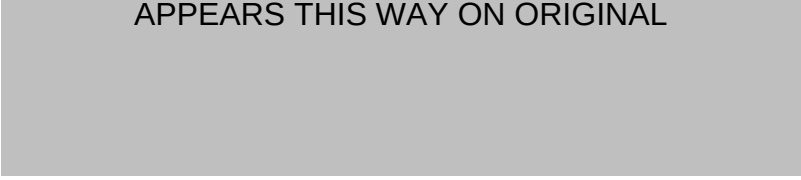
Analyte	Cross-Reactivity
IGF-1	100%
IGF-II	< 0.01%
Proinsulin	< 0.01%
Insulin	< 0.01%

Source: Validation report: IGF-1 IDS-iSYS IS-3900 (Grimminger, 2011)

The lower limit of quantification (LOQ) set by the instrument software for the determination of IGF-1 is 10 ng/mL. Concentrations below the LOQ are reported as < 10 ng/mL by the iSYS Analyzer. To verify the reproducibility of the assay at concentrations below the lowest control (27.9 ng/mL) and calibration standard (14.1 ng/mL), 3 independent human serum samples were obtained with IGF-1 concentrations between 13 and 39 ng/mL, and 2 samples below 10 ng/mL. For samples with IGF-1 concentrations below 10 ng/mL, only raw data from IDS-iSYS IS-3700 hGH assay (RLU) values are reported. These samples were assayed in replicates of 10 in a single analytical run. The lower limit of quantitation was defined as the lowest concentration measurable with an acceptable intra-assay variability of < 15%. The %CV for samples with IGF-1 concentrations > 10 ng/mL ranged from 2.0 to 8.0 %. The %CV for the two samples with IGF-1 concentration < 10 ng/mL were 6.8% and 9.3%. The limit of quantitation of 10 ng/mL demonstrates acceptable precision.

3 APPENDIX

APPEARS THIS WAY ON ORIGINAL



3.1 OCP Filing Memo

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208232	SDN	0000
Applicant	Chiasma, Inc	Submission Date	18 Jun 2015
Generic Name	Octreotide	Brand Name	MYCAPSSA
Drug Class	Somatostatin analog		
Indication	Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)		
Dosage Regimen	- Patients currently taking somatostatin analog therapy can be transitioned to MYCAPSSA with an initial dose of 20 mg BID given orally (20 mg morning + 20 mg evening). Blood levels of IGF-1 and clinical symptoms should be monitored. If IGF-1 is normal and clinical symptoms are controlled or response level (biochemical and symptomatic response) is maintained, continue MYCAPSSA dosage at 20 mg BID. - Dosage may be increased to 60 mg daily (40 mg morning + 20 mg evening) if IGF-1 levels increase, as determined by the physician. - Continue monitoring, applying the above algorithm for maintaining or increasing the dose up to 80 mg daily (40 mg morning + 40 mg evening).		
Dosage Form	Capsule	Route of Administration	Oral
OCP Division	DCP 2	OND Division	DMEP
OCP Review Team	Primary Reviewer(s)		Secondary Reviewer/ Team Leader
Division	Suryanarayana Sista, PhD		Jayabharathi Vaidyanathan, PhD
Pharmacometrics			
Genomics			
Review Classification	☒ Standard ☐ Priority ☐ Expedited		
Filing Date	8/14/2015	74-Day Letter Date	8/28/2015
Review Due Date	3/11/2016	PDUFA Goal Date	4/15/2016
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
☒ Yes			
☐ No			
If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
☐ Yes			
☒ No			
If yes list comment(s)			
Is there a need for clinical trial(s) inspection?			
☐ Yes			
☒ No			
If yes explain			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☒ Yes ☐ No	Clinical Pharmacology Summary	☒ Yes ☐ No
Bioanalytical and Analytical Methods	☒ Yes ☐ No	Labeling	☒ Yes ☐ No
Clinical Pharmacology Studies			

