Document Type:	Study Protocol
Official Title:	A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL) treatment
NCT Number:	NCT03252353
Document Date:	November 29, 2017

Investigational Product	Protocol No.
Octreotide Capsule	**OOC-ACM-303**
Phase **3**	Version and Date **SPA V6.0 November 29, 2017**

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy and Safety of Octreotide Capsules in Patients Who Previously Tolerated and Demonstrated Biochemical Control on Injectable Somatostatin Receptor Ligands (SRL) Treatment

Sponsor:	Chiasma, Inc. [redacted]
Study Chairwoman:	[redacted]
US IND Number:	[redacted]
EudraCT Number:	[redacted]
Protocol Number:	OOC-ACM-303
Study Phase:	3
Central Laboratories:	[redacted]
Contract Research Organization:	[redacted]
Sponsor Contact:	[redacted]
Study Safety Monitors:	[redacted]
Version:	Version 6.0
Protocol Date:	November 29, 2017

Protocol Revision History

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Protocol Signature Page

Protocol Title	A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL) treatment
Protocol Identification	OOC-ACM-303
Study Phase	3
Sponsor	Chiasma, Inc.

Sponsor Representatives

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

[redacted] Date

[redacted] Date

Principal Investigator

By signing below, I, the Principal Investigator approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, electronic case report forms (eCRF) and any protocol-related documents (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Chiasma, Inc. I understand that the study may be terminated or enrollment suspended at any time by Sponsor, or by me if it becomes necessary to protect the best interests of the study patients.

Investigator Signature Date

Name Institution City, Country

PROTOCOL SYNOPSIS

Study Title	A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL) treatment
Protocol No.	OOC-ACM-303
Clinical Sites	Global, Multicenter Study (including US)
Study Phase	3
Investigational Products	**Octreotide Capsules** Octreotide capsule is a novel, orally-administered formulation of the well-characterized and commercially-available parenteral drug, octreotide. It is a capsule filled with an oily suspension of octreotide, formulated with proprietary Transient Permeability Enhancer (TPE®) excipients. The TPE facilitates paracellular transit across the intestinal wall, primarily via transient and reversible opening of the tight junctions between cells, enabling intact octreotide to be absorbed. The capsule is enteric coated and designed to pass intact through the stomach and dissolve in the small intestine. Octreotide capsules (each capsule strength is 20 mg) should be administered twice daily on an empty stomach, i.e. at least 1 hour prior to a meal or at least two hours after a meal. **Placebo** Matching placebo capsules, identical in appearance to octreotide capsules, containing TPE® with no octreotide.
Target Population	Patients diagnosed with acromegaly who are treated with somatostatin receptor ligand (SRL) injections (octreotide or lanreotide) for at least 6 months, with stable dose for at least 3 months and are biochemically controlled, defined as an average insulin-like growth factor [IGF-1] of 2 assessments during the Screening period is ≤ 1 times upper limit of normal (ULN).
Study Objectives	**Primary Objective** • To assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly, who previously demonstrated biochemical control on SRLs **Secondary Objectives** • To assess maintenance of biochemical control, based on GH, with octreotide capsules compared to placebo • To evaluate the safety profile of octreotide capsules compared to placebo **Open Label Extension objectives** • To assess the long-term efficacy and safety of octreotide capsules in acromegaly patients

Study Design	This will be a phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of octreotide capsules in acromegaly patients who previously tolerated and demonstrated biochemical control on injectable SRL treatment. A Steering Committee (SC) will act in an advisory capacity to the Sponsor to provide oversight to the trial conduct and to support its successful completion. An Independent Data Monitoring Committee (IDMC) will act in an advisory capacity to the Sponsor to monitor patient safety during the study. [redacted] Following an up to 8-week Screening period, eligible patients who are biochemically controlled (defined as average IGF-1 $\leq 1 \times$ ULN based on the 2 assessments) on parenteral SRL will be randomized in a 1:1 ratio to octreotide capsules or matching placebo for a 36-week double-blind, placebo-controlled, (DPC) period. During this period, the effective dose for each patient will be determined by dose titration through Week 24 (including Week 24) and maintained through completion of the DPC period. To maintain the blind, patients on matching placebo will also undergo mock titrations increasing capsule numbers from 1 capsule twice daily to 2 capsules in the morning and 1 capsule in the evening/night to 2 capsules BID. Following completion of the 36-week core study (either on study medication or upon meeting pre-defined withdrawal criteria and being followed per protocol through week 36), patients will be offered to enter the Open-Label Extension (OLE) period and receive octreotide capsules until the last patient enrolled into the OLE completes one year or until product marketing or study termination by the sponsor. Once the last patient enrolled completes one year, the Sponsor may either extend the OLE period (via a protocol amendment for an additional one year or until product marketing or study termination) or consider compassionate use (if requested by the principal investigator under a compassionate use protocol). Patients meeting the pre-defined withdrawal criteria, IGF-1 $\geq 1.3 \times$ULN AND exacerbation of acromegaly clinical signs or symptoms, for 2 consecutive assessments, while treated for at least two weeks with 4 capsules per day, during the DPC period, will be rescued with injectable SRL treatment used prior to Screening and will continue to be followed per protocol until week 36. At week 36, these patients will be offered to enter the OLE period and receive octreotide capsules. Patients who do not complete the full 36-week DPC period will not be eligible to enter the OLE period and will not require further follow up beyond week 36. Patients who discontinue study medication early during the DPC period for reasons other than the pre-defined withdrawal criteria, should continue to be followed per protocol until week 36. The Sponsor recommends re-initiation of their prior injectable SRL treatment (as rescue or escape medication) upon meeting the pre-defined withdrawal criteria described above. These patients will not be eligible to enter the OLE period and will not require further follow up beyond week 36. Patients who discontinue study medication during the OLE period, for any reason, or have completed the 36-week DPC period on study medication and are ineligible

	or not opting to continue into the OLE period, will revert to their prior injectable SRL treatment (prior to Screening) or other treatment as determined by their physician. These patients will be followed-up for 12 weeks after end of treatment (EOT). Database lock for the core study will occur after the last patient completes week 36 of the DPC period. At this timepoint, the study will be unblinded and all data from the DPC period analyzed. Interim analyses of the OLE period will be conducted periodically, after completion of the DPC period. Data collected post DPC period (week 36) will be included in the OLE database. Details of these analyses will be outlined in the statistical analysis plan (SAP).
Study Periods and Procedures	**Screening Period (≤ 8 weeks)** [redacted] Eligible patients will have a confirmed diagnosis of acromegaly [pituitary tumor on magnetic resonance imaging (MRI) or pathology report and documented evidence of active disease (IGF-1 ≥1.3 × ULN) following most recent pituitary surgery] and have been treated with SRL injections (octreotide or lanreotide monotherapy) for at least 6 months with a stable dose for at least the last three months of therapy. Eligible patients should be biochemically controlled (average IGF-1 ≤1 × ULN based on the 2 screening assessments. Re-assessment during the screening period will generally not be allowed, unless for technical reasons (e.g. inadequate sample volume, lost sample, assay failure, other). Re-screening will be possible on a case-by-case basis following Sponsor approval. [redacted] **DPC Period** Patients meeting the eligibility criteria will be randomized at Baseline in 1:1 ratio to one of two treatment arms: 1. Octreotide capsules 2. Matching placebo capsules

	[redacted] The duration of the DPC period for each patient will be 36 weeks. The octreotide capsule dose/placebo should be 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 Sponsor recommends any one of the following guiding rules for dose escalation: • Significantly increased IGF-1 levels compared to Baseline defined as IGF-1 increase by at least 30% to >1 × ULN (this will be flagged by the central laboratory). • IGF-1 levels >1 × ULN for 2 consecutive visits. • New or worsening of any one of the following acromegaly signs/symptoms: headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia or hypertension or other signs that in view of the Investigator are related to acromegaly. The dose escalation will be done in a stepwise manner from 1 capsule twice daily; 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 can be escalated any time through Week 24 (including Week 24); thereafter the dose must be kept stable. Patients randomized to matching placebo will also undergo mock titrations increasing capsule numbers from 1 capsule twice daily to 2 capsules in the morning and 1 capsule in the evening/night to 2 capsules BID. During the DPC period, patients will return to the clinic for a site visit every four weeks up to week 36 (± 5 days) and attend an additional in-clinic visit at week 34 (± 5 days). [redacted] Pre-scheduled telephone calls will occur at Weeks 1 and 2. Unscheduled visits will be allowed throughout the study for safety, tolerability or management of active disease, per the Investigator discretion. [redacted] All efforts should be made to maintain patients on their randomized arm assignment throughout the DPC period up to completion of the core study. Patients who meet the pre-defined withdrawal criteria [(IGF-1 levels ≥ 1.3 × ULN AND exacerbation of acromegaly clinical signs or symptoms), for 2 consecutive

