CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA208232
Drug Name:	Mycapssa (Oral Octreotide capsules)
Indication(s):	Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)
Applicant:	Chiasma
Date(s):	Stamp date: December 26, 2019
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Keywords: NDA review, clinical studies, endpoint analysis

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1 EXECUTIVE SUMMARY

Chiasma submitted an addendum to 505(b)(2) NDA for Mycapssa. Mycapssa is an oral delivery drug that is designed to replace the injectable octreotide medications for subjects with acromegaly. The proposed indication of Mycapssa is long-term maintenance treatment in acromegaly patients (b) (4) (b) (4) The goals of treatment with Mycapssa were to control insulin-like growth factor-1 (IGF-1) levels and acromegaly symptoms.

The submission is comprised of two Phase 3 trials (CH-ACM-01 and OOC-ACM-303). Study CH-ACM-01 was previously submitted in June 2015. On April 15, 2016, the Agency issued a Complete Response (CR) letter citing insufficient evidence to support the approval. The key reasons outlined in the CR letter [Reference ID: 3918130] are listed below:

1. Study CH-ACM-01 was a single-arm open-label trial that did not require confirmation of disease activity prior to the baseline assessment to account for the cumulative effects of past therapies on disease activity.
2. Drugs (long-acting somatostatin analogs) known to be effective at suppressing growth hormone (GH) and IGF-1 were withdrawn close to the baseline assessment and had a lingering pharmacodynamic effect during a large portion of the efficacy phase of the study. Also, at least some responders in the trial could have been responders because they did not have active disease at last assessment or because of the carryover effects of prior treatments on disease activity.
3. The Agency noted that the overall worsening of control in the majority of patients, based on rising IGF-1 levels between baseline and last on treatment assessment. This is concerning because a subject classified as a responder and whose IGF-1 trajectory is on a rising trend may reveal himself to be a treatment failure at a later assessment time point.

The Agency recommended to conduct a double-blind placebo-controlled trial to address the deficiencies. The focus of this review is the newly submitted study OOC-ACM-303.

Similar to the study CH-ACM-01, trial OOC-ACM-303 consisted of core and extension periods. The core part of this new study was double-blind, and placebo controlled. The extension part involved only a subgroup of subjects who completed the core period and voluntarily entered the extension period. Therefore, the extension study will not be useful in evaluation of efficacy of Mycapssa in the entire population for which the drug is indicated. Consequently, my review only covers the core part of the study.

Statistical issues and findings:

1. **Limitation of use:** Although several subjects on Mycapssa did not reach the threshold of IGF-1 greater than the upper limit normal (ULN) during the trial, based on data observed in trial CH-ACM-01 and in trial OOC-ACM-303, the IGF-1 continued to rise during both trials, suggesting that over time subjects on drug might lose IGF-1 control. Therefore, long-term successful treatment with this drug might not be possible. Based on

recommendation from clinical team, patients should undergo regular monitoring of their IGF-1 levels to make sure that their acromegaly is under control.

2. **Study conduct:**
   a. **Eligibility criteria:** not all randomized subjects met pre-specified eligibility criteria (biochemical control on somatostatin analogs, i.e. average of two screening IGF-1 measurements ≤1xULN), n=7(12.5%). Most of those subjects were on placebo (n=5). To mitigate this issue, I recommend include only data from eligible subjects in the product label. The outcomes based on the study-eligible cohort did not change my conclusions about efficacy of Mycapssa.
   b. **Rescue:** subjects were rescued without meeting the prespecified rescue criteria. Specifically, several subjects on treatment were removed without reaching the threshold of IGF-1 greater than 1.3xULN. This approach to rescue makes the interpretation of time to loss of response (IGF-1>1.3xULN) more challenging, i.e. subjects were taken off treatment prior to ever reaching the threshold thus making it appear that the overall time to loss of response in the treatment group was longer than it would have been if those subjects were rescued according to the prespecified rule.

3. **Rounding of data inputs for the primary analysis model:** rounding of final IGF-1 outcomes that were subsequently put into the primary analysis model resulted in higher success rates for subjects on Mycapssa. To mitigate this issue, my recommendation is to use only the data without rounding. Based on analyses without rounding, the success rates of both, Mycapssa and placebo, were reduced. The overall treatment difference in response rates (Mycapssa-placebo) was slightly reduced from 44% to 41%.

Overall data and submission quality: multiple errors and inconsistences were identified in the reported results and in datasets provided with this submission. Detection and mitigation of these issues required additional time and effort during the review cycle.

In conclusion, the study showed that Mycapssa worked only in 50% percent of subjects. Given that all of the study participants responded favorably to the injective drug, Mycapssa might only work for some of the people with acromegaly. Similar to study CH-ACM-01, the new study did not provide a clear-cut answer regarding the subgroup of patients who could benefit from this drug. This could be due to a small sample size and potential diversity of acromegaly causes and progression between subjects. Given that the injectable octreotide is administered 3 times a day through subcutaneous injections, for some patients Mycapssa could become a more convenient alternative.

In clinical practice, convenience of administration (injection vs tablet) might outweigh the issues of efficacy profile of Mycapssa. Therefore, I recommend approval of Mycapssa. That being said, the label should only reflect the results obtained from eligible subjects without post-hoc rounding of the outcomes. Given increasing levels of IGF-1 over time, I recommend that Mycapssa not be approved for long-term replacement of injectable octreotide.

2 INTRODUCTION

2.1 Overview

A brief description of the drug indication and history of the submission is presented below.

2.1.1 Indication

Chiasma resubmitted this 505(b)(2) NDA for Mycapssa, a drug for the indication for long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)

The goals of treatment in acromegaly is to control IGF-1 levels and to control acromegaly symptoms. The sponsor intends to substitute somatostatin (an injective drug) with Mycappsa (a pill). According to the sponsor, Mycapssa contains the same active ingredient as the injectable octreotide. Currently, all acromegaly medications are administered through an injection.

2.1.2 History of Drug development

An orphan drug designation was granted for Mycapssa on 17 June 2010. The first submission of this NDA consisted of one Phase 3 trial. Study CH-ACM-01 was previously submitted in June 2015. On April 15, 2016, the Agency issued a Complete Response (CR) letter citing insufficient evidence to support the approval. As a result, the Agency recommended to conduct a double-blind placebo-controlled trial to address the deficiencies. The focus of this review is the newly submitted study OOC-ACM-303. This study was conducted under the Special Protocol Agreement (SPA).

Table 1. List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
OOC-ACM-303	**Phase 3 Randomized, double-blind, placebo-controlled**	**9 months (36 weeks)**	**1 year**	**N_{total}=56, 28 each arm**	**Acromegaly patients currently receiving parenteral somatostatin analogs, who are responders to treatment (IGF-1 ≤ 1 × ULN)**

The submission also included an extension study. In my view, the extension study (the way it was planned and conducted) could not be considered an adequate efficacy study because only 50% of the subjects (n=28) stayed for the extension study. This happened because all subjects in the extension phase participated voluntarily. Subjects who failed the treatment in the core study did not participate in the extension period. Because of the reasons indicated above, the extension period of study OOC-ACM-303 is not a part of my efficacy review.

2.2 Data Sources

This submission is in electronic common technical document (eCTD) format. The submission is archived at the following link: \\CDSESUB1\evsprod\NDA208232\0031

Study datasets were provided as SAS XPORT transport files. The analysis datasets were joinable by unique identifier (SUBJID). There were multiple errors in the Adeff.xpt dataset. Specifically, for some of the visits, the labels for treatment arm were missing or not matching the treatment arm assignment for the study period. Also, there were inconsistencies in reporting of discontinuation times, such as missing values in variable indicating discontinuation week. All of these issues contributed to the additional need for data cleaning, thus making the review and analysis much more difficult.

I derived from the submitted datasets all results presented in this review. I created all tables and figures in this review unless otherwise noted.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

As mentioned in section 2.2, the analysis datasets were having multiple errors and inconsistences which required additional need for data cleaning.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study design: Study OOC-ACM-303 (referenced as 303 in the rest of the document) was a Phase 3, double-blind, maintenance-of-response, placebo-controlled study in patients with acromegaly who previously responded to and tolerated treatment with somatostatin analogs (injectable SRL).

The Mycapssa treatment period lasted 36 weeks and comprised of an 8-week screening period (two screening visits prior to baseline), followed by double-blind placebo-controlled period (dose escalation through week 24), and single arm open-label extension. Enrollment into the extension phase was voluntary.

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 IGF-1 levels were assessed at every visit (every 4 weeks). For a subject with a single visit IGF-1 level ≥ 1.3 times ULN, a second sample was to be obtained within 2 weeks of the first assessment for a total of 2 consecutive IGF-1 assessments for confirmation of disease activity. The GH level was assessed at the first screening visit, baseline, end of treatment (for those who discontinued study drug early), and the week 36 visit.

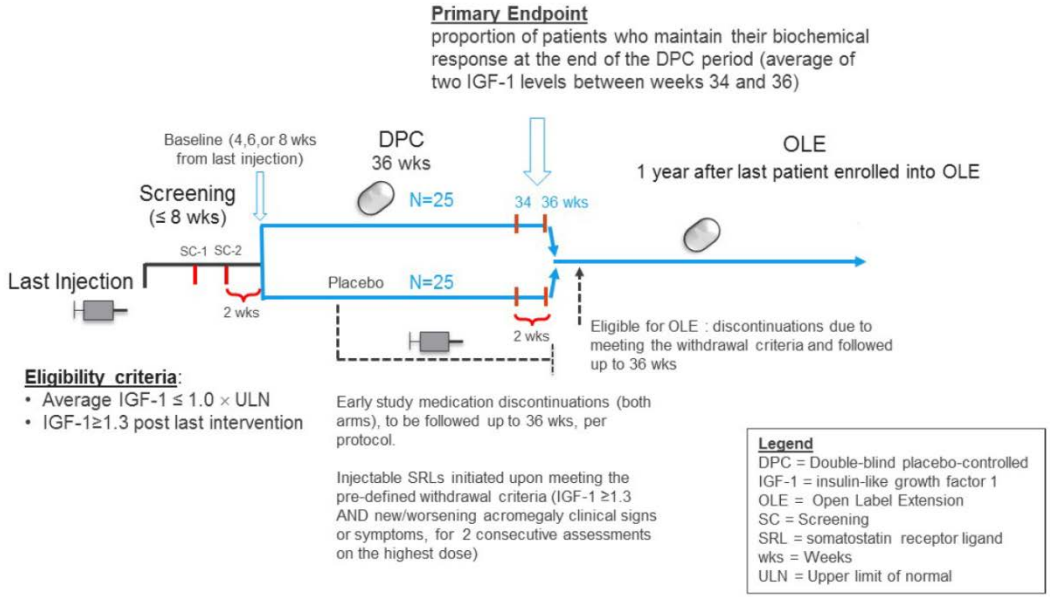
Study eligibility
According to the study protocol and SAP, eligible subjects were supposed to have two screening visits and the average IGF-1 measured at those screening visits should be ≤ 1xULN.

Rescue criteria
The subject was considered to be *inadequately controlled* if he or she experienced IGF-1 levels ≥ 1.3 times ULN and exacerbation of acromegaly (clinical signs or symptoms) for 2 consecutive assessments while treated for at least 2 weeks with 4 capsules per day. Inadequately controlled subjects were to be rescued with the injectable SRL treatment used prior to screening and continued to be followed per protocol (including all in-clinic visits and assessments) until week 36. Exacerbation of acromegaly clinical signs/symptoms was defined as new or worsening of any one of the following: headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia, hypertension, or other signs that in view of the Investigator were related to acromegaly. All of these events were recorded as adverse events of special interest (AESIs).

Patients could revert to injectable somatostatin (SRL) therapy at any time, for either safety or efficacy, at the discretion of the site.

A schematic description of the study design is presented in the Figure 1 below.

Figure 1. Study design



Sourse: Clinical Study Report, p. 37

Primary endpoint
The primary endpoint for the study was the proportion of patients who maintained their biochemical response. Maintenance of response was defined by using the average IGF-1 level of the last 2 available assessments between week 34 and week 36. If the average IGF-1 was ≤ 1 times ULN, a subject would be classified as a responder (i.e., maintained their biochemical

response). Subjects who discontinued treatment for any reason were treated as non-responders for the primary analysis, regardless of their IGF-1 values.

Secondary endpoints

1. **Proportion of patients who maintained GH response** (i.e., GH < 2.5 ng/mL) at week 36, out of those who were responders (i.e., GH < 2.5 ng/mL on SRL injections at screening). GH response was defined using the mean integrated GH value, based on 5 assessments 30 minutes apart. Patients who discontinued treatment were classified as non-responders, regardless of their IGF-1 values.

2. **Time to loss of response:** Loss of response was defined as the earliest time when the IGF-1 of 2 consecutive visits was > 1 times ULN after the patient was treated for at least 2 weeks with 4 capsules per day.

3. **Time to loss of response:** Loss of response was defined as the earliest time when the IGF-1 of 2 consecutive visits was ≥ 1.3 times ULN after the patient was treated for at least 2 weeks with 4 capsules per day.

4. **Proportion of patients who began rescue** treatment prior to and including week 36.

3.2.2 Study Design and Endpoints

Primary Analyses
The applicant utilized exact logistic regression model, with covariates for treatment, baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median) for the analysis of the primary endpoint to obtain the adjusted proportions of response and failure.
The applicant also calculated the difference in proportions and the odds ratio with associated two-sided 95% confidence intervals. All analyses utilized the Full Analysis Set (FAS) that included all randomized subjects regardless of treatment discontinuation.