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☒ Relative Bioavailability	2	CHI-001 (Module 5.3.1.2) CHI-002 (Module 5.3.1.1)
☐ Bioequivalence		
☒ Food Effect	2	CHI-002 (Module 5.3.1.1) OCT-01 (Module 5.3.3.4)
☐ Other		
Human Pharmacokinetics		
Healthy Subjects	☒ Single Dose	3
	☐ Multiple Dose	
Patients	☐ Single Dose	
	☐ Multiple Dose	
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☒ Hepatic Impairment		CHPHT01 (Module 5.3.3.3)
☒ Renal Impairment		CHI-007 (Module 5.3.3.3)
☐ Genetics		
Extrinsic Factors		
☒ Effects on Primary Drug		CHI-005 (Module 5.3.2.2) OCT-03 (Module 5.3.3.4)
☒ Effects of Primary Drug		CHI-006 (Module 5.3.2.2) OCT-02 (Module 5.3.3.4) OCT-04 (Module 5.3.2.2)
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☒ Healthy Subjects		1
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☒ Exposure-Efficacy		1
		CH-ACM-01 (Module 5.3.5.1)

☒ Exposure-Safety	1	CH-ACM-01 (Module 5.3.5.1)		
Total Number of Studies	12	In Vitro		
Total Number of Studies to be Reviewed	12		In Vivo	12

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐ Yes ☒ No ☐ N/A	According to sponsor, commercial scale (b) (4) capsules is the same formulation and uses similar equipment to the clinical trial and safety registration batches (b) (4) capsule scale).
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☒ Yes ☐ No ☐ N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☒ Yes ☐ No ☐ N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☒ Yes ☐ No ☐ N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☒ Yes ☐ No ☐ N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☒ Yes ☐ No ☐ N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☒ Yes ☐ No ☐ N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☒ Yes ☐ No ☐ N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☒ Yes ☐ No ☐ N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was	☐ Yes ☐ No ☒ N/A	An Agency requested <i>in vitro</i> ethanol dose-dumping study with MYCAPSSA showed dose dumping of octreotide capsules. At the Pre-NDA meeting, the sponsor indicated that this does not pose a safety risk and asked if the Agency agreed that no <i>in vivo</i> data was required to assess alcohol dose dumping. The sponsor submitted a biowaiver request of this study with supporting information in the NDA.

previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐ Yes ☒ No ☐ N/A	Data not in SDTM format, however, pertinent information can be imported from the provided SAS transport files.
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐ Yes ☐ No ☒ N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☒ Yes ☐ No ☐ N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐ Yes ☒ No ☐ N/A	Sponsor's dose selection was based on a review in the literature by Chanson et al (1993), which indicated that a 500 µg/day infusion of octreotide to healthy volunteers suppressed growth hormone concentrations to < 0.25 µg/L, a concentration indicative of effect in subjects with pituitary tumors
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐ Yes ☒ No ☐ N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐ Yes ☒ No ☐ N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐ Yes ☐ No ☒ N/A	The drug was granted Orphan Drug Designation on 17 July, 2010, and based on an advice letter issued by the Agency dated 30 August, 2010, pediatric studies are not required for drug products granted orphan drug designation. In addition the sponsor was informed that a Pediatric Study Plan (PSP) was not required (Pre-NDA meeting minutes 20 June, 2014).
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☒ Yes ☐ No ☐ N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐ Yes ☐ No ☒ N/A	



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NDA 208232 Filing Meeting

Octreotide (MYCAPSSA)

Sponsor: Chiasma, Inc

Submitted: 18 Jun 2015

OCP Review Team:

Clin Pharm Reviewer:

Sury Sista, PhD

Clin Pharm Team Leader:

Jayabharathi Vaidyanathan, PhD

CDER—Office of Clinical Pharmacology

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Overview



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- **Type of Submission:** 505 (b)(2)
- **Regulatory Background:**
 - Orphan Drug Designation Granted: 17 July, 2010
 - Pediatric studies are not required for drug products granted orphan drug designation: Advice letter, 30 August, 2010
 - Pediatric Study Plan (PSP) not required: Pre-NDA meeting minutes 20 June, 2014
- **Proposed Indication:**
 - Long-term maintenance treatment in acromegaly patients (b) (4)
- **Formulation:** Oral Capsules
 - 20 mg octreotide
- **Dosing Regimen (Sponsor's Proposal):**
 - Patients currently taking somatostatin analog therapy can be transitioned to MYCAPSSA with an initial dose of 20 mg BID given orally (20 mg morning + 20 mg evening). Blood levels of IGF-1 and clinical symptoms should be monitored. If IGF-1 is normal and clinical symptoms are controlled or response level (biochemical and symptomatic response) is maintained, continue MYCAPSSA dosage at 20 mg BID
 - Dosage may be increased to 60 mg daily (40 mg morning + 20 mg evening) if IGF-1 levels increase, as determined by the physician
 - Continue monitoring, applying the above algorithm for maintaining or increasing the dose up to 80 mg daily (40 mg morning + 40 mg evening)