[1] Low dose - octreotide dose 10mg /month or lanreotide < 60 mg /month or 120 mg/8 weeks

	assessments, while treated for at least 2 weeks with 4 capsules per day, will be rescued with injectable SRL treatment used prior to Screening and continue to be followed-up per protocol (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities) until week 36. At week 36, these patients will be offered to enter the Open-Label Extension (OLE) period and receive octreotide capsules. Exacerbation of acromegaly clinical signs/symptoms are defined as new or worsening of any one of the following - headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia or hypertension or other signs that in view of the Investigator are related to acromegaly that are recorded as Adverse Events of Special Interest. Per the Investigator discretion, new/worsening acromegaly clinical signs or symptoms may be medically treated while the patient remains in the study (e.g. with analgesics, antidiabetic or antihypertensive medications). Signs/symptoms which continue to require medical treatment will still be considered worsening signs/symptoms. Patients who complete the DPC period on study medication (either octreotide capsules or placebo), will also be offered to enter the OLE period. Patients who discontinue study medication, during the DPC, for reasons other than the pre-defined withdrawal criteria, should continue to be followed per protocol (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities), until week 36. [redacted] These patients will not be eligible to enter the OLE period and will not require further follow up beyond week 36. Patients completing the DPC period and are ineligible or not opting to continue into the OLE period will revert to their parenteral injectable SRL treatment (prior to Screening period), or other treatment, as determined by their physician, and will be followed-up for 12 weeks (see details in Follow-up visit below). **Open-Label Extension (OLE) period** All patients who complete the core study (Screening and DPC periods) on study medications (octreotide capsules/placebo) or patients who met the pre-defined withdrawal criteria and were followed per protocol until week 36, will be offered to enter the OLE period and receive octreotide capsules until the last patient enrolled completes one year or until product marketing or study termination. Once the last patient enrolled completes one year, the Sponsor may either extend the OLE period (via a protocol amendment for an additional one year or until product marketing or study termination) or consider compassionate use (if requested by the principal investigator under a compassionate use protocol). During the OLE period, the initial octreotide capsules dose will be 60 mg for all patients. The dose can be escalated or de-escalated upon the investigator's discretion, based on either IGF-1 and/or safety and tolerability. The Sponsor recommends the following guiding rules for dose de-escalation – • IGF-1 decreased by at least 50% on two consecutive visits, compared to baseline (average of 2 assessments within two weeks prior to randomization) and acromegaly signs/symptoms are adequately controlled (as determined by study investigator). OR • IGF-1 ≤ 1×ULN and acromegaly signs/symptoms are adequately controlled (as determined by study investigator), for two consecutive

	visits (starting from week 4) and the patient was treated with 2 capsules/day (equivalent to 40 mg/day) during the DPC period. OR • IGF-1 ≤ 1×ULN and acromegaly signs/symptoms are adequately controlled (as determined by study investigator), and the patient experience moderate to severe GI symptoms Dose escalation recommendations are similar to those in the DPC period. During the OLE period, clinic visits will be scheduled to occur every 4 weeks (±5 days) for the initial 24 weeks, at weeks 36, 46 and 48 and then every 12 weeks (±10 days) thereafter. A phone call following 2 weeks into the OLE will be made to all patients. IGF-1 will be assessed at every visit. [redacted] Growth hormone (GH) will be assessed at the beginning of the OLE period (same as DPC Week 36/EOT), Month 6, Month 12, annually thereafter and last visit of OLE period. Other procedures will be conducted as specified in the Schedule of Activities. During the OLE, patients who meet the pre-defined withdrawal criteria [(IGF-1 levels ≥ 1.3 × 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, will discontinue study medication and will be rescued with injectable SRL treatment used prior to Screening. Patients who discontinued treatment during the OLE period, for any reason will revert to their parenteral SRL treatment (prior to Screening period) or other treatment as determined by their physician and will be followed-up for 12 weeks (see Follow-up period for details). [redacted] **Follow-Up** All efforts should be made to continue and follow up, per protocol until week 36 (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities) all patients who discontinue study medication early during the DPC period for any reason. Patients who discontinue treatment during the OLE period, for any reason, or are ineligible or opt not to continue into the OLE period, will revert to their prior injectable SRL treatment (prior to Screening period) or other treatment as determined by their physician and will be followed-up for 12 weeks consisting of an in-clinic follow-up visit 4 weeks (±5 days) after their end of treatment (EOT) visit and a phone call 8 weeks later (±5 days). Concomitant medications and AEs will be assessed at these follow-up visits. Other procedures will be conducted as specified in the Schedule of Activities.
Study Duration	**Core study duration**: Up to 44 weeks, composed of:

	<table><tr><td>Screening period</td><td>up to 8 weeks</td></tr><tr><td>Double-blind Placebo-Controlled (DPC) period</td><td>36 weeks</td></tr></table> **OLE period**: at least 1 year (for the last patient who enter the OLE period), or until study medication is commercially available or Sponsor terminates the study. The Sponsor may either extend the OLE period (via a protocol amendment for an additional one year or until product marketing or study termination) or consider compassionate use (if requested by the principal investigator under a compassionate use protocol). **Follow-up period**: For patients who discontinue study medication early during DCP period: Through week 36 of the DPC period. For patients who complete the DPC period on study medication and are not eligible or do not opt to enter OLE or patients who early discontinue OLE period: 12 weeks (consisting of in-clinic visit 4 weeks ±5 days after EOT and a phone call 12 weeks after EOT).
Inclusion Criteria	All inclusion criteria should be met to be eligible to the study. 1. Adult subjects, aged ≥18 years old at the first Screening visit. 2. Patients with active acromegaly, defined as documented evidence of GH-secreting pituitary tumor based on MRI/Pathology report and documented evidence of IGF-1 levels ≥1.3 × ULN. [redacted] 3. Received parenteral SRL monotherapy (octreotide or lanreotide but not pasireotide) for at least 6 months with a stable dose for at least the last three months of therapy. 4. Average IGF-1 of 2 assessments obtained during the Screening period is ≤1 × ULN. 5. Patients able and willing to comply with the requirements of the protocol at the time of Screening. 6. Women who are of childbearing potential should use an acceptable method for birth control. Acceptable methods include hormonal contraception (oral contraceptives – as long as on stable dose, patch, implant, and injection), intrauterine devices, or double barrier methods (e.g. vaginal diaphragm/ vaginal sponge plus condom, or condom plus spermicidal jelly), sexual abstinence[2] or a vasectomized partner. Women may be surgically sterile or at least 1-year post-last menstrual period. Women taking oral contraception containing levonorgestrel should either change treatment (at least one month prior to first study medication dose) or use a mechanical barrier method. 7. Patients able to understand and sign written informed consent to participate in the study.

[2] Abstinence is defined as refraining from heterosexual intercourse during the screening, treatment phase and at least 2 weeks following treatment discontinuation.

Exclusion Criteria	Any of the following will exclude a patient from participating in the study: 1. Patients taking injections of long-acting SRLs off label (unlabeled doses or dosing interval. e.g. 60 or 90mg lanreotide every 8 weeks or 30 mg octreotide every 6 or 8 weeks). 2. Patients who previously participated in CH-ACM-01 or OOC-ACM-302 (MPOWERED study). 3. Symptomatic cholelithiasis. 4. Conventional or stereotactic radiotherapy any time in the past 5. Undergone pituitary surgery within six months prior to screening or have elective pituitary surgery (or other elective surgery that may affect compliance with protocol or confound study outcomes), planned within the course of the core study. 6. High-risk pattern[3] of pituitary tumor location on pituitary MRI/Computed tomography (CT) as per medical history or most recent MRI/CT. 7. History of unstable angina or acute myocardial infarction within the 12 weeks preceding the screening visit or other clinically significant cardiac disease at the time of screening as judged by the Principal Investigator. 8. Any clinically significant uncontrolled nervous system, gastrointestinal (GI), renal, pulmonary, or hepatic concomitant disease that in the Investigator's opinion would preclude patient participation. 9. Evidence of active malignant disease or malignancies diagnosed within the previous one year (except for basal cell carcinoma and uncomplicated – up to stage 1 squamous cell carcinoma that has been excised and cured). 10. Known allergy or hypersensitivity to any of the test compounds or materials. 11. Known uncontrolled diabetes defined as having a fasting glucose > 150 mg/dL (8.3 mmol/L) or glycosylated hemoglobin (HbA1c) ≥ 8% (patients can be rescreened after diabetes is brought under adequate control, or in case HbA1c < 8%). 12. Known defects in visual fields due to optic chiasmal compression or other neurological signs, related to the pituitary tumor mass. Patients with long-standing (>12 months), fixed, minor defects may be considered on a case-by-case basis after consultation with the medical monitor. 13. Female patients who are pregnant or lactating or intending to become pregnant during the study. 14. Known history of immunodeficiency (e.g., HIV positive). 15. Alanine transaminase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP) > 3 × ULN or total bilirubin >1.5 × ULN.