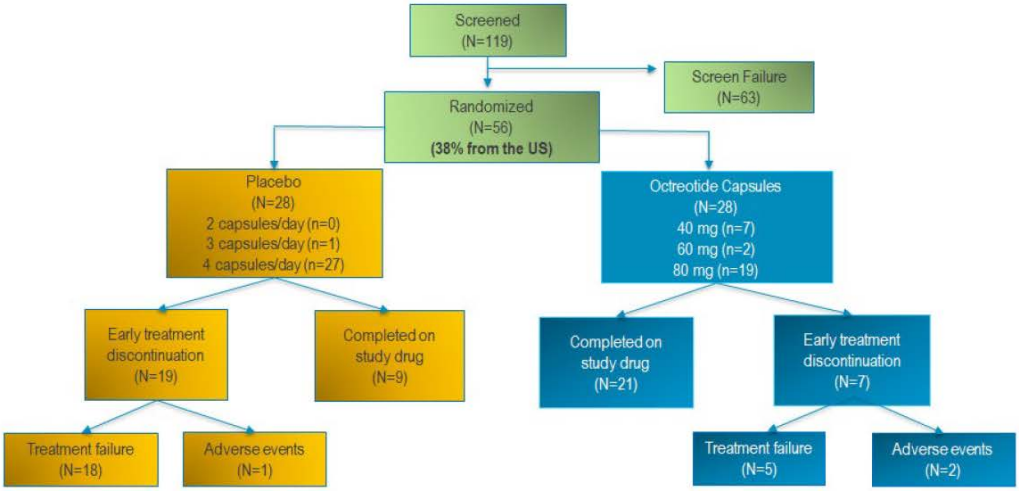
FDA analyses
Based on analyses of provided data, we detected use of undeclared rounding of IGF-1 values in the applicant's submission. The IGF-1 values were rounded at screening (average of 2 screening visits) and at the end of the trial (week 34 and 36). The statistical analysis plan (SAP) states on p.15 "No preliminary rounding should be performed; rounding should only occur after analysis." It appears that the applicant interpreted "after analysis" differently. The applicant used rounding at earlier stages, prior to the statistical analysis and randomization which affected, recruitment, trial conduct, and outcomes. For example, subject (b) (6) that was included in the study had both screening IGF-1 levels above 1xULN (1.093 and 1.006) resulting in average screening IGF-1 equal to 1.0495, i.e. above the prespecified threshold (Table 12 in the Appendix). The applicant also rounded down the data prior to including the data in the logistic regression model in order to determine the primary outcome. For example, subject (b) (6) had an average IGF-1 between week 34 and 36 equal to 1.0305. The data that was later utilized in the logistic regression model

included this subject as having its final IGF-1 below the threshold of 1xULN (Table 13 and Table 14 in the Appendix).
The submission documentation did not explicitly identify the use of rounding in these analyses. I reanalyzed the outcomes based on eligible subjects and IGF-1 data without preliminary rounding using the methodology described above.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 119 subjects was screened for this study. Fifty-six of those subjects were included in the trial and randomized to Mycapssa (n=28) or Placebo (n=28). In the end, 9 subjects on placebo and 21 subjects on Mycapssa completed the trial on treatment (Figure 2). There were no missing efficacy data since all subjects stayed until the end of the trial regardless of treatment status.

Figure 2. Study population



Source: CSR, p. 72

Demographic and baseline characteristics of study subjects are present below (Table 2 and Table 3). Overall, age range of subjects was between 30 and 79. The age range of subjects in both groups was balanced (median 56.5 on Mycapssa and 54.5 on placebo). Of note, most of the subjects were younger than 65 years old (75% of Mycappsa subjects and 78.6% of subjects on placebo). Of note, the maximum value for the average of two screening IGF-1 values was above onexULN, indicating that some of the subjects did not meet entry criteria. After careful examination, based on two screening IGF-1 values, I identified 2 (7.1%) subjects on Mycapssa and 5 (17.9%) subjects on placebo who lost control during screening and therefore were not eligible to participate in this trial.

Table 2. Baseline characteristics

	Mycapssa (n=28)					Placebo (n=28)				
	Median	Min	Max	Mean	Std Dev	Median	Min	Max	Mean	Std Dev
Age (yrs)	56.5	30	79	54.9	12	54.5	37	73	53.8	11
Average of two screening IGF-1 values xULN	0.75	0.47	1.04	0.77	0.15	0.85	0.27	1.05	0.8	0.19
Baseline IGF-1 (xULN)	0.84	0.44	1.23	0.82	0.19	0.91	0.29	1.28	0.88	0.24
Screening GH	0.4	0.1	3.5	0.66	0.75	0.6	0.1	3.9	0.9	1.01
Baseline GH	0.45	0.1	3	0.67	0.64	0.5	0.1	3.4	0.97	1.07

Among randomized subjects, a larger number of subjects on placebo (n=9, 32.1%) and a smaller number of subjects on Mycapssa (n=4, 14.3%) lost their biochemical control at baseline (IGF-1>1xULN). It was expected that some of the subjects would lose control at baseline (2 weeks after the second screening measurement) because of the SLR washout effect, but such a big difference in loss of control between treatment groups prior to the therapy is of concern. One plausible explanation for this imbalance could be related to the fact that a larger number of subjects who lost control at screening were randomized to placebo and thus those subjects were not eligible to participate in the trial.

The gender distribution among treatment groups was similar (57% of subjects on Mycapssa and 50% of subjects on placebo were female). A large fraction of subjects on Mycapssa were not from the US (78.6%) and more than a half of the subjects on placebo were from US. Based on calculations using hypergeometric distribution for selection without replacement, the probability of such a treatment assignment imbalance within US or non-US categories is 0.013, so it is low but not impossible. I calculated a probability assuming 6 or fewer successes in a sample of 21 taken from a population of 56 containing 28 successes. This corresponds to 56 subjects, 28 assigned to Mycapssa and 21 subjects in the US of which 6 were assigned to Mycapssa.

Most of the subjects in both treatment arms were white. Most subjects were on medium or high dose of SRL drugs prior to enrollment.

Table 3. Demographic characteristics

Characteristic	Category	Mycapssa N=28	Placebo N=28
Sex	Female	16.00(57.1%)	14.00(50.0%)
	Male	12.00(42.9%)	14.00(50.0%)
Age	<65 years old	21.00(75.0%)	22.00(78.6%)
	>=65 years old	7.00(25.0%)	6.00(21.4%)
Region	Non-US	22.00(78.6%)	13.00(46.4%)
	US	6.00(21.4%)	15.00(53.6%)
Race	Asian	1.00(3.6%)	2.00(7.1%)
	Black or African American	-	1.00(3.6%)
	Other	-	1.00(3.6%)
	White	27.00(96.4%)	24.00(85.7%)
Baseline SRL dose	Low	6.00(21.4%)	5.00(17.9%)
	Mid/High	22.00(78.6%)	23.00(82.1%)
Baseline IGF-1	<Median	16.00(57.1%)	12.00(42.9%)
	>=Median	12.00(42.9%)	16.00(57.1%)
Baseline GH	<Median	15.00(53.6%)	12.00(42.9%)
	>=Median	13.00(46.4%)	16.00(57.1%)

3.2.4 Results and Conclusions

Despite absence of missing primary endpoint data (all subjects completed the trial either on or off treatment), the interpretation of the overall outcomes should be considered in the light of trial conduct, i.e. participation eligibility and rescue procedures. Since the interpretation of the primary results is dependent on IGF-1 values and rescue status, I will address the impact of treatment on rescue and IGF-1 patterns prior to the discussion of primary results.

Trial eligibility

As indicated in previous section, eligible subjects were supposed to have two screening visits and the average IGF-1 measured at those screening visits should be ≤ 1xULN. In my view, only eligible subjects should be included in the analyses so that results appropriately reflect the eligibility criteria.

Prespecified rescue approach and trial conduct

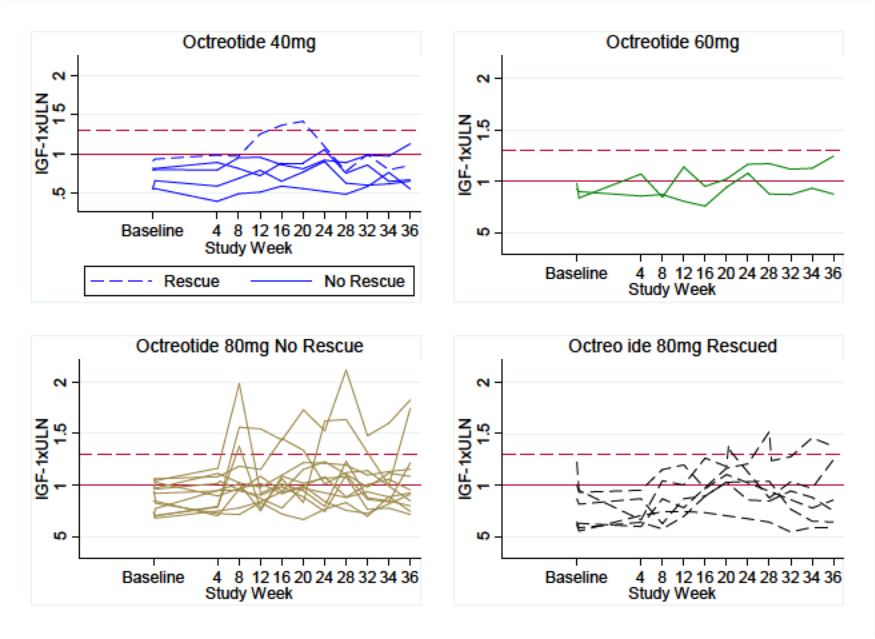
An examination of the efficacy dataset revealed that seven subjects on Mycapssa and 19 subjects on placebo were rescued during the trial. Six of the seven rescued subjects on Mycapssa were treated with the maximum dose of Octreotide (80mg). The detailed description of the rescue status, treatment, and Mycapssa dose is presented in Table 4.

Table 4. Rescue status

Treatment	Rescue		
	No	Yes	Total
Octreotide 40mg	6 (85.71%)	1 (14.29%)	7 (12.5%)
Octreotide 60mg	2 (100%)	0 (0%)	2 (3.57%)
Octreotide 80mg	13 (68.42%)	6 (31.58%)	19 (33.93%)
Placebo	9 (32.14%)	19 (67.86%)	28 (50%)
Total	31(55.36%)	25 (44.64%)	56(100%)

According to protocol, subjects were supposed to be rescued if they experienced IGF-1 ≥1.3×ULN and had exacerbation of acromegaly clinical signs or symptoms for 2 consecutive assessments while treated for at least two weeks with 4 capsules per day. Based on spaghetti plots that I generated using the efficacy dataset (Adeff.xpt, IGF-1 data without rounding), not all subjects who were rescued met the IGF-1 threshold to qualify for the rescue. Of note, among all subjects on Mycapssa, only 3 of them crossed the threshold of 1.3xULN.

Figure 3. Individual trajectories of IGF-1 (Mycapssa subjects)



Legend: Individual trajectories of IGF-1. Each line represents one study participant. Dashed lines identify subjects who were rescued, and solid lines show the trajectories for subjects who were not rescued. The solid horizontal red line delineates IGF1-1>1xULN, and the dashed horizontal red line delineates IGF-1>1.3xULN.

Longitudinal changes in IGF-1 and long-term use indication

A simple visual comparison of individual trajectories suggests similar IGF-1 patterns, the shape of IGF-1 curves, in rescued subjects on Mycapssa (Figure 4, panel B) and subjects on placebo who were not rescued (Figure 5, panel A).

Figure 4. Individual IGF-1 trajectories: comparison between subjects who were rescued

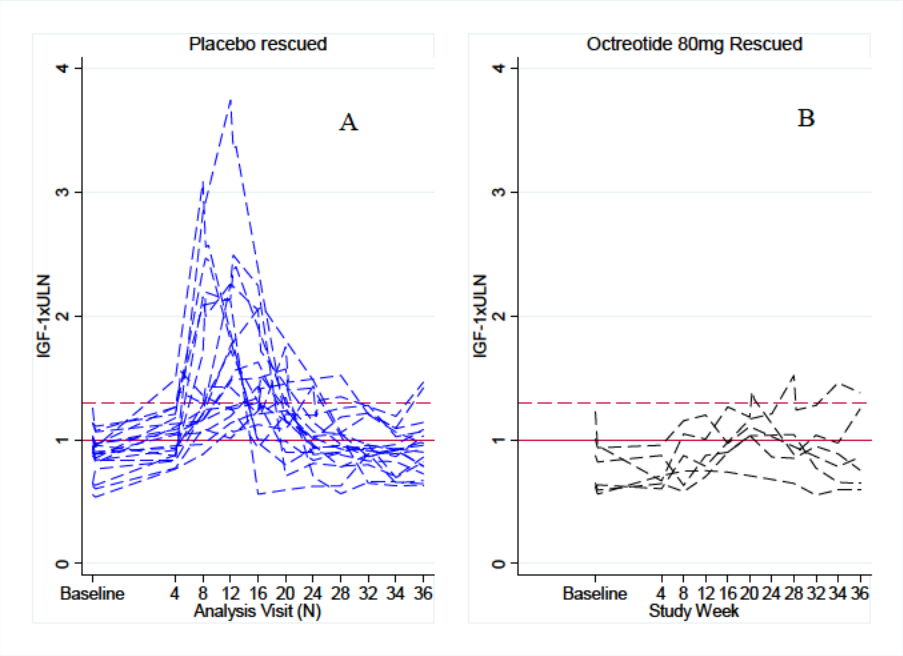
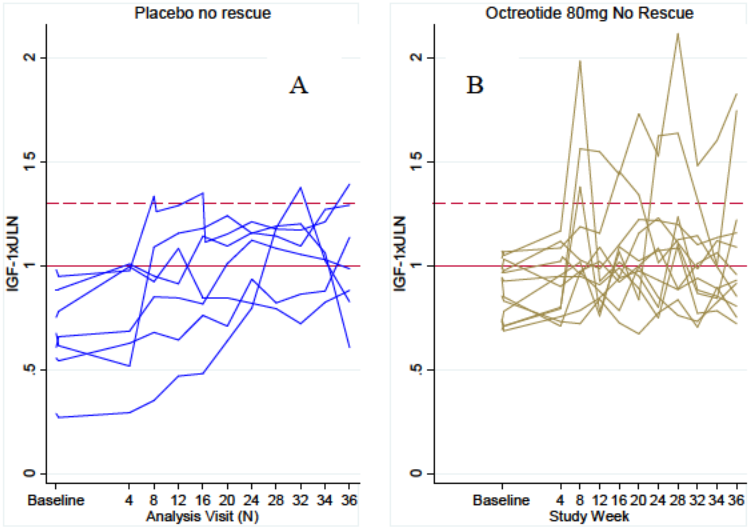


Figure 5. Individual IGF-1 trajectories: comparison between subjects who were not rescued



Analysis of primary endpoints

Since the applicant used undeclared IGF-1 rounding in determination of primary outcomes, I have reanalyzed the efficacy dataset without rounding. Based on my outcomes on all subjects, 14 (50%) subjects on Mycapssa and 3 (10.71%) subjects on placebo did not fail the primary endpoint (Table 5). The applicant calculated success rate for Mycapssa was higher (16 subjects, 57.14%) and also higher on placebo (5 subjects,17.86%). This could be explained by rounding of IGF-1 ratios, since 2 subjects on Mycapssa and 2 subjects on placebo had an average week 34 and week 36 IGF-1 level above 1.0. The applicant rounded down those values and thus marked those subjects as successes. A complete list of subjects who failed treatment and their average IGF-1 between week 34 and week 36 is listed in the Appendix (Table 13 and Table 14).