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Reference ID: 3810578

Overview

• Clinical Pharmacology/Biopharmaceutics Program

- Phase 1: 11 studies; Phase 3: 1 study

Clinical Pharmacology Studies							Efficacy and Safety Study
Bioavailability	BA/Dose Escalation	DDI	Hepatic Impairment	Renal Impairment (ESRD and Severe)	PK/Toxicokinetic Factors	PD	
CHI002	CHI001	CHI005 CHI006 OCT04	CHI0101	CHI007	OCT01 OCT02 OCT03	CHI004	CHI001

An in vitro alcohol induced dose-dumping study (40% level) showed that alcohol-induced dose dumping was apparent (I2=7) (OCP – will be addressed via labeling)

• Cross reference to other NDA and Published Literature:

- The sponsor is relying upon the reference product Sandostatin (octreotide acetate) Injection (approved under NDA 019667), as well as literature, to support this 505(b)(2) NDA application
 - Sandostatin NDA**
 - MOA, Distribution, Metabolism, Elimination (partial for healthy, renal, hepatic and acromegaly patients; full for elderly), DDI with insulin, Other concomitant drug therapy, Drug metabolism interactions (other DDI)
 - Published Literature**
 - Relationship between octreotide concentrations and IGF-1 and GH serum levels

• No Pivotal BE studies: Proposed commercial formulation is the same as the one used in Phase 1 and 3 studies

3

Sponsor's Dose Selection Rationale

• Sponsor proposed the following rationale for dose selection (from study CHI001) :

- Based on a review by Chanson et al, a 500 µg/day infusion of octreotide to healthy volunteers suppressed growth hormone concentrations to < 0.25 µg/L, a concentration indicative of effect in subjects with pituitary tumors (Chanson, 1993). This level of suppression was associated with a plasma octreotide concentration of approximately 0.5 to 1 ng/mL. The duration of plasma concentrations 0.5 and 1 ng/mL for the 4 treatments in study CHI-001 was calculated as the difference between the times of the first concentration 0.5 and 1 ng/mL and the first concentration < 0.5 and 1 ng/mL. Results of these analyses showed that a dose of Octreolin 20 mg was comparable to a 0.1 mg sc dose of octreotide (Sandostatin) in systemic exposure (AUC) and duration of time with plasma concentrations 0.5 or 1 ng/mL.

Parameter*	Octreotide 0.1 mg SC	Octreolin 5 mg PO	Octreolin 10 mg PO	Octreolin 20 mg PO
Time: 0.5 ng/mL (h)	5.92 (12) [4.92 – 7.92]	0.66 (3) [0.66 – 1.67]	3.34 (12) [0.34 – 7.67]	7.33 (9) [1.66 – 21.0]
Time: 1 ng/mL (h)	3.92 (12) [2.92 – 4.92]	—†	1.34 (9) [0.33 – 5.00]	4.17 (8) [0.33 – 11.0]

*Median (N) [Range]

†There were no concentrations ≥ 1 ng/mL.