[3] High risk tumor burden is defined by the presence of any of the following:
- Tumor recurrence or growth of residual tumor within one year after surgery or radiation (except for tumor regrowth occurring if SRLs have been stopped in the past)
- Tumor compression of the optic chiasm and invasion of adjacent brain structures (except for sphenoid sinus and cavernous sinus)
- Anticipated need for surgery or radiation during the study period based on tumor growth on serial MRIs
- Metastatic pituitary carcinoma or prior chemotherapy for pituitary carcinoma

	16. Undergone major surgery/surgical therapy for any cause within four weeks prior to enrollment or planned procedure during the study. 17. Known hypothyroidism or hypocortisolism not adequately treated with a stable dose of thyroid or steroid hormone replacement therapy for ≥ 12 weeks. 18. Any condition that may jeopardize study participation (e.g., clinically significant abnormal screening clinical or laboratory finding during screening), the interpretation of study results or may impede the ability to obtain informed consent (e.g., mental condition). 19. History of illicit drug or alcohol abuse within five years. 20. Intake of an investigational drug within 30 days prior to initiation of study treatment. 21. Treatment with pegvisomant within 24 weeks before the first screening visit. 22. Treatment with dopamine agonists within 12 weeks before the first screening visit. 23. Treatment with pasireotide within 24 weeks before the first screening visit.
Inclusion Criteria to OLE period	1. Patient complying with any one of the following criteria: a. Completed the full 36-week duration of the DPC period on study medication b. Met the pre-defined withdrawal criteria during the DPC period and completed follow-up per protocol through week 36 of DCP period 2. Patient not currently having study medication withheld for a study medication-related AE. 3. Patient not having a clinically significant or unstable medical or surgical condition detected or worsening during the study, which would preclude safe participation and completion of the OLE period. 4. Patient willing and able to comply with the protocol requirements for the duration of the OLE period. 5. Patient preference to continue treatment with octreotide capsules and able to understand and sign an additional written informed consent prior to entering the OLE period.
Outcome Measures / Endpoints	**Efficacy Endpoints** [redacted] **Primary Endpoint** • The proportion of patients who maintain their biochemical response at the end of the DPC period. Maintenance of response will be defined by using the average IGF-1 level of the last 2 available assessments [redacted] in the DPC period. If the average IGF-1 is ≤ 1×ULN, a patient will be classified as a responder (i.e., maintained their biochemical response). If the

average IGF-1 is > 1×ULN, a patient will be classified as a non-responder. Patients who discontinue study medication during the DPC period for any reason will be classified as non-responders for the primary analysis, regardless of their IGF-1 values.

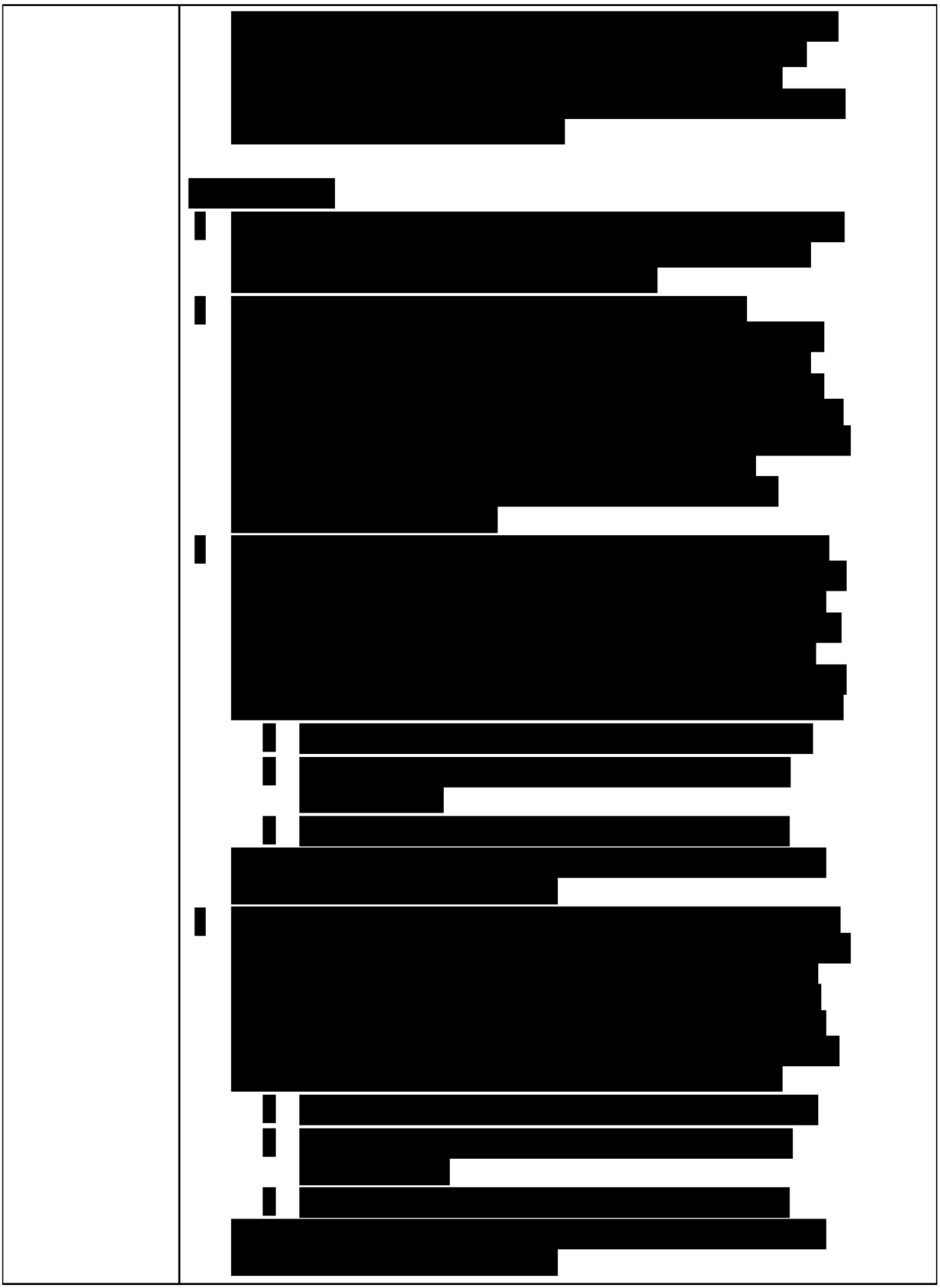
Secondary Endpoints

- Proportion of patients who maintain 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 will be defined using the mean integrated GH value, based on 5 assessments, 30 minutes apart. Patients who discontinue treatment during the DPC period for any reason will be classified as non-responders, regardless of their IGF-1 values.
- Time to loss of response: Loss of response is defined as the earliest time when the IGF-1 of 2 consecutive visits is > 1×ULN, after the patient is treated for at least 2 weeks with 4 capsules per day.
- Time to loss of response: Loss of response is defined as the earliest time when the IGF-1 of 2 consecutive visits is > 1.3×ULN, after the patient is treated for at least 2 weeks with 4 capsules per day .
- Proportion of patients who begin rescue treatment prior to and including week 36.

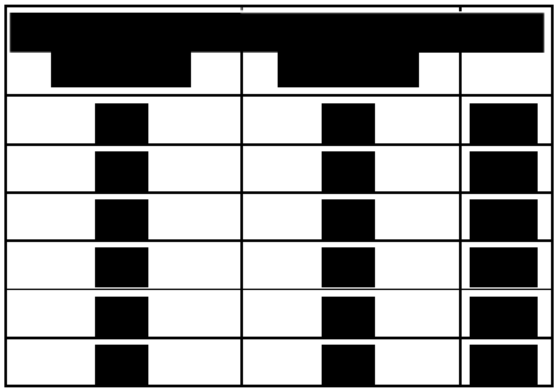
Descriptive Endpoints

- Change from Baseline (screening assessment) to end of treatment in mean growth hormone (GH).
- Change in IGF-1 (ULN), from Baseline (average of 2 assessments within 2 weeks prior to randomization) to end of treatment.

[redacted]



	• [redacted] [redacted] [redacted] [redacted] [redacted] **Safety** • Incidence of adverse events (AEs) • Incidence of new or worsening adverse events of special interest (AESI). • Absolute and change from baseline to each study visit in blood chemistry parameters • Absolute and change from baseline to each study visit in blood hematology parameters • Absolute and change from baseline to each study visit for Vital Signs (heart rate, blood pressure, body weight) and 12-lead ECG (PR, QRS, QTcF, heart rate) • Incidence of clinically significant findings on abdominal ultrasound
Planned Sample Size	Approximately 50 patients will be randomized into the DPC period of the study on either octreotide capsules or matching placebo in a 1:1 ratio. An assessment of superiority will be made by comparing the octreotide capsule group with the placebo group using the primary endpoint described above. [redacted]