Similar to the first analysis, the results based on data from eligible subjects only (as prespecified) produced a 50% (n=13) success rate on Mycapssa and slightly higher success on placebo than in the first analysis, 13.04% (n=3). The success of Mycapssa was reduced to 48% when baseline IGF-1 values were used to identify the eligible subjects (Table 5).

Table 5. Treatment success under different eligibility assumptions

Treatment	Fail or rescue			Cohort
	No	Yes	Total	
Mycapssa n(%)	14 (50%)	14 (50%)	28	All subjects selected by applicant (cohort 1)
Placebo n(%)	3 (10.71%)	25 (89.29%)	28	
Total	17	39	56	
Mycapssa n(%)	13 (50%)	13 (50%)	26	Average of 2 screening measurements* (cohort 2)
Placebo n(%)	3 (13.04%)	20 (86.96%)	23	
Total	16	33	49	
Mycapssa n(%)	12 48%	13 (52%)	25	Baseline measurement alone (cohort 3)
Placebo n(%)	3 (13.04%)	20 (86.96%)	23	
Total	15	33	48	

*prespecified entry criteria

After the adjustment for baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median), the difference in adjusted proportions and odds ratios demonstrated that

Mycapssa was better than placebo (the 95% CI did not include 1 under any scenario). The complete list of results is presented in Table 6.

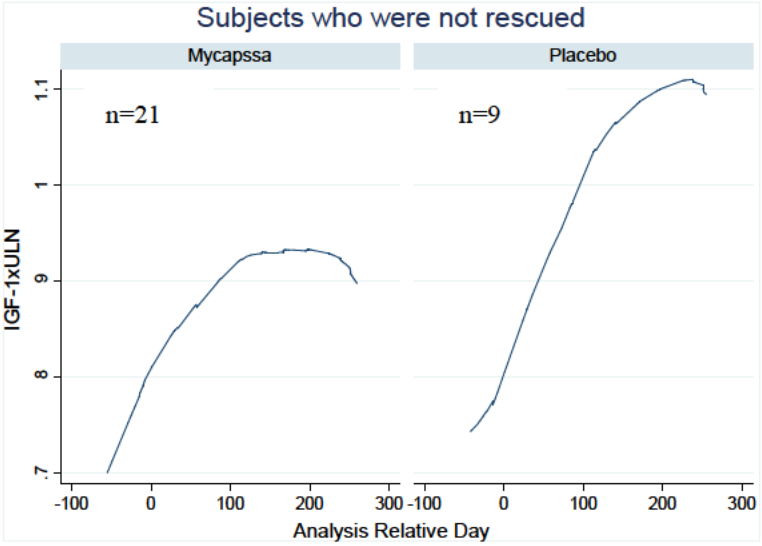
Table 6. Baseline IGF-1 and SRL dose -adjusted response rates under different eligibility assumptions

Cohort		Adjusted proportions			Odds ratio Octreaotide/placebo
		Placebo	Mycapssa	Difference and 95%CI	estimate 95%CI
All subjects selected by applicant (Cohort 1)	Responder	10.93	54.39		
	Non-responder	89.07	45.61		
				43.46(16.48, 64.43)	9.717(1.802, 86.926)
Average of 2 screening measurements (Cohort 2)	Responder	10.74	51.34		
	Non-responder	89.26	48.66		
				40.61(13.91, 60.96)	8.774 (1.495, 89.221)
Baseline measurement alone (Cohort 3)	Responder	9.36	48.39		
	Non-responder	90.64	51.61		
				39.03(12.81, 59.47)	9.08(1.372, 118.702)

Long-term use of Mycapssa

Overall, in subjects who were not rescued during the trial, i.e. based on data that did not involve use of injectable SLR, IGF-1 values increased (compared to baseline) in both Mycapssa and placebo groups. This is especially of concern since IGF-1 growth for subjects treated with Mycapssa was also observed in the first trial. Therefore, Mycapssa might not be a suitable long-term replacement of treatment with injectable SLR.

Figure 6. Overall IGF-1 patterns for subjects who were not rescued



Legend: Lowess plots for subjects who were not rescued (21 subjects on Mycapssa and 9 on placebo). Analysis day of zero indicates the baseline measurement.

Time to first increase in IGF-1

The evaluation of time to increase in IGF-1 was confounded by the fact that many subjects were rescued prior to reaching the prespecified IGF-1 rescue criteria (IGF-1>1.3) thus leaving only random subgroups for the evaluation. To better understand the data, I looked at the subjects who ended up reaching the IGF-1 of 1.3. Overall, seven subjects on Mycapssa and 23 subjects on placebo reached IGF-1>1.3 at least once. Among only subjects who reached IGF-1>1.3, those subjects on Mycapssa had a longer time to the IGF-1 threshold than subjects on placebo (median 112 days and mean 106.6 days on Mycapssa and median 59 days and mean 83.5 days on placebo). The results are presented in Table 7.

Table 7. Time to first IGF-1>1.3: treatment group analysis

Time to first IGF-1>1.3xULN (days)						
Treatment	**N**	**Median**	**Minimum**	**Maximum**	**Mean**	**Std Dev**
Mycapssa	7	112	57	197	106.57	54.14
Placebo	23	59	30	225	83.48	46.71

When examined by treatment and rescue status, subjects who were rescued had a longer median time to the IGF-1 threshold. Based on other distribution parameters, the time to IGF-1 threshold might not be symmetric and therefore the directionality of means do not follow the directionality of medians (Table 8). Based on these data, rescued subjects on placebo were rescued earlier in the study. At the same time subjects who were not rescued reached 1.3 almost at the same time as subjects on placebo (median 58 days).

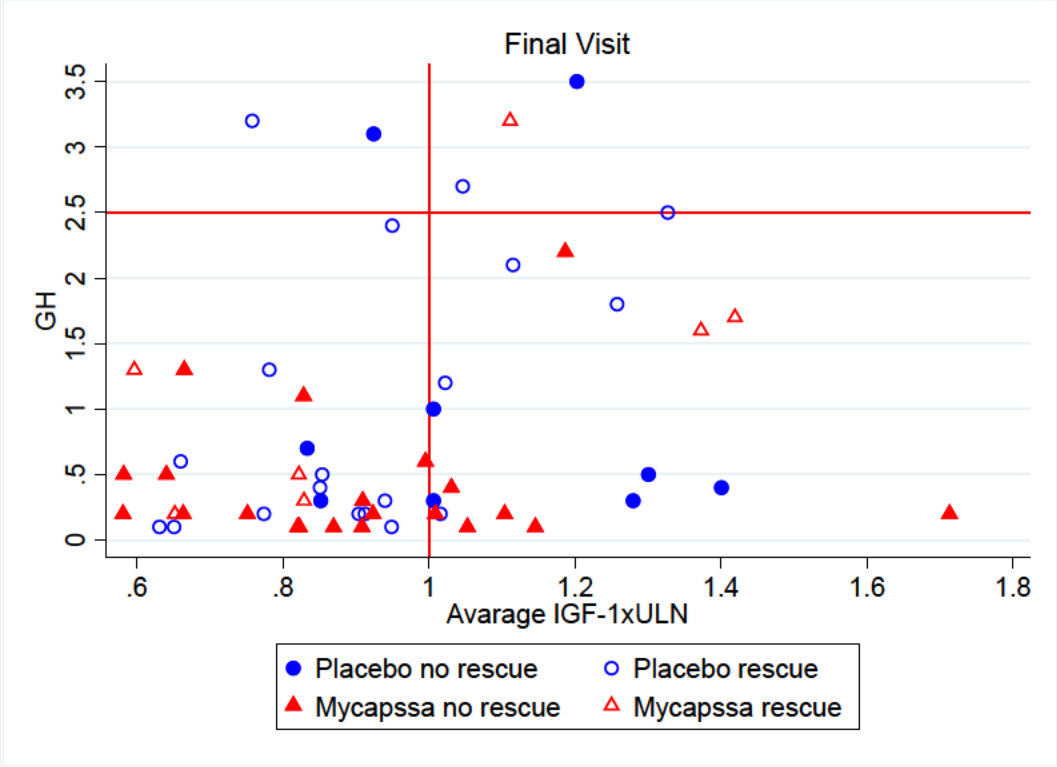
Table 8.Time to first IGF-1>1.3: analysis by treatment and rescue status

		Time to first IGF-1>1.3xULN (days)					
Treatment	**Rescue**	**N**	**Median**	**Minimum**	**Maximum**	**Mean**	**Std Dev**
Mycapssa	No	3	58	57	112	75.67	31.47
	Yes	4	132.5	57	197	129.75	59.42
Placebo	No	4	58.5	55	225	99.25	83.85
	Yes	19	84	30	169	80.16	37.8

Growth Hormone measurements

GH was measured on two occasions, at the start and at the end of the trial. Only one subject randomized to Mycapssa and 5 subjects on placebo had GH≥2.5 at the end of the trial (Figure 7). Of note, the same threshold for GH was a part of the composite primary endpoint in the first trial.

Figure 7. Scatter plot IGF-1 vs GH (final result)



Legend: Plot of average IGF-1 values obtained at weeks 34 and 36 versus last GH measurement. Each symbol represents one person. Circles identify subjects randomized to placebo and triangles identify subjects randomized to Mycapssa. Filled symbols represent subjects who were not rescued, and hollow symbols represent rescued subjects. The rectangular area below the vertical line and to the left of the horizontal line delineate IGF-1 below 1 and GH<2.5, showing the subjects who completed the trial and were controlled on both biomarkers.

3.3 Evaluation of Safety

My safety review only provides a high-level summary of potential safety issues. Safety events were also reviewed by Dr. Sonia Doi from Medical Division of General Endocrinology. For more detailed safety events review, readers are referred to Dr. Doi's review for this section.

The trial had three safety concerns:

1. Gastrointestinal Disorders (19 patients [67.9%] in the octreotide capsule group vs 17 patients [60.7%] in the placebo group).

2. Infections and Infestations (13 patients [46.4%] in the octreotide capsule group vs 8 patients [28.6%] in the placebo group).

3. Musculoskeletal and Connective Tissue Disorders (11 patients [39.3%] in the octreotide capsule group vs 21 patients [75.0%] in the placebo group)

A summary of serious treatment-emergent adverse events is presented in Table 9.

Table 9. Summary of serious adverse events

System Organ Class Preferred Term	Octreotide Capsules (N = 28) n (%)	Placebo (N = 28) n (%)	Overall (N = 56) n (%)
Patients with at least 1 serious TEAE	2 (7.1)	1 (3.6)	3 (5.4)
Hepatobiliary disorders	1 (3.6)	0	1 (1.8)
Cholecystitis acute	1 (3.6)	0	1 (1.8)
Injury, poisoning and procedural complications	0	1 (3.6)	1 (1.8)
Joint dislocation	0	1 (3.6)	1 (1.8)
Musculoskeletal and connective tissue disorders	1 (3.6)	0	1 (1.8)
Arthritis	1 (3.6)	0	1 (1.8)

Source CSR, p.119

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The subgroup analyses provided by the applicant were based on the cohort that included subjects who were not eligible to participate as well as calculations performed using the inappropriate rounding of the final outcome status described earlier. Also, on page 106 of the CSR, the applicant stated that "As shown in Figure 5, the treatment effect was consistent across all sub-groups." Based on the figure presented, it is not clear whether the numerical or graphical results presented in the applicant's plot were accurate since the numerical lower bounds of the 95% confidence intervals for the subgroups containing subjects from US, age<65, and women were below zero. At the same time, none of the plotted subgroups had a confidence interval that included zero (Figure 8 in the Appendix). In addition to the statement, prior to the figure, the graph provides a visual impression that the results in all subgroups yielded the estimated confidence intervals that did not include zero.

My subgroup analysis was performed using trial eligible subjects only (Cohort 2 as defined in section 3.2.4). The analysis utilized the same approach as analysis of the primary endpoint.

First, the raw, unadjusted summaries of success and failure rates in each treatment group were calculated (Table 10). Based on those counts, female subjects had a lower success rates than males (40% vs 63.6%), and US subjects did not have as much success as non-US subjects (40% vs 52.3%). At the same time, subjects age 65 or older had a larger unadjusted rate of success than younger subjects (83.3% vs 40%). All these numbers should be interpreted with caution since most subgroup sizes were very small and therefore estimates may not be precise.

Table 10. Subgroup analyses: Unadjusted success/failure rates

Subgroup	Treatment	IGF-1 failure		
		No	Yes	Total
Women	Mycapssa n(%)	6 40%	9 60%	15
	Placebo n(%)	1 8.33%	11 91.67%	12
	Total	7	20	27
Men	Mycapssa n(%)	7 63.64%	4 36.36%	11
	Placebo n(%)	2 18.18%	9 81.82%	11
	Total	9	13	22
US	Mycapssa n(%)	2 40%	3 60%	5
	Placebo n(%)	2 15.38%	11 84.62%	13
	Total	4	14	18
Non-US	Mycapssa n(%)	11 52.38%	10 47.62%	21
	Placebo n(%)	1 10%	9 90%	10
	Total	12	19	31
Age<65	Mycapssa n(%)	8 40%	12 60%	20
	Placebo n(%)	2 10.53%	17 89.47%	19
	Total	10	29	39
Age≥65	Mycapssa n(%)	5 83.33%	1 16.67%	6

	Placebo n(%)	1 25%	3 75%	4
	Total	6	4	10
Age<60	**Mycapssa n(%)**	5 29.41%	12 70.59%	17
	Placebo n(%)	2 11.76%	15 88.24%	17
	Total	7	27	34
Age≥60	**Mycapssa n(%)**	8 88.89%	1 11.11%	9
	Placebo n(%)	1 16.67%	5 83.33%	6
	Total	9	6	15

Second, after adjusting for baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median), the only group of subjects who demonstrated a potentially better outcome on placebo (the 95% CI for the difference in adjusted proportions was below zero) were subjects from the US. The adjusted success rate for that subgroup was 18.8 with 95%CI (-7.56, 42.21). All other subgroups had their complete 95% confidence interval above zero. The adjusted outcomes for subjects age 65 or older could not be calculated because of the small sample size.