PO = oral administration; SC = subcutaneous

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Reference ID: 3810578

Overview: PK & PD

- **Pharmacokinetics**
 - Relative bioavailability following single-dose (oral compared to sc): 0.5%
 - Median T_{max} ~ 1.67 – 2.5 hours; $t_{1/2}$ ~ 2-4 h
 - Food leads to an approximately 90% decrease in extent of absorption
 - Mean AUC and C_{max} appear to increase in a approximately dose-proportional manner
 - Bioavailability decreased 60% when MYCAPSSA was administered 1 hour before a reduced-size high-fat meal
 - Volume of distribution (Vd_{ss}) ~ 13.6 L
 - Total body clearance: 7 L/h - 10 L/h
 - 65% bound in the plasma mainly to lipoprotein and, to a lesser extent, to albumin
 - **Acromegaly Patients:** Mean peak concentration of 2.8 ng/mL (100- μ g dose) reached in 0.7 hours after sc dosing; Volume of distribution (Vd_{ss}) estimated to be 21.6 ± 8.5 L; Total body clearance increased to 18 L/h; Mean percent of drug bound was 41.2%; $t_{1/2}$ ~ 1.7 – 1.9 hours
- **Pharmacodynamics**
 - Serum GH concentrations were reasonably constant over the 2.5 to 4 hour period after dosing in all 3 dosing cohorts (40-mg, 60-mg and 80-mg)
 - Response defined as IGF-1 < 1.3 times ULN adjusted for age and an integrated GH level over 2 hours < 2.5 ng/mL
 - There does not seem to be a relationship between octreotide AUC_{0-4hr} and GH C_{max} or normalized IGF-1 levels
- **QT**
 - There was no apparent effect of octreotide on $\Delta QTcF$ in the sub-population assessed in study CHACM01

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Overview: Extrinsic/Intrinsic Factors

	C_{max}	AUC	T_{max}
Effect of Other Drugs on Octreotide			
PPI	↓48%	↓50%	↔
Metoclopramide 2 hrs pre-octreotide	↓5%	↓10%	↔
Loperamide 2 hrs pre-octreotide	↓10%	↔	↑1 hr
Effect of Octreotide on Other Drugs			
Metformin	↔	↔	↑2 hrs
Warfarin (R- and S-Warfarin)	↔	↔	↑1 hr R-Warfarin ↑0.5 hrs S-Warfarin
Levonorgestrel	↓38%	↓24%	↑1 hr
HCTZ	↓8%	↓15%	↑1.25 hrs
Ethinyl Estradiol	↔	↔	↑0.9 hrs
Cyclosporine	↓70%	↓60%	↑1.5 hrs
Digoxin	↑37%	↔	↑2 hrs
Lisinopril	↑50%	↑40%	↓0.5 hrs

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Reference ID: 3810578

Overview: Extrinsic/Intrinsic Factors

	C_{max}	AUC	T_{max}
Effect of Meal on Octreotide			
1 hour before full high-fat meal	↓80%	↓86%	↓1.5 hrs
1 hour after full high-fat meal	↓91%	↓92%	↔
0.5 hours before reduced size high-fat meal	↓74%	↓80%	↓1.5 hrs
1 hour before reduced size high-fat meal	↓64%	↓42%	↓1 hr
2 hour after full high-fat meal	↓89%	↓87%	↑1.25 hrs
Effect of Volume of Water on Octreotide Absorption			
75 mL water compared to 240 mL	↓25%	↓24%	↓0.5 hrs
Effect of Posture on Octreotide Absorption			
Morning Standing vs. Semi-Sitting	↓29%	↓39%	↔
Morning, Semi-Sitting vs. Evening Semi-Sitting/Laying	↓70%	↓45%	↑1.5 hrs

Sponsor's Recommendation: MYCAPSSA should be taken with a glass of water on an empty stomach (i.e., at least 1 hour before a meal or at least 2 hours after a meal). Drinking of water is allowed during these times

Overview: Extrinsic/Intrinsic Factors

- Hepatic Impairment:**

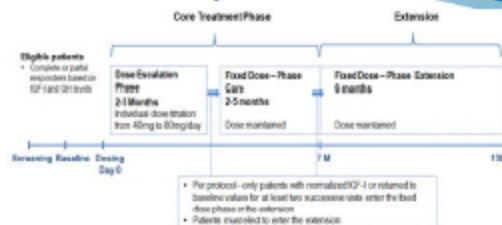
- PK of octreotide following 10 mg or 20 mg of oral octreotide in subjects with stable cirrhosis and portal hypertension is comparable to the PK in healthy volunteers.
- No substantive differences in C_{max} , AUC_{0-4h} , AUC_{0-24h} , or $t_{1/2}$ between Child-Pugh Classes
- Dosing Recommendation (per sponsor):**
 - In patients with Child Pugh A and B no dose adjustment is necessary; the dose of MYCAPSSA should be titrated upward based on clinical response. However, careful monitoring of patients with Child Pugh C liver cirrhosis initiating treatment with MYCAPSSA is recommended