	
Statistical Methods	The Full Analysis Set (FAS) is defined as all randomized patients. This population will serve as the primary efficacy analysis population for the DPC period of the study. Patients will be included in the group to which they were randomized. The per-protocol (PP) set will consist of all subjects in the FAS set who were compliant with study medication, and do not have any major protocol violation (e.g., administration of a prohibited concomitant medication, violation of inclusion/exclusion criteria, non-compliance with study medication). Protocol violations that will exclude a subject from the PP set will be identified prior to breaking the blind. This set will be used to assess efficacy and will provide support to the primary analyses with the FAS set. The safety set will consist of all randomized subjects who received any amount of study medication. Assuming no dosing errors, the safety set will be the same as the FAS. The safety set will be used for all safety analyses. Subjects will be assigned to a treatment group based on the treatment they received. Therefore, if a subject received octreotide at any time during the DPC period, they will be included in the octreotide group for safety analyses. For the OLE phase, several different analysis sets will be defined; • The open label extension (OLE) set will consist of all patients enrolled into the OLE phase of the study who received at least one dose of open label study drug. • Octreotide capsules patients from the DPC period who enrolled into the OLE phase and received at least one dose of open label study drug (OLE-OCT) • Octreotide capsules patients from the DPC period, who were classified as treatment responders based on the primary endpoint, at the end of the DPC period, and who enrolled into the OLE phase and received at least one dose of open label study drug (OLE-OCT-RESP). **Primary Efficacy Analysis** The primary efficacy analysis will estimate the proportion of responders, based on the primary endpoint, at the end of the DPC period, within the octreotide capsules and placebo arms. An assessment of superiority will be made using an exact logistic regression model, with covariates for treatment, baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median). If the two-sided p-value is < 0.05, octreotide capsules will be declared superior to

placebo. The adjusted proportions, difference in proportions and associated two-sided 95% confidence intervals will be reported. The odds ratio and two-sided 95% confidence interval (CI) will be reported. The FAS will be the primary population used for this analysis, with the PP population used as a supportive analysis. Sensitivity analyses will be conducted to examine the impact of missing data using multiple imputation.

Secondary Efficacy Analyses

To adjust for multiplicity among the secondary endpoints, a fixed testing order will be used. The secondary endpoints will be tested in the pre-specified order listed above, if the primary endpoint is found to be statistically significant. Testing will proceed to the next endpoint if the preceding endpoint is found to be statistically significant at the 5% (two-sided) level. The moment and endpoint is found not to be significant at the 5% (two-sided) level, all remaining endpoints will be considered exploratory, instead of confirmatory.

The proportion of patients who maintain GH response will be analyzed using the same methods as outlined above for the primary endpoint. The time to loss of response will be summarized using the Kaplan-Meier method, and treatment groups will be compared using a Log-Rank test. The proportion of patients who begin rescue treatment prior to and including week 36 will be compared using Fisher's exact test.

Descriptive Endpoint Analyses

The change from baseline for both GH and IGF-1 will be summarized using descriptive statistics.

[redacted]

Safety Analyses

All safety analyses for data collected during the DPC period will be presented using the safety set. All safety analyses for data collected during the OLE will be presented using the OLE set (summaries by treatment group will be based on the treatment group in the DPC period). Safety analyses for the DPC period will only use data collected during the DPC period. Safety analyses for the OLE will include data collected during the OLE. No formal hypothesis testing will be

	conducted. Data will be summarized using appropriate descriptive statistics. Missing data will be maintained as missing, unless indicated. **Interim Analysis** No interim analysis is planned for the core study.

TABLE OF CONTENTS

List of Tables

List of Figures

GLOSSARY

Subject and patient will be used interchangeably throughout this document.

Abbreviation/Term	Definition
%	Percent
AACE	American Association of Clinical Endocrinologists
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	Twice Daily; bis in die
BL	Baseline
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CPK	Creatine Phosphokinase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
d	Day
DPC	Double-blind, Placebo-Controlled period
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form; any reference to recording data into the eCRF refers to the process of initially recording data in the patient's medical files or study-specific source documents, by the relevant study personnel, followed by upload into the eCRF, as detailed in the Study Monitoring Plan.
EMA	European Medicines Agency
EOT	End-of-Treatment
ESRD	End Stage Renal Disease
EXT-AS	Extension Analysis Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FU	Follow-up
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase

Abbreviation/Term	Definition
GH	Growth Hormone
GHRH	Growth Hormone-Releasing Hormone
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOT (AST)	Glutamic Oxaloacetic Transaminase (aspartate aminotransferase)
GPT (ALT)	Glutamic Pyruvic Transaminase (alanine transaminase)
HbA1c	Glycosylated Hemoglobin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor 1
im	Intramuscular
IMP	Investigational Medicinal Product
INR	International Normalized Ratio (for blood coagulation tests)
IR	Immediate Release
IRB	Institutional Review Board
IV	Intravenous
IWRS/IVRS	Interactive Web / Voice Response System
kDA	Kilo Dalton
kg	Kilogram
L	Liter
LAR	Long-acting Release
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MID	Minimal Important Difference
min	Minute
mL	Milliliter
mmol	Millimole
MRI	Magnetic Resonance Imaging
NDA	New Drug Application
ng	Nanogram
NI	Non-inferiority
OGTT	Oral Glucose Tolerance Test

Abbreviation/Term	Definition
OLE	Open-Label Extension
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PPI	Proton Pump Inhibitor
PT	Preferred Term
QA	Quality Assurance
RA	Regulatory Authority
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
sc (injection)	Subcutaneous
SC	Steering Committee
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulator
SOC (treatment)	Standard of Care
SOC (safety)	System Organ Class
SOP	Standard Operation Procedures
SRL	Somatostatin Receptor Ligands
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TPE	Transient Permeability Enhancer
TSH	Thyroid Stimulating Hormone
TWA	Time Weighted Average
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization
Wk	Week

1 INTRODUCTION

1.1 THERAPEUTIC INDICATIONS

Acromegaly is a rare disorder of disproportionate skeletal, tissue, and organ growth arising from hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). The elevated GH and IGF-1 levels lead also to a wide range of cardiovascular, respiratory, endocrine, and metabolic co-morbidities. In over 95% of cases the etiology is attributed to GH-producing benign pituitary adenoma (Ben-Shlomo and Melmed 2008; Melmed 2009; Melmed et al. 2009).

The annual incidence of acromegaly is 3 to 5 cases per one million individuals, and estimated prevalence is 40 to 70 cases per million with men and women equally affected (Holdaway and Rajasoorya 1999). Owing to its insidious onset it is often diagnosed late (4 to more than 10 years after onset), at an average age of about 40 years. At diagnosis, patients generally exhibit coarsened facial features, exaggerated growth of hands and feet, and soft tissue hypertrophy. The diagnosis of acromegaly requires demonstration of dysregulated and enhanced GH secretion or elevated IGF-1 levels, reflective of peripheral tissue exposure to tonically elevated GH concentrations (Chanson and Salenave 2008; Melmed 2009).

1.2 CURRENT THERAPY

Treatment options for acromegaly include surgical resection of the pituitary adenoma, radiotherapy, and drug therapy to reduce GH and IGF-1 levels to normal values. Currently, there are three drug classes available for the treatment of acromegaly: somatostatin receptor ligands (SRLs) or somatostatin analogs (octreotide, lanreotide and pasireotide), dopamine agonists (bromocriptine and cabergoline), and a GH receptor antagonist (pegvisomant) (Melmed et al. 2009; Melmed et al. 2014).

SRLs are, at present, the most widely used drugs to control acromegaly. Octreotide is an octapeptide, displaying a high affinity for somatostatin receptor subtypes 2 and 5, effectively suppressing GH hypersecretion in up to ~60% of patients with acromegaly (Colao et al. 2004; Chanson and Salenave 2008; Melmed 2009; Fleseriu 2014; Melmed et al. 2014).

Octreotide has been approved as an immediate-release (IR) injectable solution by the FDA since 1988 and in UK in 1989. Octreotide IR formulation is available under the brand name Sandostatin® by Novartis or as a generic form sold by several different suppliers. It is administered as a three times a day subcutaneous (sc) injection. A long-acting depot formulation of octreotide has been initially approved in France in 1995 and in 1998 in the US, for the treatment of acromegaly. Octreotide long-acting formulation is marketed under the brand name Sandostatin LAR by Novartis. It is administered as monthly deep intragluteal intramuscular (im) injection. Lanreotide long-acting formulation is marketed under the brand name Somatuline Autogel by Ipsen. It is administered every four weeks (or six to eight weeks at the higher dose).

Treatment with SRLs is routinely done by dose titration, based on individual biochemical disease control.

1.3 INVESTIGATIONAL THERAPY

Chiasma has developed octreotide capsules, a new formulation of octreotide for oral delivery. It is an enteric coated capsule filled with an oily suspension of unmodified octreotide formulated with

transient permeability enhancer (TPE®)[1] excipients. The enteric coating allows the intact capsule to pass through the stomach and disintegrate when it reaches the higher pH of the small intestine to discharge octreotide capsules suspension.

The TPE platform facilitates intestinal absorbance of drug molecules with limited intestinal bioavailability. The TPE formulation protects the drug molecule from inactivation by the hostile gastrointestinal (GI) environment and at the same time acts on the GI wall to induce local, transient and reversible opening of the paracellular route allowing permeation of the drug molecules through the tight junctions. These two attributes ensure that when delivered in TPE formulation, the drug reaches the bloodstream effectively in its native active form.

The TPE is a combination of excipients assembled in a process leading to an oily suspension of hydrophilic particles containing medium-chain fatty acid salts and the active pharmaceutical ingredient (API) suspended in a lipophilic medium. All of the TPE formulation ingredients are pharmaceutical grade and are safe for pharmaceutical use.