Table 11. Subgroup analyses: adjusted success/failure rates

Subgroup		Adjusted proportions*		
		Placebo N=23	**Mycapssa N=26**	**Difference and 95%CI**
Women (n=27)	Responder	10.31	46.93	
	Non-responder	89.69	53.07	
				36.62 (10.40, 57.40)
Men (n=22)	Responder	13.86	75.13	
	Non-responder	86.14	24.87	
				61.27(33.38, 77.76)
US (n=18)	Responder	20.79	39.61	
	Non-responder	79.21	60.39	
				18.83(-7.56, 42.21)
Non-US (n=31)	Responder	10.05	46.67	
	Non-responder	89.95	53.33	
				36.62(10.48, 57.38)
<65 yrs (n=39)	Responder	21.21	71.81	
	Non-responder	78.79	28.19	
				50.6(22.09, 69.64)
<60 yrs (n=34)	Responder	26.59	57.12	
	Non-responder	73.41	42.88	
				30.53(2.26, 53.24)
≥60 yrs (n=15)	Responder	28.56	75.14	
	Non-responder	71.44	24.86	
				46.58(17.93, 66.49)

*results based on logistic regression models with adjustment for baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were several issues that were of concern:

1. **Limitation of use:** Although several subjects on Mycapssa did not reach the threshold of IGF-1>1xULN during the trial, based on data observed in trial CH-ACM-01 and in trial OOC-ACM-303, the IGF-1 continued to rise during both trials, suggesting that over time subjects on drug might lose IGF-1 control. Therefore, long-term successful treatment with this drug might not be possible. Based on recommendation from clinical team, patients should undergo regular monitoring of their IGF-1 levels to make sure that their acromegaly is under control.

2. **Study conduct:**
   c. **Eligibility criteria:** not all randomized subjects met pre-specified eligibility criteria (biochemical control on somatostatin analogs, i.e. average of two screening IGF-1 measurements ≤1xULN) n=7(12.5%). Most of those subjects were on placebo (n=5). To mitigate this issue, I recommend including only data from eligible subjects in the product label.
   d. **Rescue:** subjects were rescued without meeting the prespecified rescue criteria. Specifically, several subjects on treatment were removed without reaching the threshold of IGF-1 greater than 1.3xULN. This approach to rescue makes the interpretation of time to loss of response (IGF-1>1.3xULN) more challenging, i.e. subjects were taken off treatment prior to ever reaching the threshold thus making it appear that the overall time to loss of response in the treatment group was longer than it would have been if those subjects were rescued according to the prespecified rule.

3. **Rounding of data inputs for the primary analysis model:** rounding of final IGF-1 outcomes that were subsequently put into the primary analysis model resulted in higher success rates for subjects on Mycapssa. To mitigate this issue, my recommendation is to use only the data without rounding. Based on analyses without rounding, the success rates of both, Mycapssa and placebo, were reduced

Overall data and submission quality: the subgroup section in the CSR contained multiple errors and incorrect statements indicating Mycapssa's success in all subgroups. Specifically, there were discrepancies between numeric values and the plots. All adjusted subgroup results were plotted having their 95% confidence intervals above zero suggesting better results for the Mycapssa arm in each subgroup. In contrast, the numeric data on the same plot indicated negative lower bounds of the confidence intervals for women, US, and age<65. In addition to the statement "As shown in Figure 5, the treatment effect was consistent across all sub-groups." (CSR, p. 106) the figure provides a visual impression that the results in all subgroups yielded the estimated confidence intervals that did not include zero.

The submission also contained errors in the submitted data, such as not all subjects who discontinued treatment had discontinuation week marked in the dataset. Further, the variable indicating treatment group did not match the treatment assignment during double-blind period. Detection and mitigation of these issues required additional time and effort during the review cycle.

5.2 Conclusions and Recommendations

The study showed that Mycapssa worked only in 50% percent of subjects. Given that all study subjects responded favorably to the injective drug, Mycapssa maintained their responses only in some of them. Similar to study CH-ACM-01, the new study did not provide a clear-cut answer regarding the subgroup of patients who could benefit from this drug. Given that the injectable octreotide is administered 3 times a day through subcutaneous injections, for some patients Mycapssa could become a more convenient alternative.

In clinical practice, convenience of administration (injection vs tablet) might outweigh the issues of efficacy profile of Mycapssa. Therefore, I recommend approval of Mycapssa. That being said, the label should only reflect the results obtained from eligible subjects without post-hoc rounding of the outcomes. Given increasing levels of IGF-1 over time, I recommend that Mycapssa not be approved for long-term replacement of injectable octreotide.

5.3 Labeling Recommendations

I recommend revising the label to include only subjects eligible for the trial without post-hoc rounding of the outcomes.

APPENDICES

Table 12. Subjects who did not meet entry criteria

Subject Identifier for the Study= (b) (6)				
Mean Screening IGF1	**IGF-1**	**VISIT**	**VISIT NUMBER**	**RANDOMIZED GROUP**
1.0065	1.097	Screening 1	1	Placebo
	0.916	Screening 2	2	Placebo
Subject Identifier for the Study= (b) (6)				
Mean Screening IGF1	**IGF-1**	**VISIT**	**VISIT NUMBER**	**RANDOMIZED GROUP**
1.041	1.005	Screening 1	1	Octreotide 80mg
	1.077	Screening 2	2	Octreotide 80mg
Subject Identifier for the Study= (b) (6)				
Mean Screening IGF1	**IGF-1**	**VISIT**	**VISIT NUMBER**	**RANDOMIZED GROUP**
1.024	1.079	Screening 1	1	Placebo
	0.969	Screening 2	2	Placebo
Subject Identifier for the Study= (b) (6)				
Mean Screening IGF1	**IGF-1**	**VISIT**	**VISIT NUMBER**	**RANDOMIZED GROUP**
1.019	1.028	Screening 1	1	Placebo
	1.01	Screening 2	2	Placebo
Subject Identifier for the Study= (b) (6)				
Mean Screening IGF1	**IGF-1**	**VISIT**	**VISIT NUMBER**	**RANDOMIZED GROUP**
1.0225	0.948	Screening 1	1	Octreotide 80mg
	1.097	Screening 2	2	Octreotide 80mg
Subject Identifier for the Study= (b) (6)				
Mean Screening IGF1	**IGF-1**	**VISIT**	**VISIT NUMBER**	**RANDOMIZED GROUP**
1.028	1.041	Screening 1	1	Placebo
	1.015	Screening 2	2	Placebo
Subject Identifier for the Study= (b) (6)				
Mean Screening IGF1	**IGF-1**	**VISIT**	**VISIT NUMBER**	**RANDOMIZED GROUP**
1.0495	1.093	Screening 1	1	Placebo
	1.006	Screening 2	2	Placebo

Subjects who failed treatment on Mycapssa (based on average IGF-1 between week 34 and 36). The primary outcome status (treatment success/failure) for the subjects marked with a star was reclassified to success by the applicant based on the rounding of the mean IGF-1values.

Table 13. Subjects who failed treatment on Mycapssa

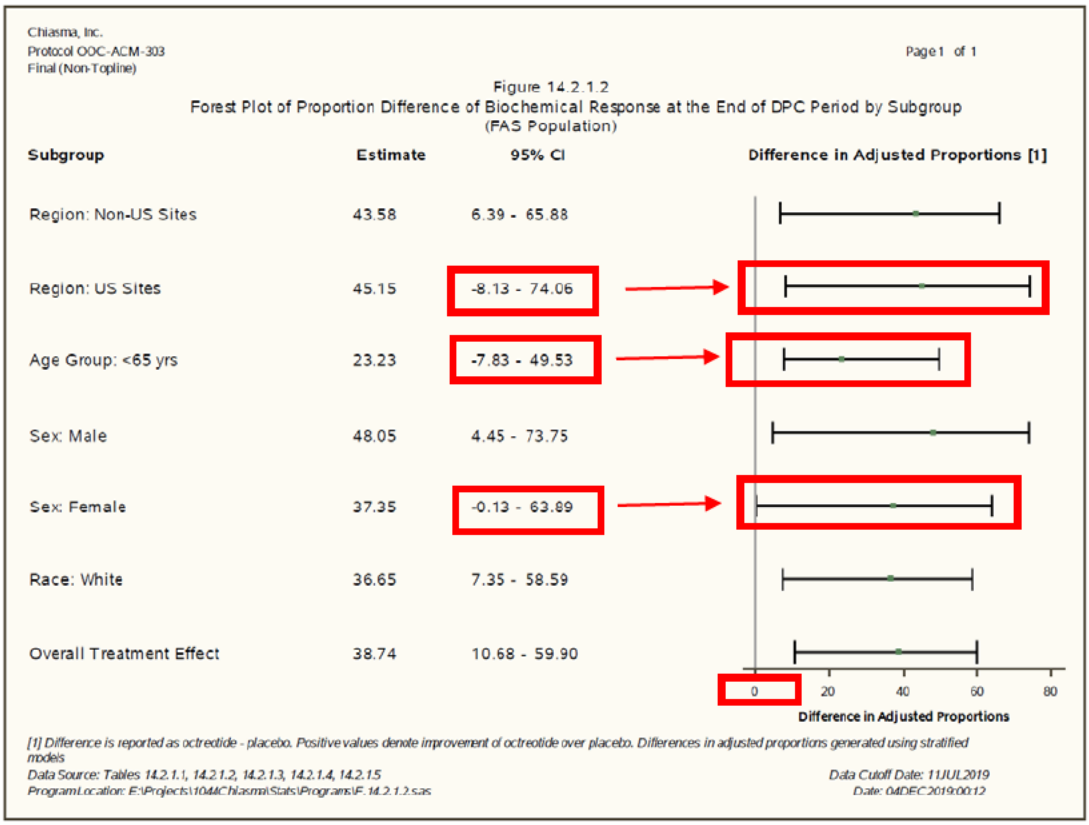
MYCAPSSA ARM			
IGF-1 failure with rescue			
	SUBJID	Mean IGF-1	Rescue status 0=No, 1=Yes
1*	(b) (6)	**1.0305**	**0**
2*		**1.0085**	**0**
3		1.1455	0
4		1.419	1
5		0.596	1
6		0.8285	1
7		0.8215	1
8		1.3725	1
9		1.1035	0
10		0.6515	1
11		1.1865	0
12		1.713	0
13		1.111	1
14		1.0525	0
***subjects that did not match submitted documentation**			

Subjects who failed Placebo (based on average IGF-1 between week 34 and 36). The primary outcome status (treatment success/failure) for the subjects marked with a star was reclassified to success by the applicant based on the rounding of the mean IGF-1 values.

Table 14. Subjects who failed on placebo

PLACEBO ARM			
IGF failure with rescue			
	SUBJID	Mean IGF-1	Rescue status 0=No, 1=Yes
1	(b) (6)	0.6595	1
2*		**1.006**	**0**
3*		**1.006**	**0**
4		1.3005	0
5		1.2795	0
6		0.9495	1
7		0.7575	1
8		0.9485	1
9		0.9395	1
10		1.046	1
11		1.022	1
12		0.8535	1
13		0.7735	1
14		0.8505	1
15		1.115	1
16		1.327	1
17		1.2575	1
18		0.9035	1

Figure 8. Subgroup analyses provided by the sponsor



Source: CSR p. 107 Post-text Figure 14.2.1.2
For clarity, the highlights in red were added to indicate incongruences between numerical values and the graph depicting adjusted proportions.

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/s/

ANNA E KETTERMANN
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MARK D ROTHMANN
06/01/2020 04:03:58 PM
I concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208232
Drug Name:	Mycapssa (Oral Octreotide capsules)
Indication(s):	Long-term maintenance treatment in acromegaly patients (b) (4) (b) (4)
Applicant:	
Date(s):	PDUFA Goal Date: April 15, 2016
	Review due March 11, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Anna Kettermann, Dipl. Math, MA
Concurring Reviewers:	Mark Rothmann, Ph.D., Statistical Team Leader
	Thomas Permutt, Ph.D., Division Director
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Smita Abraham, M.D., Medical Officer
	Marina Zemskova, M.D., Medical team Leader
Project Manager:	Jennifer Johnson

Keywords: NDA review, clinical studies, endpoint analysis, open-label

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CI	confidence interval
GH	growth hormone
IGF-1	insulin-like growth factor 1

1 EXECUTIVE SUMMARY

Chiasma submitted a new 505(b)(2) NDA for Mycapssa. Mycapssa is an oral delivery drug that is designed to replace the injectable octreotide medications for subjects with acromegaly. The proposed indication of Mycapssa is long-term maintenance treatment in acromegaly patients (b) (4) (b) (4).
The goals of treatment with Mycapssa were to control GH and IGF-1 levels and acromegaly symptoms.

The submission consists of one study assessing the efficacy of Mycapssa. The study consisted of core and extension periods. The core part of the study was an open label study with only one trial arm. There was no comparator arm. The extension part involved only a part of the participants of the core study. Only a subgroup of subjects who completed the core period entered the extension period. Participation in the extension period was voluntary. Therefore, the extension would only be useful in evaluation of subjects for whom Mycapssa was already effective in the core part. Based on this design, the extension study will not be useful in evaluation of Mycapssa when applied to the entire population for which the drug is indicated. Because of the reasons listed above, my review only covers the core part of the study.

Statistical Issues and findings

The shortcomings of this submission include:

1. The study did not have a comparator arm (treatment arm consisted of 155 subjects who previously responded to injective drug, 102 (65.8%) of those subjects completed the efficacy portion).
2. There was only one study, no second study to support the results.
3. Based on analysis when dropouts were considered to be failure, the rate of success in the trial was modest. Only 52.9 (n=82) percent of subjects succeeded in this scenario CI(44.73, 60.96).
4. Missing data: Only 65.8%(n=102) of all study participants completed the core part. Most of the subjects dropped out because of inefficacy (45.8% (n=24) of dropouts) or adverse events (39.62% (n=21) of dropouts).
5. During the trial the IGF-1 increased in all groups (responders and non-responders). The study duration was too short to determine how many responders would later be classified as non-responders if the IGF-1 continued to rise through prolonged use similarly to how it rose during the trial. That could be a potential issue because the drug indication is for long-term maintenance.