- Renal Impairment:**

- Subjects with ESRD on dialysis had higher mean plasma concentrations compared to subjects with severe renal impairment, as well as higher mean values for C_{max} , AUC_{0-4h} , AUC_{0-24h} , and $t_{1/2}$.
- Subjects with ESRD on dialysis had a decrease in CL/F with a corresponding increase in AUC_{0-24h} and $t_{1/2}$ compared to matched healthy subjects
- Subjects with severe renal impairment had 18% reduced AUC and 30% reduced C_{max} compared to matched healthy subjects
- Dosing Recommendation (per sponsor):**
 - In patients with mild, moderate, or severe renal impairment there is no need to adjust the starting dose of MYCAPSSA. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in non-renal patients

Overview: Phase 3 Study

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GH = growth hormone; IGF-1 = insulin-like growth factor-1

Efficacy results:

- Overall response to MYCAPSSA was 65% at 7 month and 62% at 13 months, 59% at the end of the Core Treatment Period, compared to 89% on injectable therapy at baseline
- 85% of patients who entered the Fixed Dose Phase as responders maintained response at the End of Treatment (Core + Extension).
- 76% of the complete responders at baseline still responded to MYCAPSSA at the End of Treatment (Core + Extension)
- High response rates were seen particularly at the 40 mg and 60 mg, 87% and 67%, respectively (measured at the End of the Core Treatment Period)
- Similar high response was observed in the analysis of all patients entering the Fixed Dose Phase who showed responses of 88% at 40 mg, 84% at 60 mg, and 47% at 80 mg (measured at the End of the Core + Extension Treatment Period)

Overview: Phase 3 Study

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- Determination of the effect of MYCAPSSA therapy on IGF-1 levels and GH levels, as measures of response

PK sub-study results:

- An approximately dose-proportional increase in mean plasma octreotide concentrations was noted after chronic administration of MYCAPSSA at 40 mg (20 mg BID), 60 mg (40 mg AM/20 mg PM), and 80 mg (40 mg BID)
- Mean plasma octreotide trough values (at time zero), were comparable for the 40 and 60 mg regimens, each of which represent a prior 20 mg overnight dose, with a higher mean trough for the 80 mg regimen, which represents a 40 mg prior overnight dose
- Elimination of octreotide was slightly slower than that observed in healthy volunteers, with apparent mean half-life values at steady state ranging from 3.19 ± 1.07 (mean $\pm$ SD, on 40mg) to 4.47 ± 2.02 hours (on 80 mg)
- There was no apparent effect of octreotide on AQTcF in the sub-population assessed

Key Questions: Key Review Focus

- What are the PK and PD features of octreotide?
- Is there an exposure-efficacy relationship?
- Is there an exposure-safety relationship?
- Is there any need for dose adjustment based on intrinsic factors?
- Is there any need for dose adjustment based on extrinsic factors?

11

Application Filability and Consults

- Yes, this application is filable from Clinical Pharmacology perspective
- OSI consults – None
- Request for Sponsor – None at the moment. SAS datasets may be in non-standard format. If data cannot be imported properly, sponsor will be notified in the 74-day letter

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Reference ID: 3810578

Filing Memo									
IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?	☒ Yes ☐ No								
If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.									
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.									
Comments to Sponsor:									
<table> <tr> <td><u>Survanaravana M. Sista</u></td> <td><u>24 Aug. 2015</u></td> </tr> <tr> <td><u>Reviewing Clinical Pharmacologist</u></td> <td><u>Date</u></td> </tr> <tr> <td><u>Jayabharathi Vaidyanathan</u></td> <td><u>24 Aug. 2015</u></td> </tr> <tr> <td><u>Acting Team Leader</u></td> <td><u>Date</u></td> </tr> </table>		<u>Survanaravana M. Sista</u>	<u>24 Aug. 2015</u>	<u>Reviewing Clinical Pharmacologist</u>	<u>Date</u>	<u>Jayabharathi Vaidyanathan</u>	<u>24 Aug. 2015</u>	<u>Acting Team Leader</u>	<u>Date</u>
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/s/

SURYANARAYANA M SISTA

08/24/2015

JAYABHARATHI VAIDYANATHAN

08/24/2015

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SURYANARAYANA M SISTA
04/08/2016

JAYABHARATHI VAIDYANATHAN
04/08/2016