[redacted]

1.3.2 Clinical Studies

Octreotide capsules have been evaluated in an extensive clinical program in which the PK, pharmacodynamics (PD), safety and tolerability have been assessed under various conditions. In addition, the long-term efficacy, safety and tolerability of octreotide capsules were investigated in a Phase 3 study in patients with acromegaly (CH-ACM-01). Another phase 3 study, OOC-ACM-302 study (MPOWERED) is ongoing; this randomized, open-label, active controlled, multicenter study evaluates the maintenance of response, safety and patient reported outcomes (PROs) in acromegaly patients treated with octreotide capsules vs. parenteral SRLs, who previously tolerated and demonstrated biochemical control on both treatments.

Overall, 214 subjects were exposed in 11 Phase 1 pharmacology studies (184 healthy volunteers, 18 patients with hepatic impairment, six patients with severe renal impairment, and six patients with ESRD on dialysis). Drug exposure in the pharmacology studies was typically 1 day and not

[1] TPE is a proprietary excipient mixture that permits oral administration.

more than 6 days.

A total of 155 acromegaly patients were exposed in the Phase 3 study CH-ACM-01. The mean exposure to octreotide capsules from baseline to the End of Treatment (core + Extension) was 42.4 weeks (n = 155, including all patients who prematurely discontinued from the study). Most patients (82 patients, 53%) were exposed to octreotide capsules for more than 12 months.

As of December 2016, 40 patients were enrolled to receive octreotide capsules in the MPOWERED study (OOC-ACM-302).

1.3.2.1 Clinical Pharmacology Studies

[redacted]

- [redacted]

[redacted] affected octreotide absorption from octreotide capsules. [redacted]

- [redacted]

[redacted]

[2] Sandostatin label - "Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs". Somatuline label - "The pharmacological gastrointestinal effects of Somatuline Depot may reduce the intestinal absorption of concomitant drugs".

[redacted]

1.3.2.2 Phase 3 Study (CH-ACM-01) in Acromegaly Patients

Study CH-ACM-01 was a Phase 3, open-label, dose-titration, maintenance of response, baseline controlled, withdrawal study conducted to evaluate the efficacy and safety of octreotide capsules in patients with acromegaly who responded to and tolerated treatment with parenteral SRLs. The study consisted of a core treatment period of at least 7 months and an optional extension treatment period of 6 months. The core Treatment period consisted of a Dose Escalation Phase of 2 to 5 months to identify the therapeutic dose (20 + 20 mg, 40 + 20 mg, or 40 + 40 mg) for each patient on the basis of measurements of IGF-1 and a Fixed Dose Phase of 2 to 5 months, during which the therapeutic dose was maintained. Octreotide capsules were administered twice daily (BID) as morning and evening doses ≥ 1 hour prior to or ≥ 2 hours after a meal. Efficacy was assessed as the proportion of patients who maintained their baseline biochemical (GH and IGF-1) response to parenteral SRLs following a switch to octreotide capsules for up to 13 months. Octreotide capsules safety profile was assessed for new signals, possibly related to the new formulation or route of administration, in comparison with the known safety profile of octreotide.

Efficacy analyses demonstrated that octreotide capsules are effective as a maintenance therapy in most patients for whom treatment with SRL injections has been shown to be effective and tolerated. The response to octreotide treatment was maintained in a clinically relevant proportion of patients after switching from parenteral SRL treatment to octreotide capsules, 65% (98/151) at 7 months and 62% (93/151) at 13 months - compared to 89% on parenteral SRL at baseline. Patients initially responding to octreotide capsules maintained this response through 13 months, with a response rate similar to that known from the literature with parenteral SRLs (Chieffo et al. 2013). Furthermore, acromegaly symptoms improved significantly under octreotide capsules compared to parenteral SRL therapy.

The PK of octreotide capsules was studied in 46 patients. There was a dose-related increase in the mean plasma octreotide concentrations after chronic administration of 40 mg (20 mg BID), 60 mg (40 mg in the morning / 20 mg in the evening/night), and 80 mg BID. Similar trends in octreotide PK between healthy subjects and patients with acromegaly were seen following oral administration, compared to injections, with exception of longer half-life in acromegaly patients treated with octreotide capsules.

The safety profile of octreotide capsules was consistent with the known safety profile of octreotide and the disease burden of acromegaly. No new or unexpected safety signals were detected during the study. The most commonly reported adverse events (AEs) were similar to those reported with parenteral SRLs but with no injection site reactions, reflecting the potential benefit of the oral

application of octreotide over the parenteral SRLs.

More detailed information, including Overall Benefit to Risk Assessment (Section 6.3) is available in the octreotide capsules IB.

[redacted]

[redacted]

[redacted]

1.4.4 Rationale for Endpoints

[redacted]

[redacted]

[3] Low dose - octreotide dose 10 mg /month or lanreotide 60 mg /month or lanreotide 120 mg/8 weeks

1.4.7 [redacted]

[redacted]

[redacted]

[redacted]

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

Primary Objective

- To assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly, who previously demonstrated biochemical control on SRLs.

Secondary Objectives

- To assess maintenance of biochemical control, based on GH, with octreotide capsules compared to placebo;
- To evaluate the safety profile of octreotide capsules compared to placebo.

OLE objectives

- To assess the long-term efficacy and safety of octreotide capsules in acromegaly patients.

2.2 STUDY ENDPOINTS/OUTCOMES

2.2.1 Efficacy Endpoints

[redacted]

Primary Endpoint

- The proportion of patients who maintain their biochemical response at the end of the DPC period.

  Maintenance of response will be defined by using the average IGF-1 level of the last 2 available assessments [redacted] in the DPC period. If the average IGF-1 is $\leq 1 \times$ ULN, a patient will be classified as a responder (i.e., maintained their biochemical response). If the average IGF-1 is $> 1 \times$ ULN, a patient will be classified as a non-responder. Patients who discontinue study medication during the DPC period for any reason will be classified as non-responders for the primary analysis, regardless of their IGF-1 values.

Secondary Endpoints

- Proportion of patients who maintain 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 will be defined using the mean integrated GH value, based on 5 assessments, 30 minutes apart. Patients who discontinue treatment during the DPC period for any reason will be classified as non-responders, regardless of their IGF-1 values.
- Time to loss of response: Loss of response is defined as the earliest time when the IGF-1 of 2 consecutive visits is > 1×ULN, after the patient is treated for at least 2 weeks with 4 capsules per day.
- Time to loss of response: Loss of response is defined as the earliest time when the IGF-1 of 2 consecutive visits is > 1.3×ULN, after the patient is treated for at least 2 weeks with 4 capsules per day
- Proportion of patients who begin rescue treatment prior to and including week 36.

[redacted]

Exploratory Endpoints

- [redacted]

[redacted]

OLE Endpoints

- [redacted]

[redacted]

–

2.2.2 Safety Outcomes

- Incidence of adverse events (AEs)
- Incidence of new or worsening adverse events of special interest (AESI)
- Absolute and change from baseline to each study visit in blood chemistry parameters
- Absolute and change from baseline to each study visit in blood hematology parameters
- Absolute and change from baseline to each study visit for Vital Signs (heart rate, blood pressure, body weight) and 12-lead ECG (PR, QRS, QTcF, heart rate)
- Incidence of clinically significant findings on abdominal ultrasound

3 STUDY DESIGN

This will be a phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of octreotide capsules in acromegaly patients who previously tolerated and demonstrated biochemical control on injectable SRL treatment.

A Steering Committee (SC) will act in an advisory capacity to the Sponsor to provide oversight to the trial conduct and to support its successful completion.

An Independent Data Monitoring Committee (IDMC) will act in an advisory capacity to the

Sponsor to monitor patient safety during the study.

Following completion of the 36-week core study (either on study medication or upon meeting pre-defined withdrawal criteria, and being followed per protocol through week 36), patients will be offered to enter the OLE period and receive octreotide capsules until the last patient enrolled into the OLE completes one year or until product marketing or study termination by the sponsor. Once the last patient enrolled completes one year, the Sponsor may either extend the OLE period (via a protocol amendment for an additional one year or until product marketing or study termination) or consider compassionate use (if requested by the principal investigator under a compassionate use protocol).

Patients meeting the pre-defined withdrawal criteria, IGF-1 ≥1.3×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, during the DPC period, will be rescued with injectable SRL treatment used prior to Screening and will continue to be followed per protocol until week 36. At week 36, these patients will be offered to enter the OLE period and receive octreotide capsules. Patients who do not complete the full 36-week DPC period will not be eligible to enter the OLE period and will not require further follow up beyond week 36.

Patients who discontinue study medications during the DPC period for reasons other than the pre-defined withdrawal criteria should continue to be followed per protocol (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities), until week 36. The Sponsor recommends re-initiation of their prior injectable SRL treatment (as rescue or escape medication) upon meeting the pre-defined withdrawal criteria described above. These patients will not be eligible to enter the OLE period and will not require further follow up beyond week 36.