In conclusion, the study showed that Mycapssa worked only in 52.9% percent of subjects. Given that all of the study participants responded favorably to the injective drug, Mycapssa might only work for some of the people with acromegaly. The study did not provide a clear cut answer regarding the subgroup of patients who could benefit from this drug. The submitted study could be considered to be an exploratory (pilot) study because it provides some idea of how the drug works, but, at this point, the results do not seem to be convincing.

My recommendations regarding these shortcomings are as follows:

1. Conduct a new study that would have a control arm (reference: Acromegaly guideline[1] (p. 3946), " Considering the prolonged nature of the course of most patients with acromegaly, interruption of medical therapy for 9–12 months should not have a particularly adverse effect on the long-term outcome".)

2. The new study should have a longer follow-up (similar to the injective somatostatin analogues).
3. To reduce missing data, all subjects should be followed regardless of adherence to the drug.

2 INTRODUCTION

2.1 Overview

A brief description of the drug indication and history of the submission is presented below.

2.1.1 Indication

Chiasma submitted this 505(b)(2) NDA for Mycapssa, a drug for the indication for long-term maintenance treatment in acromegaly patients (b) (4)

(b) (4)

The goals of treatment in acromegaly are to control GH and IGF-1 levels and to control acromegaly symptoms. The sponsor intends to substitute somatostatin (an injective drug) with Mycappsa (a pill). According to the sponsor, Mycapssa contains the same active ingredient as the injectable octreotide. Currently, all acromegaly medications are administered through an injection.

2.1.2 History of Drug Development

An orphan drug designation was granted for Mycapssa on 17 June 2010. Based upon agreement at the end-of-phase-2 meeting in August 2011, the clinical evaluation of Mycapssa is comprised of one Phase 3 safety and efficacy study (CH-ACM-01) in patients with acromegaly and 11 clinical pharmacology studies (9 studies in healthy subjects, 1 in renally impaired subjects [CHI-007] and 1 in hepatically impaired subjects [CH-PHT-01]) to support the NDA requirements for the 505(b)(2) pathway. This review is focused only on the Phase 3 efficacy study.

The drug was initially sponsored by Chiasma and on March 12, 2014, Genentech took over the responsibility for the submission. On June 20, 2014 the submission was transferred back to Chiasma.

The proposed dosing regimen of Mycapssa is 20 mg given twice daily (at least 1 hour prior to a meal or at least 2 hours after a meal) (1 capsule in morning and 1 capsule in evening) with doses being individually titrated upward to a maximum of 80 mg/day based on measured levels of IGF-1 to achieve optimal hormonal suppression.

2.1.3 Specific Study reviewed

Table 1. List of all studies included in analysis

Study	Phase and Design	Type of study	Follow-up Period	# of Subjects per Arm	Study Population
CH-ACM-01 core	Phase 3	Open label One arm Baseline-controlled	7 months	155	Subjects with confirmed acromegaly (confirmed biochemically). On injective somatostatin for at least 3 months before screening. All subjects were responders to somatostatin at baseline (IGF-1 < 1.3 xULN and GH < 2.5 ng/mL)
CH-ACM-01 Extension study	Phase 3	Open label One arm	6 months	88	Subjects who participated in core study and voluntarily enrolled into this extension

The submission also included study CH-ACM-01, a six-month extension study. In my view, the extension study (the way it was planned and conducted) could not be considered to be an adequate efficacy study because only a half of the core study (53.5%) stayed for the extension study. This happened because all subjects in the extension phase participated voluntarily. Subjects who failed the treatment in the core study did not participate in the extension. Because of the reasons indicated above, study CH-ACM-01 extension is not a part of my efficacy review.

2.2 Data Sources

This submission is in electronic common technical document (eCTD) format. The submission is archived at the following link: \\CDSESUB1\EVSPROD\NDA208232\208232.enx

Study datasets were provided as SAS XPORT transport files. The analysis datasets were joinable by unique identifier (SUBJID). The datasets were in good organization. Define.pdf file was clear enough. My analysis on the primary and secondary efficacy endpoints gives approximately the same results as those reported in the clinical study report (CSR).

I derived from the submitted datasets all of the results presented in this review. I created all tables and figures in this review unless otherwise noted.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submission quality was found to be reasonable.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

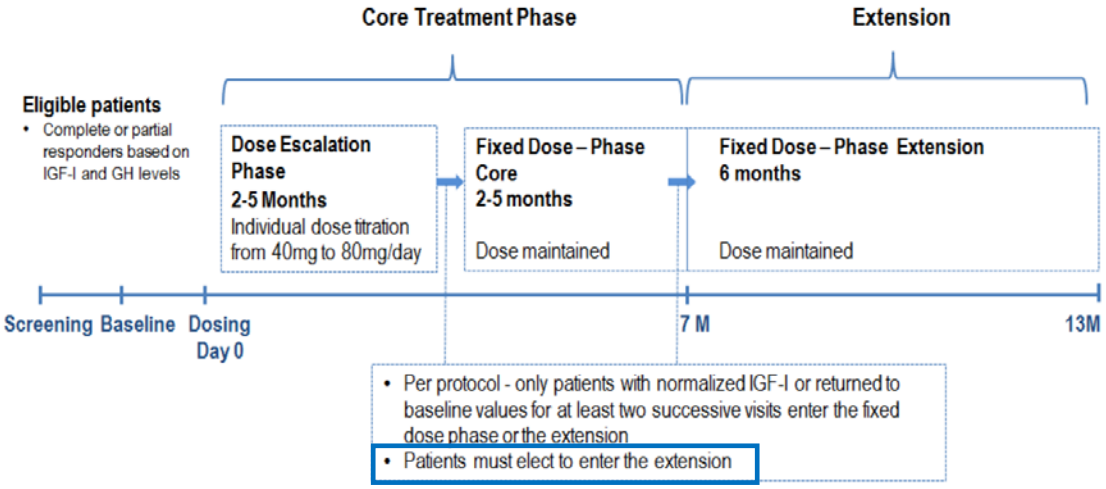
Study design: Study CH-ACM-01 was a Phase 3 open-label, maintenance-of-response, baseline-controlled study in patients with acromegaly who previously responded to and tolerated treatment with somatostatin analogs.

The Mycapssa treatment period lasted 13 months and comprised a dose escalation (2 – 5 months) followed by a fixed-dose period (8 – 11 months). The fixed-dose period included the time periods up to the completion of the core and extension treatment phases (at 7 and 13 months, respectively). Enrollment into the extension phase was voluntary. Mycapssa was administered in the morning and evening (at least 1 hour before a meal or at least 2 hours after a meal).

The subject was considered to be inadequately controlled if he or she experienced at least a 20% increase over prior levels of IGF-1, or if patient's acromegaly symptoms emerged. Visits occurred every 14 days for IGF-1 measurements. Integrated GH levels (measured 2 – 4 hours after Mycappsa administration) were measured with every dose escalation. Patients could revert to injectable somatostatin (SRL) therapy at any time, for either safety or efficacy, at the discretion of the site.

A schematic description of the study design is presented in the Figure 1 below.

Figure 1. Study design



Source: Clinical overview page 40

The study involved only one study arm, i.e. there was no comparator arm. The subjects switched from their prior therapy that involved injective drug to Mycapssa without any washout period. The washout period is needed to examine whether the patent still has acromegaly. Acromegaly could be in remission or gone due to many medical conditions. For example, acromegaly could be gone if the patient had a tumor infarction. In this case scenario, both IGF-1

and GH will be in the range of normal without any medications. The sponsor brings justifications for no-washout design utilizing previously published medical literature. Because this is a purely clinical decision, I would refer the question of carryover effect and validity of this design to the clinical reviewer, Dr. Smita Abraham.

Study endpoints: The primary efficacy endpoint was defined as the proportion of responders at the end of the core treatment. Response was defined, similar to the inclusion criteria, as IGF-1 < 1.3 times ULN for age and integrated GH < 2.5 ng/mL (utilizing last observation carried forward [LOCF] imputation).

Primary analysis population: The sponsor utilized modified intent-to-treat (mITT) population (i.e., all patients who had > 1 post-first-dose efficacy assessment).

Sample size: The sponsor calculated a sample size of 150 to detect 50% response (with exact CI of 42% to 58%). Nowhere in the text of submission was I able to find numerical calculations justifying those numbers. The sponsor refers to efficacy of Octreolin as a justification of clinically meaningful response rate. Because this is a clinical decision, I would refer the question of selection of appropriate response rate and validity of this selection to the clinical reviewer, Dr. Smita Abraham.

Primary analysis endpoint: Concentrations of IGF-1 and mean GH over 2 hours at the end of the Core Treatment Period. Response was defined as IGF-1 < 1.3 x ULN adjusted for age and an integrated GH level over 2 hours < 2.5 ng/mL.

Secondary endpoints:

I. Proportion of patients with the following IGF-1 and GH values at baseline and at the end of the Core Treatment Period:

1. IGF-1 < 1.3 times ULN and GH < 5.0 ng/mL;
2. IGF-1 < 1.3 times ULN and GH < 1.0 ng/mL;
3. IGF-1 ≤ 1.0 times ULN and GH < 5.0 ng/mL;
4. IGF-1 ≤ 1.0 times ULN and GH < 2.5 ng/mL;
5. IGF-1 ≤ 1.0 times ULN and GH < 1.0 ng/mL;
6. IGF-1 < 1.3 times ULN;
7. IGF-1 ≤ 1.0 times ULN;
8. GH < 5.0 ng/mL;
9. GH < 2.5 ng/mL;
10. GH < 1.0 ng/mL;
11. GF-1 ≥ 1.3 times ULN and GH < 2.5 ng/mL;
12. IGF-1 < 1.3 times ULN and GH ≥ 2.5 ng/mL; and
13. IGF-1 ≥ 1.3 times ULN and GH ≥ 2.5 ng/mL.

II. Maintenance of IGF-1 response during the Fixed Dose Phase (Core) - Proportion of patients with IGF-1 levels (adjusted for age) < 1.3 times ULN at the end of the Core Treatment Period who also had IGF 1 levels (adjusted for age) < 1.3 times ULN at the first assessment in the Fixed Dose Phase.

III. Maintenance of IGF-1 and GH response during the Fixed Dose Phase (Core)- Proportion of responders (IGF 1 levels [adjusted for age] < 1.3 times ULN and integrated GH < 2.5 ng/mL) at the end of the Core Treatment Period who also had IGF 1 levels (adjusted for age) < 1.3 times ULN and GH< 2.5 ng/mL at the first assessment in the Fixed Dose Phase.

3.2.2 Statistical Methodologies

Sponsor's primary analysis: Initially, the sponsor calculated the percentage of subjects who achieved or maintained the response using mITT population and LOCF approach for missing data. 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.

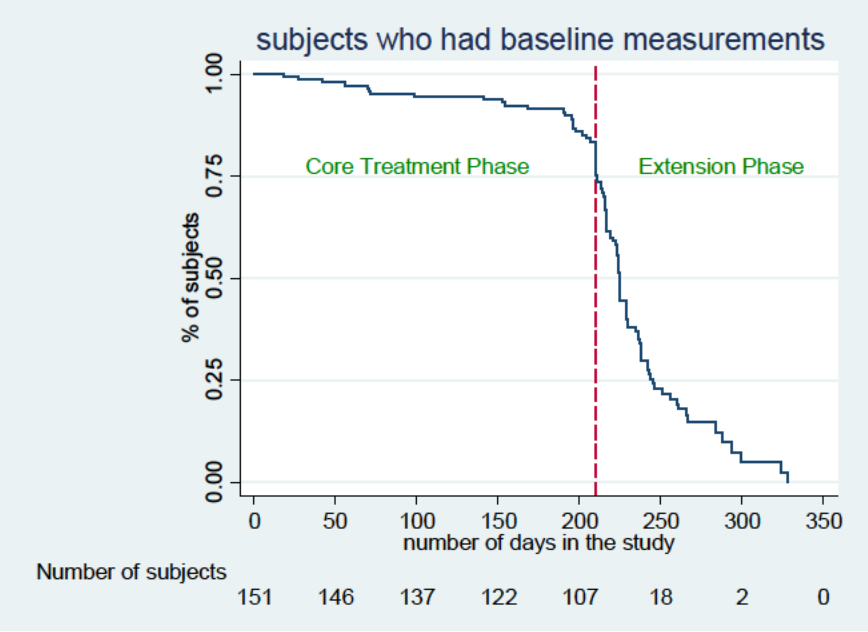
Following the Agency's feedback (20 February 2014), an additional analysis of the primary endpoint was performed using the Intention-to-Treat (ITT) Population (defined as all patients enrolled in the study) considering all patients who were prematurely withdrawn to be non-responders.
Sensitivity analyses were performed in the mITT Population using a multiple imputation approach where missing data were imputed using the Markov chain Monte Carlo (MCMC) method.
No formal comparisons and adjustments for type I error were made.

FDA primary analysis: The primary endpoint was examined based on the ITT principle, considering all enrolled subjects irrespective of adherence to treatment. Subjects who received Mycapssa and did not have any post-baseline measurements were considered as non-responders to the drug. A detailed clarification to the choice of this approach is presented in the missing data section. Additionally, missing data analysis and graphical visualization of changes of both IGF-1 and GH were performed. Each biomarker was examined separately. Because the primary outcome was based on IGF-1 in conjunction with GH, the trajectories of both biomarkers were also examined simultaneously.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Of the 155 patients enrolled (67 males, 88 females), 151 underwent at least 1 biochemical assessment after the first Mycapssa dose, and 110 entered the fixed-dose period. The empirical distribution plot below provides an illustration of study participation pattern. The red vertical dashed line delineates the core treatment phase. The table under the graph provides the number of subjects participating in the trial at each time point.

Figure 2. Empirical distribution plot of study participants



Demographics

A brief description of demographic characteristics of study participants is presented in Tables 2-4. All demographic variables were examined for ITT and mITT scenarios. The age of responders was slightly higher than the age of non-responders (mean 55 with standard deviation 12 vs 52.9 with standard deviation of 11 for the mITT scenario and 55 vs 53.3 for the ITT case). The majority of study participants were female (56.77%). The percentage of female patients was similar among non-responders and responders. Most study participants were white (88.39%). The participants came from 13 European countries. The largest number of participants came from Hungary (n=21).The smallest number of subjects came from Slovenia (n=3). Because the number of subjects that were participating in each country was not very large, no robust results could be produced using country-specific data. The demographic characteristics were similar in both ITT and mITT. Out of 155, four subjects did not have any post-baseline data and therefore were not included in the mITT-based analyses. A detailed description of those subjects is presented in the missing data section.

Table 2. Demographic table: Age of the subjects

Age(yrs)						
Category	**#subjects**	**Median**	**Minimum**	**Maximum**	**Mean**	**Std Dev**
mITT						
All subjects	151	54	22	73	54	11.6
Responder	82	59	22	73	55	12
Non-responder	69	53	31	71	52.9	11
ITT						
All subjects	155	54	22	73	54.2	11.5
Responder	82	59	22	73	55	12
Non-responder	73	53	31	71	53.3	11

Table 3. Demographic table: sex and race

	mITT			ITT		
	All subjects	**Non-responder**	**Responder**	**All subjects**	**Non-responder**	**Responder**
Sex						
Female	85	39	46	88	42	46
Male	66	30	36	67	31	36
Race						
ASIAN	2	1	1	2	1	1
OTHER	15	8	7	16	9	7
WHITE	134	60	74	137	63	74
Ethnicity						
HISPANIC OR LATINO	19	10	9	20	11	9
NOT HISPANIC OR LATINO	132	59	73	135	62	73

Table 4. Demographic table: country

	mITT			ITT		
COUNTRY	All subjects	Non-responder	Responder	All subjects	Non-responder	Responder
Germany	12	4	8	12	4	8
Hungary	21	11	10	21	11	10
Israel	16	5	11	17	6	11
Italy	6	4	2	6	4	2
Lithuania	7	3	4	7	3	4
Mexico	15	8	7	16	9	7
Netherlands	17	9	8	17	9	8
Poland	13	7	6	14	8	6
Romania	12	5	7	12	5	7
Serbia	13	6	7	13	6	7
Slovakia	4	2	2	4	2	2
Slovenia	3	1	2	4	2	2
United Kingdom	12	4	8	12	4	8

Missing data and treatment adherence

Out of 155, fifty-three subjects (34.2%) did not complete the core part of the trial. Only 35 of those subjects were considered to be non-responders (based on the levels of IGF1 and GH). Twenty-four subjects (15.48% of all subjects) were considered a treatment failure by the sponsor and 21 (13.55%) discontinued because of the adverse event. A description of discontinuation patterns is presented in the Table 5 below.

Table 5. Study completion status

Reason for Treatment Discontinuation	Treatment Termination Phase		
	Dose Escalation Phase N=155 (100%)	Fixed Dose Phase N=110 (70.97%)	Total
ADVERSE EVENT %	16 30.19	5 9.43	21 39.62
LOST TO FOLLOW-UP %	2 3.77	0 0.00	2 3.77
SPONSOR REQUEST %	1 1.89	0 0.00	1 1.89
SUBJECT REQUEST %	5 9.43	0 0.00	5 9.43
TREATMENT FAILURE %	21 39.62	3 5.66	24 45.28
Total %	45 84.91	8 15.09	53 100.00
Subjects who completed the study: 102 (65.8%)			

Among all 155 subjects who were randomized, four subjects did not have post-baseline data and therefore were not included in mITT dataset. A careful examination of the dataset revealed that 3 of those four patients discontinued because of the adverse event and only one was lost to follow-up. All three subjects who discontinued because of the adverse event were female. A description of subjects who discontinued and did not have any post-baseline is presented in Table 6.

Table 6. Table Subjects who did not have post-baseline data (i.e. excluded from mITT analysis)

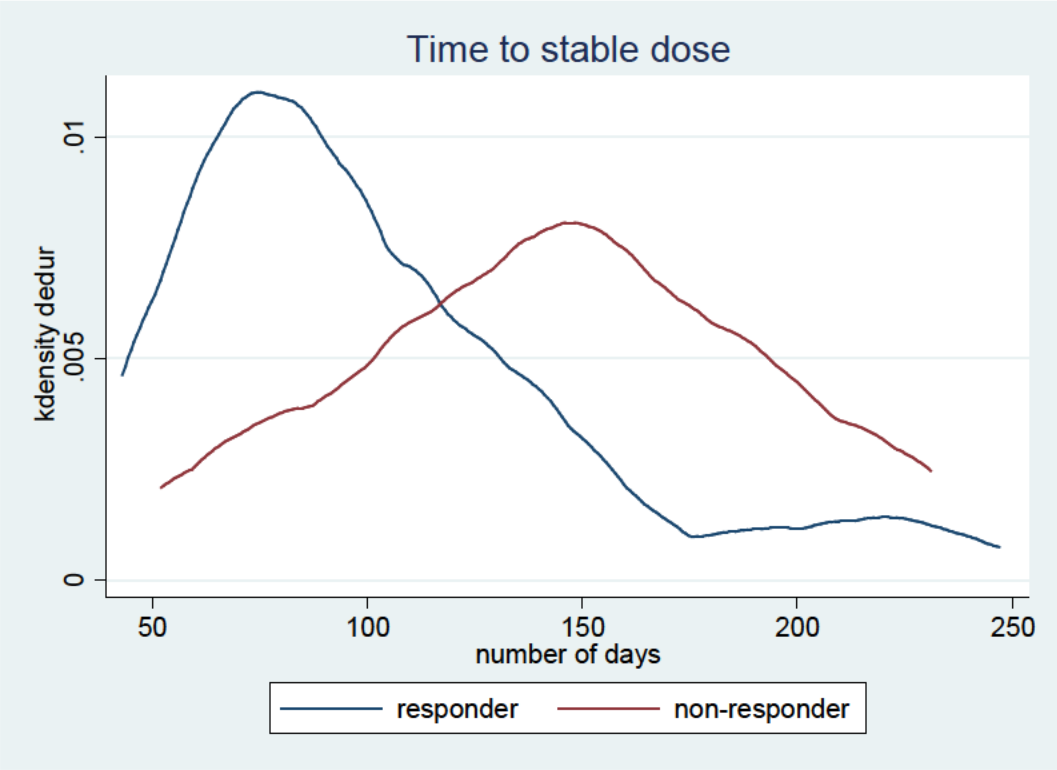
Age	Gender	Race	Ethnicity	Country	Reason for discontinuation	Termination phase
63	F	White	Not Hispanic or Latino	Israel	Adverse event	Dose Escalation
67	M	Other	Hispanic or Latino	Mexico	Lost to follow-up	Dose Escalation
63	F	White	Not Hispanic or Latino	Poland	Adverse event	Dose Escalation
45	F	White	Not Hispanic or Latino	Slovenia	Adverse event	Dose Escalation

3.2.4 Results and Conclusions

Because the design of the study did not include a comparator arm, there were no formal comparisons to the subjects who were not on the drug. My data examination mostly included graphical data exploration comparing subjects that showed response to Mycapssa to those who did not respond.

The dose escalation time, which I examined using a kernel density plot i.e. a plot that is similar to a histogram, was longer in the non-responder group than in those who responded to the drug. The peaks of each of the lines on the Figure 3 indicate values that were most frequently observed in each of the group. That means that the subjects who favorably responded to the drug had their symptom/biochemical stabilization earlier in the trial than those who did not respond.

Figure 3. Time to dose stabilization



An examination of individual trajectories (IGF-1 and GH) over time for each of the study participants revealed that for many subjects, IGF-1 went up during the course of treatment. Please see individual biomarker profiles presented in the spaghetti plot below. Each line represents biomarker values for one subject.

Figure 4. Individual profile plots IGF-1

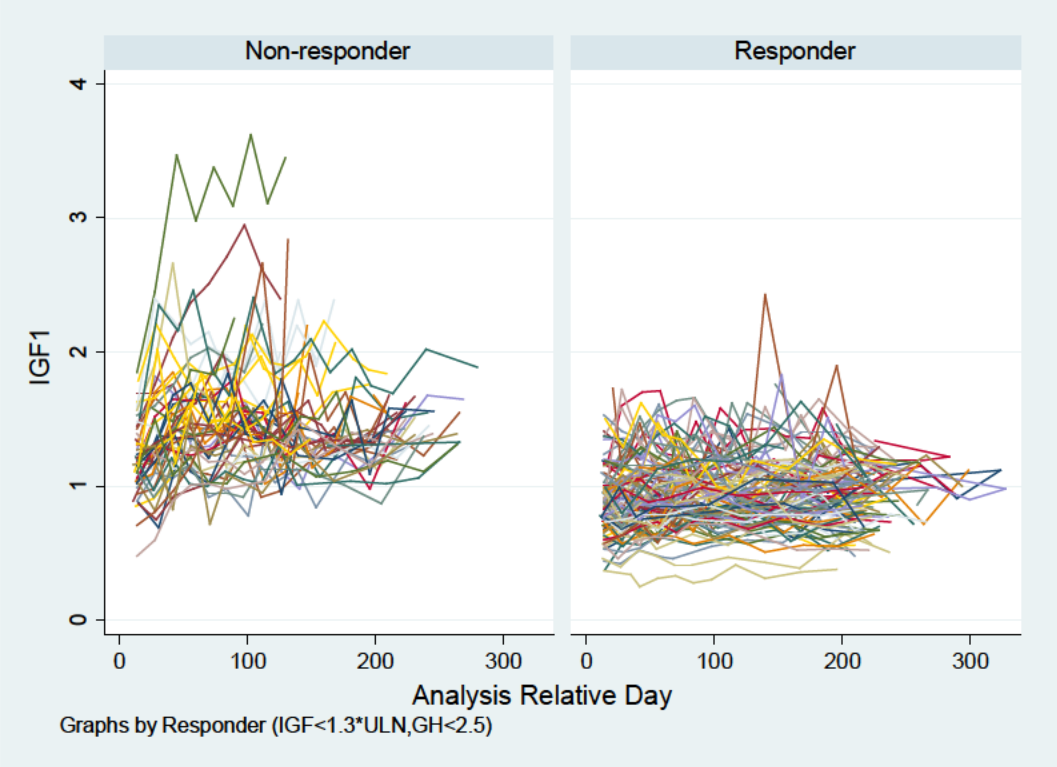
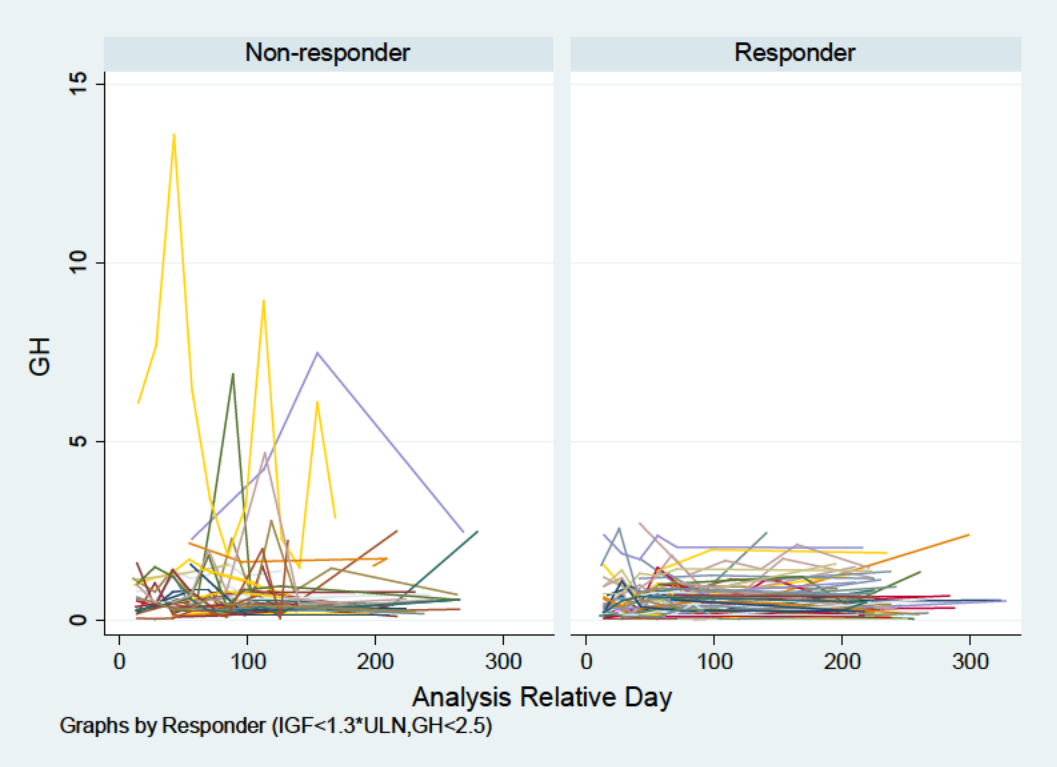
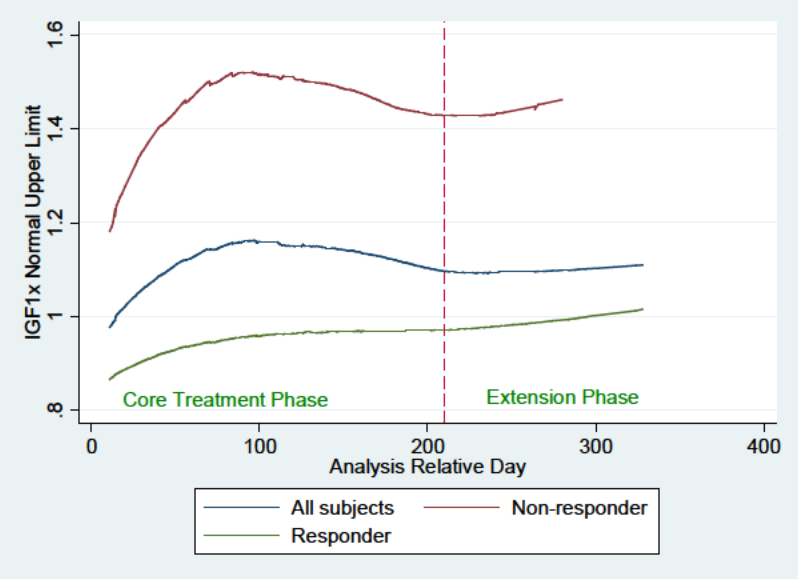


Figure 5. Individual profile plots (spaghetti plots) GH



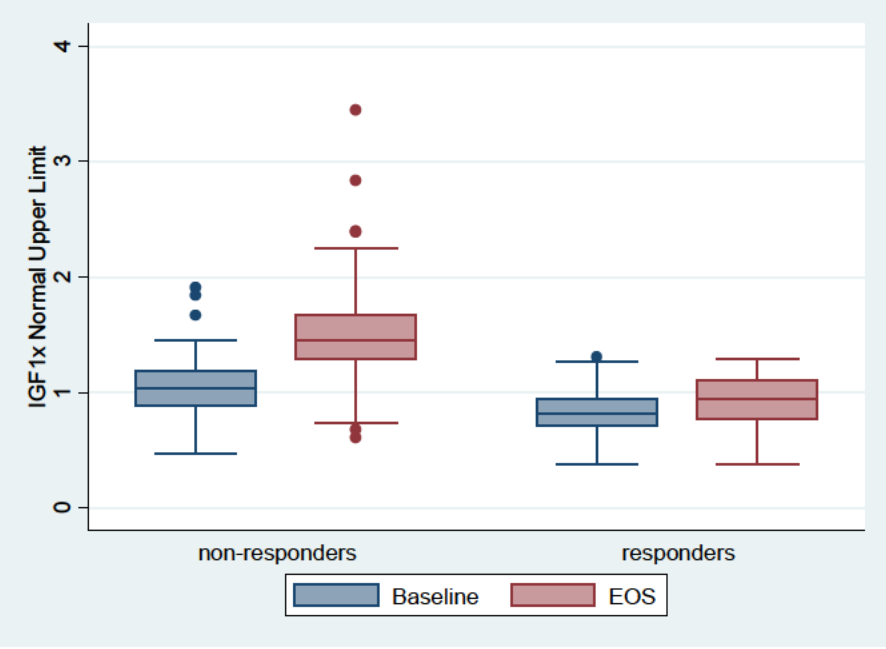
The lowess curves plotted to examine changes in IGF-1 over time suggest that the rate of IGF-1 increase was higher in subjects who did not respond to the treatment. At the same time, both lowess lines and boxplots presented below are indicating that non-responders started with slightly higher baseline IGF-1 levels (of note that the range of y scale is relatively narrow 0.8-1.6) .