Patients who discontinue study medication during the OLE period, for any reason, or have completed the 36-week DPC period and are ineligible or not opting to continue into the OLE period, will revert to their prior injectable SRL treatment (prior to Screening) or other treatment as determined by their physician. These patients will be followed-up for 12 weeks after their last treatment visit.

All efforts should be made to continue and follow up, per protocol until week 36 (including all in-clinic visits and assessments as detailed in DPC Schedule of Assessments) all patients who discontinue study medication early during the DPC period for any reason.

Database lock for the core study will occur after the last patient completes the DPC period. At this timepoint, the study will be unblinded and all data from the DPC period analyzed. Interim analyses

of the OLE period will be conducted periodically, after completion of the DPC period. Data collected post DPC period (week 36) will be included in the OLE database. Details of these analyses will be outlined in the statistical analysis plan (SAP).

Study duration will be as follows:

Core study duration: Up to 44 weeks, composed of:

Screening period	up to 8 weeks
Double-blind Placebo-Controlled (DPC) period	36 weeks

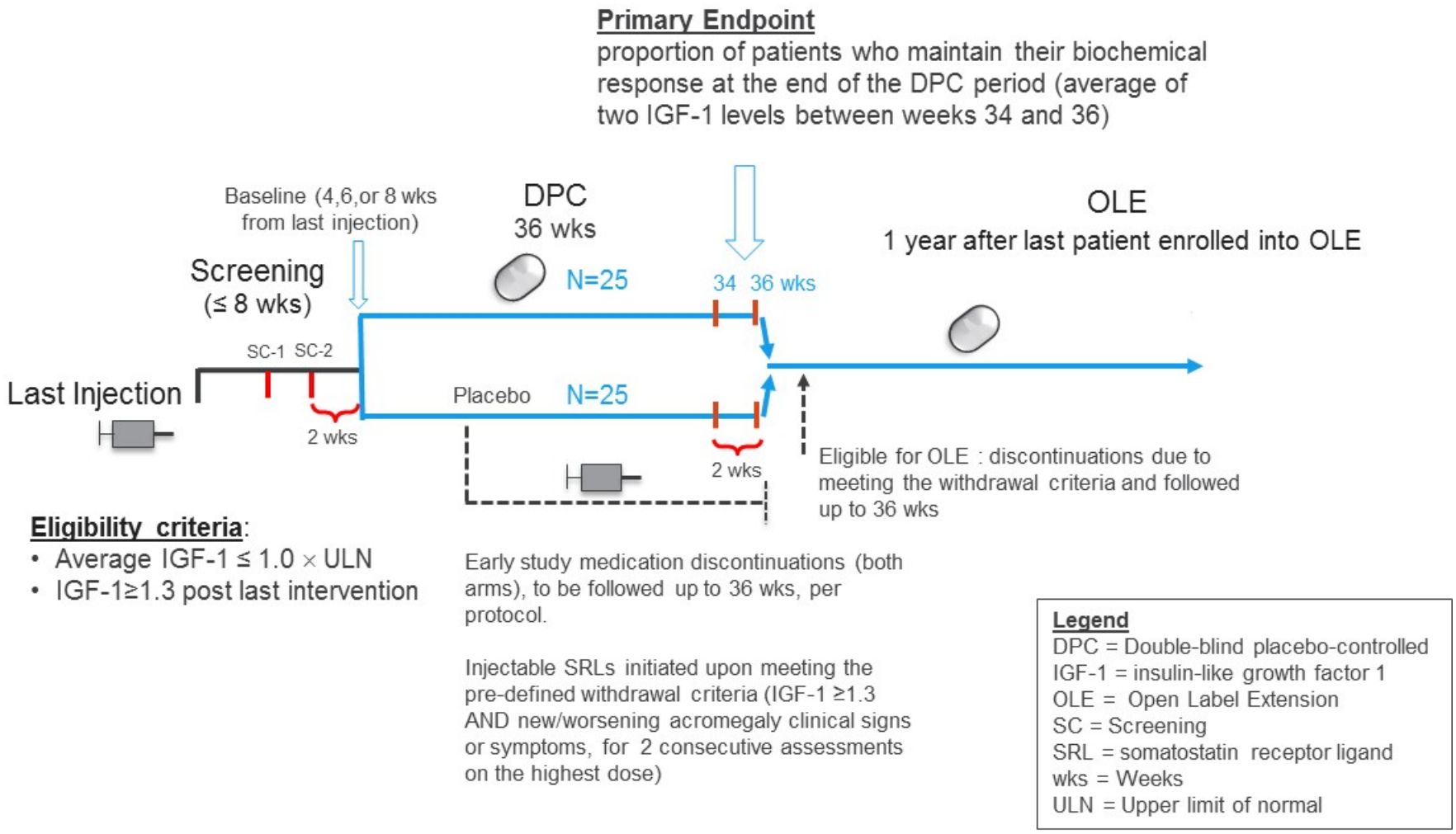
OLE period: at least one year (for the last patient who enter the OLE period), or until study medication is commercially available or Sponsor terminates the study. The Sponsor may either extend the OLE period (via a protocol amendment for an additional one year or until product marketing or study termination) or consider compassionate use (if requested by the principal investigator under a compassionate use protocol).

Follow-up period:

For patients who discontinue study medication early during DPC period: Through week 36 of the DCP period.

For patients who complete the DPC period on study medication and are not eligible or do not opt to enter OLE or patients who early discontinue OLE period on study medications: 12 weeks (consisting of in-clinic visit 4 weeks ±5 days after end of treatment [EOT] and a phone call 12 weeks after EOT).

Figure 1 Study Overview



4 STUDY POPULATION

Patients diagnosed with acromegaly who are treated with SRL injections (octreotide or lanreotide) for at least 6 months, with stable dose for at least 3 months and are biochemically controlled (defined as an average IGF-1 ≤ 1 × ULN for 2 consecutive screening samples).

4.1 INCLUSION CRITERIA

Patients must meet all inclusion criteria to be eligible for the study.

1. Adult subjects, aged ≥18 years old at the first Screening visit.
2. Patients with active acromegaly, defined as documented evidence of GH-secreting pituitary tumor based on MRI/Pathology report and documented evidence of IGF-1 levels ≥1.3 × ULN. [redacted]
3. Received parenteral SRL monotherapy (octreotide or lanreotide but not pasireotide) for at least 6 months with a stable dose for at least the last three months of therapy.
4. Average IGF-1 of 2 assessments obtained during the Screening period is ≤1 × ULN.
5. Patients able and willing to comply with the requirements of the protocol at the time of Screening.
6. Women who are of childbearing potential should use an acceptable method for birth control. Acceptable methods include hormonal contraception (oral contraceptives – as long as on stable dose, patch, implant, and injection), intrauterine devices, or double barrier methods (e.g. vaginal diaphragm/ vaginal sponge plus condom, or condom plus spermicidal jelly), sexual abstinence[1] or a vasectomized partner. Women may be surgically sterile or at least 1-year post-last menstrual period. Women taking oral contraception containing levonorgestrel should either change treatment (at least one month prior to first study medication dose) or use a mechanical barrier method.
7. Patients able to understand and sign written informed consent to participate in the study.

4.2 EXCLUSION CRITERIA

Any of the following will exclude a patient from participating in the study:

1. Patients taking injections of long-acting SRLs off label (unlabeled doses or dosing interval. e.g. 60 or 90 mg lanreotide every 8 weeks or 30 mg octreotide every 6 or 8 weeks).
2. Patients who previously participated in CH-ACM-01 or OOC-ACM-302 (MPOWERED).
3. Symptomatic cholelithiasis.
4. Conventional or stereotactic Radiotherapy any time in the past.
5. Undergone pituitary surgery within six months prior to screening or have elective pituitary surgery (or other elective surgery that may affect compliance with protocol or confound study outcomes), planned within the course of the core study.

[1] Abstinence is defined as refraining from heterosexual intercourse during the screening, treatment phase and at least 2 weeks following treatment discontinuation.

6. High-risk pattern[1] of pituitary tumor location on pituitary magnetic resonance imaging (MRI)/Computed tomography (CT) as per medical history or most recent MRI/CT.
7. History of unstable angina or acute myocardial infarction within the 12 weeks preceding the screening visit or other clinically significant cardiac disease at the time of screening as judged by the Principal Investigator.
8. Any clinically significant uncontrolled nervous system, gastrointestinal (GI), renal, pulmonary, or hepatic concomitant disease that in the Investigator's opinion would preclude patient participation.
9. Evidence of active malignant disease or malignancies diagnosed within the previous one year (except for basal cell carcinoma and uncomplicated – up to stage 1 squamous cell carcinoma that has been excised and cured).
10. Known allergy or hypersensitivity to any of the test compounds or materials.
11. Known uncontrolled diabetes defined as having a fasting glucose > 150 mg/dL (8.3 mmol/L) or glycosylated hemoglobin (HbA1c) ≥ 8% (patients can be rescreened after diabetes is brought under adequate control, or in case HbA1c < 8%).
12. Known defects in visual fields due to optic chiasmal compression or other neurological signs, related to the pituitary tumor mass. Patients with long-standing (>12 months), fixed, minor defects may be considered on a case-by-case basis after consultation with the medical monitor.
13. Female patients who are pregnant or lactating or intending to become pregnant during the study.
14. Known history of immunodeficiency (e.g., HIV positive).
15. ALT, AST or ALP > 3 × ULN or Total Bilirubin >1.5 × ULN.
16. Undergone major surgery/surgical therapy for any cause within four weeks prior to enrollment or planned procedure during the study.
17. Known hypothyroidism or hypocortisolism not adequately treated with a stable dose of thyroid or steroid hormone replacement therapy for ≥ 12 weeks.
18. Any condition that may jeopardize study participation (e.g., clinically significant abnormal screening clinical or laboratory finding during screening), the interpretation of study results or may impede the ability to obtain informed consent (e.g., mental condition).
19. History of illicit drug or alcohol abuse within five years.
20. Intake of an investigational drug within 30 days prior to initiation of study treatment.
21. Treatment with pegvisomant within 24 weeks before the screening visit.

[1] High risk tumor burden is defined by the presence of any of the following:

- Tumor recurrence or growth of residual tumor within one year after surgery or radiation (with the exception of tumor regrowth occurring if SRLs have been stopped in the past)
- Tumor compression of the optic chiasm and invasion of adjacent brain structures (with the exception of sphenoid sinus and cavernous sinus)
- Anticipated need for surgery or radiation during the study period based on tumor growth on serial MRIs
- Metastatic pituitary carcinoma or prior chemotherapy for pituitary carcinoma

22. Treatment with dopamine agonists within 12 weeks before the screening visit.
23. Treatment with pasireotide within 24 weeks before the screening visit.

4.3 ELIGIBILITY CRITERIA TO OLE PERIOD

Patients must meet the following inclusion criteria to be eligible for OLE period:

1. Patient complying with any one of the following criteria:
   a. Completed the full 36-week duration of the DPC period on study medication
   b. Met the pre-defined withdrawal criteria during the DPC period and completed follow-up per protocol through week 36 of DCP period
2. Patient not currently having study medication withheld for a study medication-related AE.
3. Patient not having a clinically significant or unstable medical or surgical condition detected or worsening during the study, which would preclude safe participation and completion of the OLE period.
4. Patient willing and able to comply with the protocol requirements for the duration of the OLE period.
5. Patient preference to continue treatment with octreotide capsules and able to understand and sign an additional written informed consent prior to entering the OLE period.

4.4 PATIENT IDENTIFICATION

Each patient who signed informed consent will be assigned a screening number. This screening number will be used as the primary identification for the complete duration of the study (core and OLE period).

4.5 SCREENING FAILURES

Patients who fail to meet the entrance criteria at any stage during the screening period are defined as screen failures. All screen failures will be recorded on the screening log, which documents the screening number, patient's initials and reason(s) for screen failure. The screening log will be kept in the Investigator's Site File.

Patients who are considered screen failures will be withdrawn from the study and receive standard of care as practiced at that particular site. Screen failures will not count towards the total enrolled and evaluable patients. Re-assessment during the screening period will generally not be allowed, unless for technical reasons (e.g. inadequate sample volume, lost sample, assay failure, other). Re-screening will be possible on a case-by-case basis following Sponsor approval.

4.6 REMOVAL, REPLACEMENT, OR EARLY WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients are free to discontinue study medication and/or their participation in the study at any time and without prejudice to further treatment. The Investigator must discontinue study medication if that patient requests to be withdrawn, or if it is determined that continuing study medication would result in a significant safety risk to the patient.

Patients discontinued or withdrawn from the study will not be replaced.

A patient may discontinue treatment due to the following reasons:

1. Request of Investigator
2. Patient withdrew consent
3. AE
4. Treatment failure
5. Patient is lost-to-follow-up
6. Patient is non-compliant with study procedures or study protocol
7. Request of Sponsor or regulatory authority
8. Pregnancy
9. Other (to be specified in the electronic case report form; eCRF)

4.6.1 Early Study Medication Discontinuation During DPC Period

Patients who discontinue study medication during the DPC period due to pre-defined withdrawal criteria will be rescued with injectable SRL treatment used prior to Screening and continue to be followed-up per protocol (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities) until week 36. Their visit schedule will be customized to correspond with their SRL injection schedule. At week 36, these patients will be offered to enter the OLE and receive octreotide capsules. Patients who do not complete the full 36-week DPC period will not be eligible to enter the OLE period and will not require further follow up beyond week 36.

Patients who discontinue study medication during the DPC period for reasons other than the pre-defined withdrawal criteria should continue to be followed per protocol (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities), until week 36. The Sponsor recommends re-initiation of their prior injectable SRL treatment (as rescue or escape medication) upon meeting the pre-defined withdrawal criteria. These patients will not be eligible to continue into the OLE and will not require further follow up beyond week 36.

4.6.2 Early Termination from OLE Period

Patients who discontinue treatment during the OLE period for any reason will revert to their prior injectable SRL treatment (prior to Screening) or other treatment as determined by their physician. These patients will be followed-up for 12 weeks after EOT (consisting of in-clinic visit 4 weeks ±5 days after EOT and a phone call 8 weeks ±5 days later).

4.7 HANDLING OF WITHDRAWALS

Patients discontinuing study medication during DPC period will be followed-up for per protocol and return for all scheduled visits through Week 36. In case the patient is lost-to-follow-up or withdraws consent to attend the remaining study visits, all efforts should be made to invite the patient to attend EOT visit as soon after their last dose of study medication and to attend a follow up visit 36 weeks after Baseline. Patients discontinuing OLE period. will be followed for 12 weeks after their last octreotide capsules dose.

Patients will be asked to agree that study assessments be performed as stated in the protocol for the remaining study visits, even if the patient discontinues treatment by his/her decision, or that of the Principal Investigator.

4.8 SPONSOR'S TERMINATION OF STUDY

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Lack of efficacy of the study medication
- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs
- Medical, scientific or ethical reasons affecting the continued performance of the study.

Regulatory Authorities also have the right to terminate the study for any reason.

5 STUDY PROCEDURES AND ASSESSMENTS

A schedule of activities for this study is shown in Appendix A.

No protocol-related procedures, should be performed before patients provide written informed consent. Study-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study medications, and descriptions of AEs should be recorded in the appropriate source documents and eCRF.

If possible, a woman taking oral contraception will attend any clinical visit during the time of active hormonal contraception and not during the menstruating period to decrease confounding effects on IGF-1 and GH assessments.

5.1 SCREENING PERIOD (≤8 WEEKS)

The purpose and procedures of the study will be fully explained to potential participants. Those wishing to enroll in the study will sign a written informed consent prior to initiating any study-related evaluations or procedures. Eligible patients will have a confirmed diagnosis of acromegaly [pituitary tumor on MRI or pathology report and documented evidence of active disease (IGF-1 ≥1.3 × ULN) following most recent pituitary surgery/radiotherapy)] and have been treated with SRL injections (octreotide or lanreotide monotherapy) for at least 6 months with a stable dose for at least the last three months of therapy. [redacted]

Re-assessment during the screening period will generally not be allowed, unless for technical reasons (e.g. inadequate sample volume, lost sample, assay failure, other). Re-screening[1] will be possible on a case-by-case basis following Sponsor approval.

[redacted]

The following evaluations should be done at the Screening visit 1:

[1] Assessments required to be repeated for re-screening will be determined on a case-by-case basis with Sponsor's medical monitor.

- Informed consent signature
- Inclusion and exclusion criteria review
- An MRI must be completed during the Screening period unless an MRI image and/or report is available within 12 months prior to screening. If tumor remnants were not visible or were less than 5 mm on the last MRI, an MRI performed within 2 years is also acceptable. CT scans may be done if an MRI is contraindicated.
- Acromegaly history – date of diagnosis, Number of surgeries, first and most recent surgery, first pathology report findings, most recently documented MRI/CT findings – prior to surgery, following surgery, elevated IGF-1 following surgery[1]
- Medical history; any diseases that are present prior to screening or present prior to but diagnosed during screening will be documented in the medical history eCRF.
- Prior and concomitant medications recording – general use since diagnosis (list of prior medications for acromegaly any time in the past), medications for acromegaly within the last year (with start and stop dates), including the last dose of SRL injection and medications for other conditions – within the last 12 weeks.
- Demographic data
- Height and weight measurements
- Vital signs
- 12-lead ECG
- Safety laboratory tests: hematology, chemistry, urinalysis, HbA1c, fasting plasma glucose (FPG; for diabetic patients only) and serum pregnancy test, if applicable (for women with childbearing potential)
- IGF-1
- GH: Five samples every 30 ± 5 minutes over two hours from time 0 to 2 hours
- Complete physical examination
- Acromegaly directed and treatment directed physical examination
- Adverse events
- Gall bladder ultrasound

The following evaluations will be done at Screening visit 2:

- IGF-1
- Adverse events
- Concomitant medications

5.2 DOUBLE-BLIND PLACEBO-CONTROLLED (DPC) PERIOD (WEEK 1 TO WEEK 36)

Patients meeting the eligibility criteria will be randomized at Baseline in 1:1 ratio to one of two treatment arms: Octreotide capsules or matching placebo capsules. All efforts should be made to

[1] Including assay used and/or reference ranges

maintain patients on their randomized arm assignment throughout the DPC period up to completion of the core study.