Figure 6. Lowess lines for IGF-1



Legend: Lowess plots for each type of response. The red line delineates an approximate time of core treatment.

Figure 7. Boxplots for IGF-1



Legend: Boxes represent the 25th to 75th percentiles (interquartile range = IQR); horizontal lines within boxes, the median values; and vertical lines, 1.5 times the IQR; circles represent outliers, the values exceeding 1.5 times the IQR.

The next figure shows the final change IGF-1 for all the study participants. The horizontal red line separates subjects who had an increase in IGF-1 from those who did not have an increase in IGF-1. The figure also reveals that many subjects who did not respond to the drug discontinued the study early.

Figure 8. Change in IGF-1

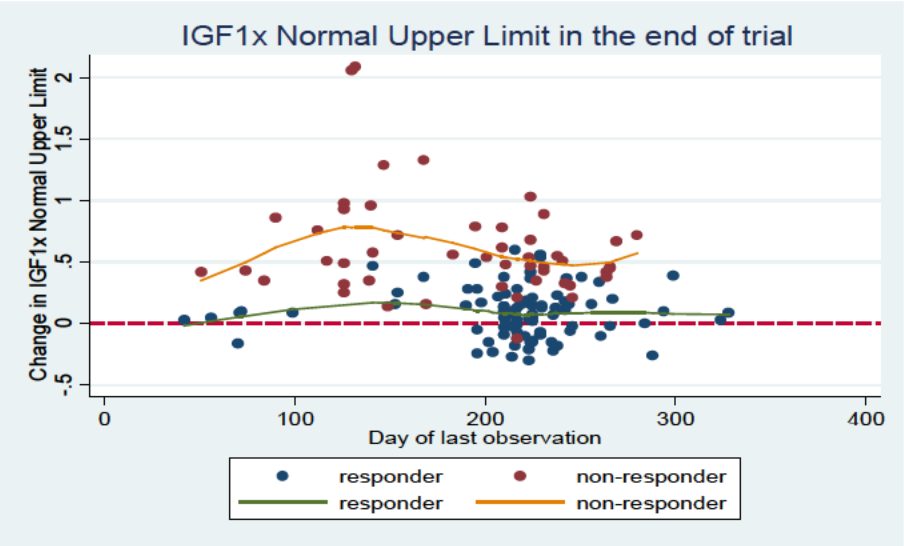
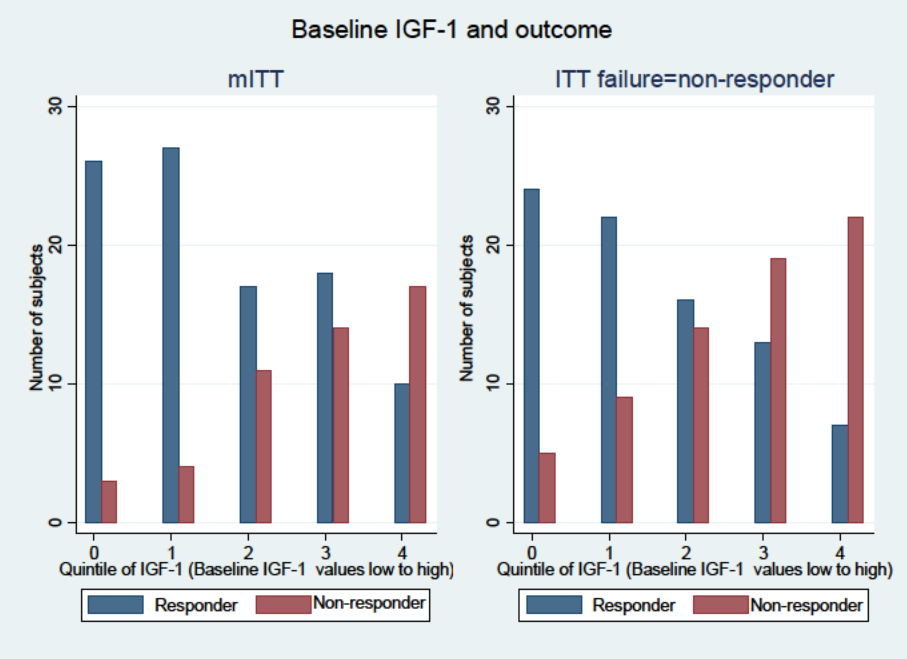


Figure 9. Relationship between baseline IGF-1 and outcome



Legend: The difference between left and right panel is in the definition of the analysis population (mITT for the left panel and ITT for the right panel). Also, the definition of responder in ITT analysis was based on biochemical response and dropout status.

The goal of this analysis was to examine the relationship between baseline IGF-1 and the outcome. Subjects were categorized based on the quintiles of the baseline IGF-1 distribution.

Smaller number of the quintile corresponds to lower baseline IGF-1 values and a larger number of quintile corresponds to higher baseline IGF-1 values. The figure demonstrates that subjects who started with lower values of IGF-1 were more likely to be responders to the treatment than those subjects who started with higher IGF-1 values.

Similar to the IGF-1 analysis, I examined changes in GH using lowess plots and box plots.The lowess plot suggests that non-responders had generally higher levels of GH. Of note is the fact that the range of GH in the study was rather narrow (the values were between 0.4 and 1.2). The boxplots revealed that there was a slight reduction in GH in both non-responder and responder groups.

Figure 10. Lowess lines for GH

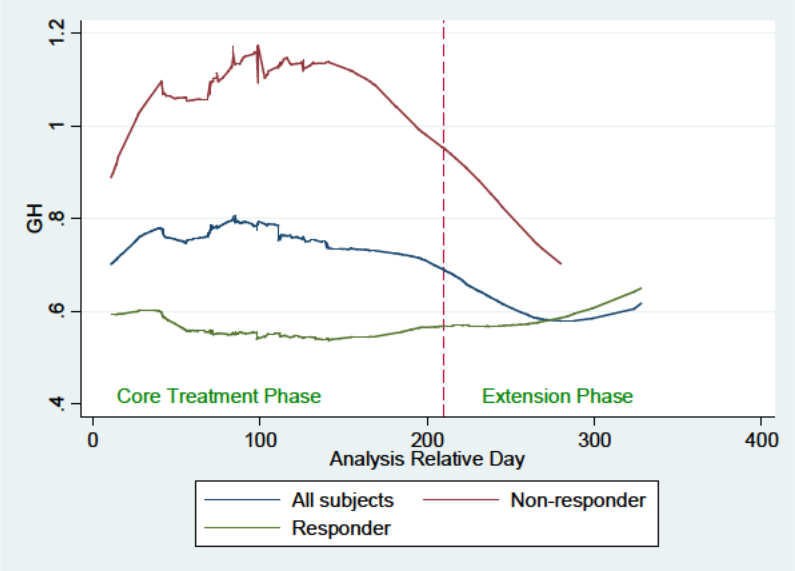
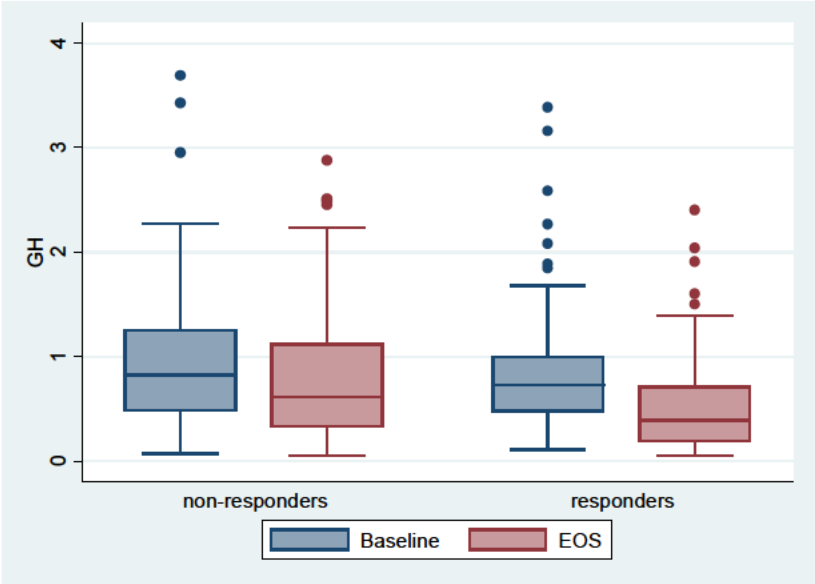
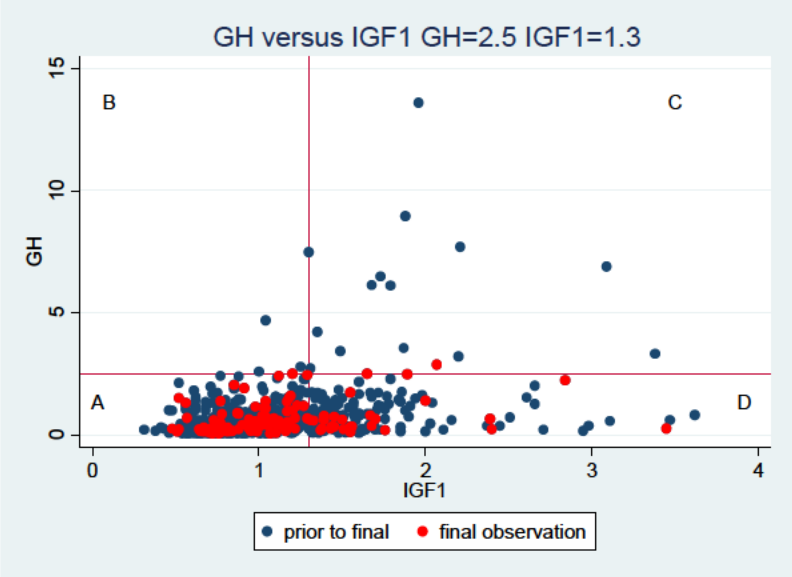


Figure 11. Boxplots for GH



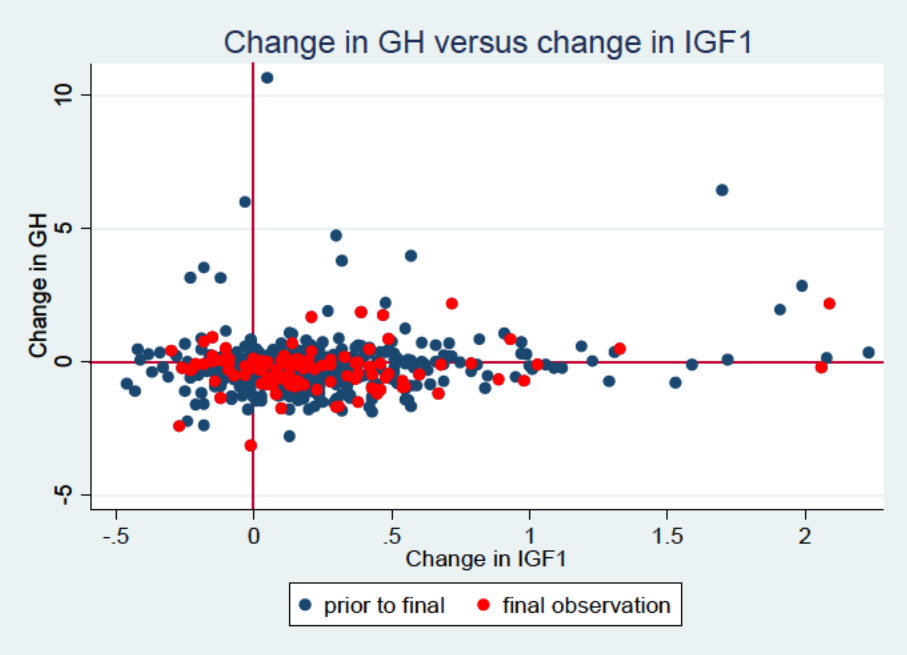
Because the response definition was based on values of both GH and IGF-1, a visual inspection of both markers at the same time would provide more clarity to the study outcomes. I plotted values of GH versus IGF-1 for those observations where both markers were available. Each circle represents one observation. Red circles show final observations where both markers were available. Two red lines indicate the cut points utilized for the study outcome. The goal of the study was to have all final observations in the quadrant A. Red circles outside quadrant A correspond to the subjects who did not meet biochemical definition of response at their last visit. The figure below shows that a big fraction of the red circles was outside of the desired area. The interpretation of this plot also comes with several caveats: 1. The scatter plot shows only visits when IGF-1 and GH were available simultaneously. The GH was collected less frequently than IGF-1 and therefore subjects who demonstrated non-response based on IGF-1 and did not have GH measured at the time of IGF-1 were not included in the plot (among observations marked in red). 2. Subjects who dropped out because of adverse event and did not have elevated IGF-1 or GH would still appear in quadrant A. Therefore, the graph shows a more optimistic picture of the trial.

Figure 12. Scatter plot IGF-1 vs GH



Similar to the previous analysis, a change in both markers was examined in the similar fashion as the raw data. Here, the study goal was to demonstrate no change or reduction (change is negative) in both of the markers.

Figure 13. Scatter plot: Change in GH vs Change in IGF-1



Missing data

Because only 65.8% of all subjects completed the core phase, accounting for missing data in the interpretation of final outcomes is crucial. As it is depicted in the boxplots below, the subjects who did not complete the study had similar trend in the IGF-1 raise, although the variability of the outcomes for the subjects who prematurely discontinued was larger.

Figure 14. IGF-1 by response and dropout status

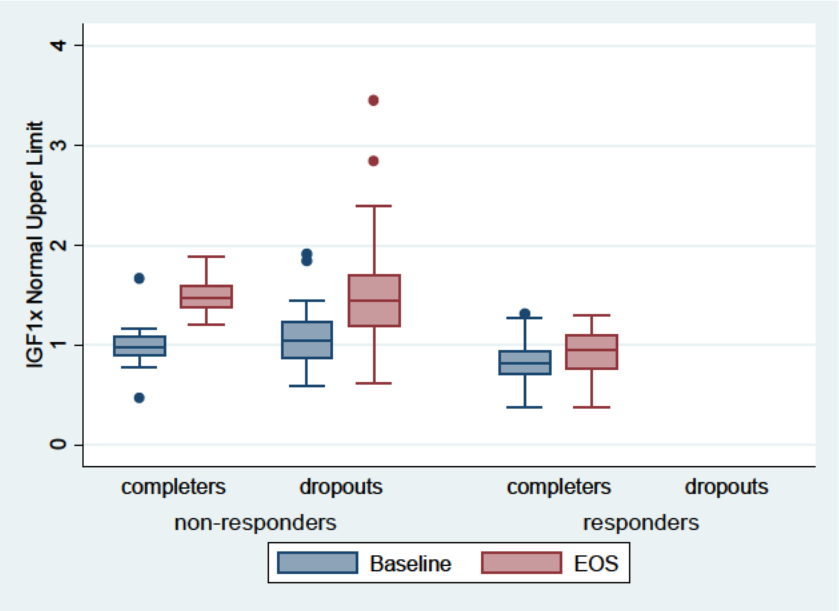
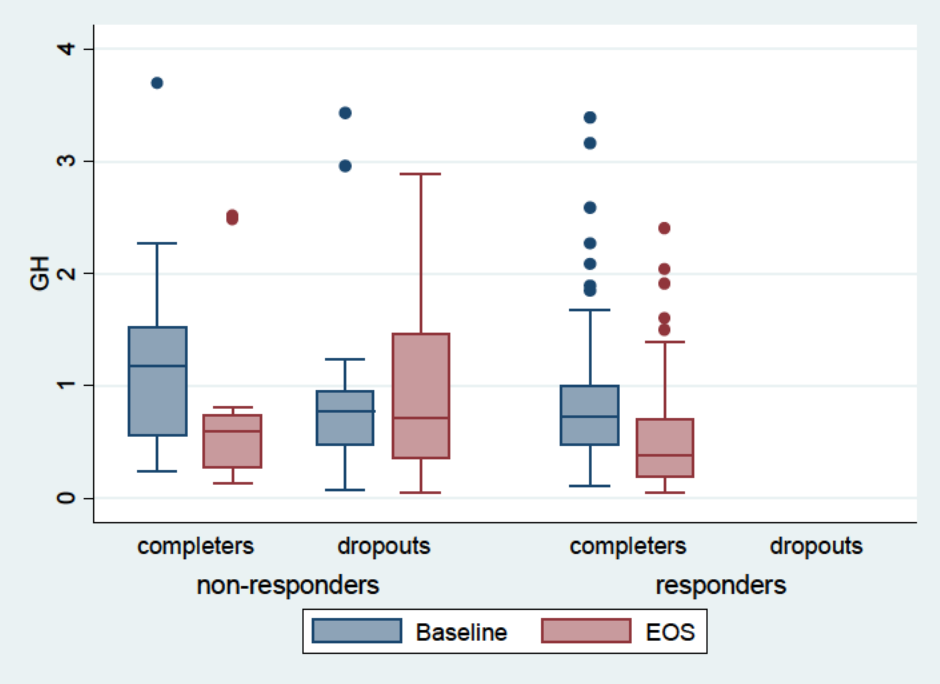


Figure 15. GH by response and dropout status



Based on examination utilizing ITT principle and considering dropouts to be failure, the rate of success in the trial is modest.
As we saw in the previous section, during the trial, IGF1 increased.
Dropouts showed less progress than subjects who completed the study, therefore, the assumption of dropout equivalence to failure makes sense.

Primary outcome

Initially, the sponsor provided the results for the study based on LOCF approach, i.e. utilizing an assumption that subjects who discontinued their participation because of the adverse event had a chance to become a success of the trial, i.e. having normal IGF-1 and GH prior to discontinuation. Because no retrieved drop out was conducted, there was no way for us to determine what happened to those subjects. After communication with FDA, the sponsor provided an analysis based on the mITT dataset. Because there were subjects who did not have post-baseline observations and the majority of those people had an adverse event, removing those subjects from the efficacy analysis can be misleading. In my view, examination of the endpoint based on the ITT principle, i.e. including all participants, will be more appropriate to reflect those dropouts.

The results of my analyses are presented below.
In the study report table on page 112, the sponsor provided results for all subjects but confidence intervals based on only evaluable subjects. Additionally, the tables in the product label do not reflect the efficacy outcomes that include subjects who did not have post-baseline observations.
My tables below clarify the matter by clearly indicating the subjects included and providing confidence intervals for the stated samples.

Table 7. All evaluable subjects

responder	Frequency	Percent	95%CI	
All evaluable subjects				
Yes	98	66.67	58.43	74.22
No	49	33.33		
All study participants				
Yes	98	64.9	56.72	72.48
No	53	35.1		
Assuming that dropouts were non-responders (all evaluable subjects)				
Yes	82	54.30	46.01	62.43
No	69	45.70		
Assuming that dropouts were non-responders adding subjects who did not have post-baseline values (as failures)				
Yes	82	52.90	44.73	60.96
No	73	47.10		

3.3 Evaluation of Safety

Safety events were reviewed by Dr. Smita Abraham from Medical Division of Metabolism and Endocrinology Products. Readers are referred to Dr. Abraham's review for this section.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The subgroup analysis was performed using mITT approach with sponsor-defined definition of responder. Additionally, the analysis was repeated using the entire study population and considering all dropouts to be non-responders. The analysis was repeated for each subgroup.

Because the number of non-white study participants was rather small, no robust conclusions could be made about those subgroups. White subjects were the majority of the study population. For those participants, the percent of responders went from 67.94 (sponsor-defined analysis) to 54.01% using the ITT population and considering all dropouts as non-responders. The results for female and male subjects were similar to each other. Analogously to the race subgroup, the rate of response was maximal in the sponsor-defined analyses and the response was more modest when the ITT principle was applied. The analysis by country did not reveal robust results because the number of subjects in each country was rather small.

Table 8. Subgroup analysis by race

Subjects Events	RACE	Number of subjects (responders)	Percent (within subgroup)	CI(95%)	
All evaluable subjects Sponsor-defined response	ASIAN	2	100.00	0.1581	1.0000
	OTHER	7	50.00	0.2304	0.7696
	WHITE	89	67.94	0.5923	0.7582
All subjects Sponsor-defined response	ASIAN	2	100.00	0.1581	1.0000
	OTHER	7	46.67	0.2127	0.7341
	WHITE	89	66.42	0.5775	0.7441
All subjects dropouts are non-responders	ASIAN	1	50.00	0.0126	0.9874
	OTHER	7	43.75	0.1975	0.7012
	WHITE	74	54.01	0.4530	0.6256

Table 9. Subgroup analysis by gender

Subjects Events	SEX	Number of subjects (responders)	Percent (within subgroup)	CI(95%)	
All evaluable subjects Sponsor-defined response	F	55	65.48	0.5431	0.7552
	M	43	68.25	0.5531	0.7942
All subjects Sponsor-defined response	F	55	64.71	0.5359	0.7477
	M	43	65.15	0.5242	0.7647
All subjects dropouts are non-responders	F	46	52.27	0.4135	0.6304
	M	36	53.73	0.4112	0.6600

Table 10. Subgroup analysis by country

Subjects Events	Country	Number of subjects (responders)	Percent (within subgroup)	CI(95%)	
All evaluable subjects Sponsor-defined response	Germany	11	91.67	0.6152	0.9979
	Hungary	12	57.14	0.3402	0.7818
	Israel	12	85.71	0.5719	0.9822
	Italy	4	66.67	0.2228	0.9567
	Lithuania	4	57.14	0.1841	0.9010
	Mexico	7	50.00	0.2304	0.7696
	Netherlands	10	62.50	0.3878	0.8480
	Poland	9	69.23	0.3857	0.9091
	Romania	7	58.33	0.2767	0.8483
	Serbia	7	53.85	0.2513	0.8078
	Slovakia	4	100.00	0.3976	1.0000
	Slovenia	2	66.67	0.0943	0.9916
	United Kingdom	9	75.00	0.4281	0.9451
All subjects Sponsor-defined response	Germany	11	91.67	0.6152	0.9979
	Hungary	12	57.14	0.3402	0.7818
	Israel	12	75.00	0.4762	0.9273
	Italy	4	66.67	0.2228	0.9567
	Lithuania	4	57.14	0.1841	0.9010
	Mexico	7	46.67	0.2127	0.7341
	Netherlands	10	58.82	0.3292	0.8156
	Poland	9	69.23	0.3857	0.9091
	Romania	7	58.33	0.2767	0.8483
	Serbia	7	53.85	0.2513	0.8078
	Slovakia	4	100.00	0.3976	1.0000
	Slovenia	2	66.67	0.0943	0.9916
	United Kingdom	9	75.00	0.4281	0.9451
All subjects dropouts are non-responders	Germany	8	66.67	0.3489	0.9008
	Hungary	10	47.62	0.2571	0.7022
	Israel	11	64.71	0.3833	0.8579
	Italy	2	33.33	0.0433	0.7772
	Lithuania	4	57.14	0.1841	0.9010
	Mexico	7	43.75	0.1975	0.7012
	Netherlands	8	47.06	0.2298	0.7219
	Poland	6	42.86	0.1766	0.7114
	Romania	7	58.33	0.2767	0.8483
	Serbia	7	53.85	0.2513	0.8078
	Slovakia	2	50.00	0.0676	0.9324
	Slovenia	2	50.00	0.0676	0.9324
	United Kingdom	8	66.67	0.3489	0.9008

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were several issues that were of concern:

1. Absence of comparator arm (or second efficacy study).

2. A large fraction of population did not respond to the treatment

3. The results of the initial analysis provided by the sponsor using mITT dataset artificially increased the proportion of subjects that succeeded in the trial. This happened because the subjects that did not have post-baseline observations were not included in the denominator of the proportion. As I illustrated, the majority of those subjects did not have any observations because they experienced an adverse event prior to the first biomarker analysis.

4. Subjects who were considered to be responders did not achieve stabilization of IGF-1 although their IGF-1 levels remained below the target threshold over the time period of the study. It is not clear whether IGF-1 will continue to go up or whether it will stabilize after prolonged treatment. Therefore, a relatively short duration of exposure to the drug is of concern.

5. Of note, the responders had lower baseline levels of both biomarkers.

6. All study participants had a response to injective sandostatin before taking Mycapssa (oral sandostatin). The purpose of starting on oral sandostatin was to maintain the response on an oral formulation of a drug that they were already tolerating. Therefore, the response status of a subject , who prematurely discontinued treatment with Mycapssa due to an adverse event or intolerability of the drug should be considered as failure. This assumption is reasonable in this particular circumstance because this study did not have a comparator arm.In a real life situation, it is unlikely that those subjects would continue to use the drug that they cannot tolerate and would most likely stay with the injective drug that previously worked for them.

5.2 Conclusions and Recommendations

Because the amount of data and study design (no comparator arm and short study duration) did not provide sufficient information on long-term effects of Mycapssa, further research is needed to understand the effects of this drug.

5.3 Labeling Recommendations

The efficacy outcomes obtained in the core period of the study (first 7 months) were presented in section 14. No results for the efficacy obtained in the extension part were presented in the label.It is my recommendation to revise tables in section 14 of the label to reflect the results based on results obtained from all study participants. Currently all efficacy results presented in section 14 do not include the subjects who had an adverse event and dropped out prior to the first efficacy evaluation. Also, subjects who had observations and dropped out because of sponsor's or patients' request or due to the adverse event should be considered as subjects who did not respond to the drug.

Reference

J Clin Endocrinol Metab. 2014 Nov;99(11):3933-51. doi: 10.1210/jc.2014-2700. Epub 2014 Oct 30. Acromegaly: an endocrine society clinical practice guideline. Katznelson L1, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA; Endocrine Society.

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/s/

ANNA E KETTERMANN
03/11/2016

MARK D ROTHMANN
03/11/2016
I concur

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA Number:	208232
ESTABLISHED NAME	Octreotide Acetate
NAME OF DRUG	Mycapssa (conditionally accepted name)
STRENGTH	20 mg
DOSAGE FORM:	Capsule
ROUTE OF ADMINISTRATION	Oral
PROPOSED INDICATION FOR USE	for long term maintenance treatment in acromegaly patients (b) (4) (b) (4)
APPLICANT	Chiasma, Inc.
REVIEW FINISHED	February 18, 2016
STATISTICAL REVIEWER	Xiaoyu (Cassie) Dong, Ph.D.

_____

Reviewer: Xiaoyu (Cassie) Dong, Mathematical Statistician, CDER/OTS/OB/DB VI

Concur: _____

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/s/

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02/18/2016

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