The octreotide capsule dose/placebo should be 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 (see Section 6.2).

During the DPC period, patients will return to the clinic for a site visit every four weeks (±5 days) up to week 36 and attend an additional in-clinic visit at week 34 to collect 2 consecutive assessments [redacted]. Patients who miss week 34 visit will be scheduled to attend an unscheduled visit.

Pre-scheduled telephone calls will occur at weeks 1 and 2. Unscheduled visits will be allowed throughout the study for safety, tolerability or management of active disease, per the Investigator discretion. If IGF-1 ≥1.3 × ULN at any visit, or upon physician assessment of exacerbation of clinical symptoms, the patient should be invited to an unscheduled visit within two weeks of the first assessment.

5.2.1 Baseline Visit

[redacted]

Patients meeting the eligibility criteria will be randomized at Baseline in 1:1 ratio to one of two treatment arms:

1. Octreotide capsules
2. Matching placebo capsules

[redacted]

The following assessments and procedures will be performed at Baseline (BL) Visit[2]:

- Inclusion and exclusion criteria review and confirmation
- Vital signs
- Weight
- Safety laboratory tests: hematology, biochemistry, TSH, free T4, and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density

[1] Low dose - octreotide dose 10 mg /month or lanreotide 60 mg /month or lanreotide 120 mg/8 weeks
[2] Time from last dose should not exceed injection interval +3 days

lipoprotein)

- Urine pregnancy test for women of childbearing potential, Positive urine pregnancy test will be followed by a confirmatory serum pregnancy test. In case of positive urine pregnancy test subjects could not be dosed, until the results of the serum pregnancy test will be available. Positive serum pregnancy test will result in a subject being a screening failure.
- IGF-1
- GH: Five samples every 30 ± 5 minutes over two hours from time 0 to 2 hours
- Acromegaly directed and treatment directed physical examination
- Concomitant medications and AE recording
- Randomization and dispense study medication (call IVRS/IWRS)
- Study medication administration at the site (first dose, after the collection of blood samples for GH)
- Drug administration instructions:
  - apply food habits questionnaire, and adjust study medication administration and timing to the patient habits. Instruct the patient how he/she should take his/her other concomitant drugs (thyroid hormones, anti-diabetic medications, PPIs or H2 blockers).
  - Instruct the patient that study medications should be taken on an empty stomach at least one hour prior to a meal or at least two hours after. Optional drug administration timing for patients:

Morning Dose

  - Take the morning dose first thing in the morning with a glass of water and have your breakfast at least one hour later, or
  - Have breakfast and take your morning dose at least two hours later and at least one hour prior to lunch

Evening Dose

  - Take your evening dose before going to bed, at least two hours after dinner or any other snack or
  - Take your evening dose at least 1 hour prior to dinner and at least two hours following an earlier snack/meal.

5.2.2 Telephone Call at Week 1 and Week 2

The following assessments and procedures will be performed on the pre-scheduled telephone calls at Week 1 and 2:

- AEs recording
- Drug administration instructions (including assessments for dose titration)
- Address any potential questions the patient may have with the new treatment

5.2.3 DPC Clinic Visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 34, 36)

The following procedures and assessments will be conducted during DPC period visits:

- Weight
- Vital signs
- Safety laboratory tests: hematology and biochemistry
- IGF-1
- Acromegaly directed and treatment directed physical examination
- AEs including GI
- Concomitant medications recording
- Assess pre-define withdrawal criteria (based on clinical judgement, consider the option for an unscheduled visit in case IGF-1 levels ≥ 1.3 × ULN while treated for at least 2 weeks with 4 capsules a day and/or patient reports significant exacerbation of acromegaly symptoms)
- Assessment of dose titration (through week 24)
- Dispense study medication (call IVRS/IWRS)
- Drug administration instructions
- Study medication accountability
- Compliance assessment (with drug administration instructions)

When results of IGF-1 are available from this visit assess whether additional unscheduled visits are required to confirm active disease. For a patient with a single visit IGF-1 level ≥ 1.3 × ULN a second sample will be obtained within 2 weeks of the first assessment. for a total of 2 consecutive IGF-1 assessments for confirmation of disease activity. Patients who miss week 34 visit, or have missing IGF-1 level from week 34 visit, will be scheduled to attend an unscheduled visit to collect blood draw for IGF-1 levels.

In addition to the above assessments, the following assessments will be done at Week 36:

- Laboratory tests: urinalysis, TSH, free T4, and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) and HbA1c; serum pregnancy test in women of childbearing potential
- GH[1]
- Physical examination
- ECG
- Gall bladder ultrasound
- Treatment Period completion form

Patients who meet the pre-defined withdrawal criteria, IGF-1 ≥1.3×ULN AND exacerbation of

[1] GH: Five samples collected every 30 ± 5 minutes over two hours, 2-4 hours after study medication administration in the clinic, (patients to fast 4 hours prior to and the 2 hours during GH sampling)

acromegaly clinical signs or symptoms) for 2 consecutive visits, while the patient is treated with study medication for at least two weeks with 4 capsules per day, will be rescued with injectable SRL treatment used prior to Screening and continue to be followed-up per protocol (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities) until week 36. Exacerbation of acromegaly clinical signs or symptoms are defined as new or worsening of either one of the following - headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia or hypertension or other signs that in view of the Investigator are related to acromegaly that are recorded as Adverse Events of Special Interest. Per the Investigator discretion, new/worsening acromegaly clinical signs or symptoms could be medically treated (e.g. with analgesics, antidiabetic or antihypertensive medications) while the patient remains in the study. Signs/symptoms which continue to require treatment will still be considered worsening signs/symptoms.

Patients who discontinue study medication, during the DPC, for reasons other than the pre-defined withdrawal criteria, should continue to be followed per protocol (including all in-clinic visits and assessments as detailed in DPC Schedule of Activities), until week 36. The Sponsor recommends re-initiation of their prior injectable SRL treatment (as rescue or escape medication) upon meeting the pre-defined withdrawal criteria described above. These patients will not be eligible to enter the OLE period and will not require further follow up beyond week 36. Patients completing the DPC period and are ineligible or not opting to continue into the OLE period will revert to their prior parenteral injectable SRL treatment (prior to Screening), or other treatment, as determined by their physician, and be followed-up for 12 weeks after EOT (see Follow-up period Section 5.5).

5.3 OPEN-LABEL EXTENSION (OLE) PERIOD

All patients who complete the core study (Screening and DPC period) on study medications (octreotide capsules or placebo), or patients who met the pre-defined withdrawal criteria and were followed per protocol until week 36 on prior SRL injections (as rescue medication), will be offered to enter the OLE period and receive octreotide capsules until the last patient enrolled completes one year or until product marketing or study termination. Beyond one year, the Sponsor will either extend the OLE period (via protocol amendment for an additional one year or until product marketing or study termination) or consider compassionate (if requested by the principal investigator under compassionate use protocol).

During the OLE period the initial octreotide capsules dose will be 60 mg for all patients. The dose can be escalated or de-escalated upon the investigator's discretion, based on either IGF-1 and/or safety and tolerability (See Section 6.2).

All patients will be contacted by phone after two weeks. The following assessments and procedures will be performed on the pre-scheduled telephone calls at Week 2:

- AEs recording
- Compliance assessment and drug administration instructions (including dose titrations)
- Address any potential questions the patient may have with the new treatment

Clinic visits will be scheduled to occur every 4 weeks (±3 days) for the initial 24 weeks, at weeks 36, 46 and 48 and every 12 weeks (±10 days) thereafter. An additional visit at OLE week 46 will be conducted to collect IGF-1 samples.

The following procedures will be done on OLE visits:

- Octreotide capsules administration at the site
- Safety laboratory tests: hematology, biochemistry, urinalysis, TSH, free T4, and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein); HbA1c will be done every six months
- Serum pregnancy test every six months
- Weight
- Vital signs
- Acromegaly directed and treatment directed physical examination
- AEs and concomitant medications recording
- Dispense study medication (call IVRS/IWRS)
- Study medication accountability
- IGF-1[1] (OLE Months 3 and 6 followed by every six months, including OLE week 46 and 48)
- GH[2] (OLE Month 6, Month 12, annually thereafter and last visit of OLE period)
- Abdominal gall bladder (every six months)

During the OLE, patients who meet the pre-defined withdrawal criteria [(IGF-1 levels ≥ 1.3 × 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, will discontinue study medication and will be rescued with injectable SRL treatment used prior to Screening.

Patients who discontinued study medication, for any reason, during the OLE period, will revert to their parenteral SRL treatment (prior to Screening) or other treatment as determined by their physician and will be followed-up for 12 weeks after EOT (see Follow-up period, Section 5.5).

After the last patient has completed the core study, the database has been locked and study results are available, the investigators will be informed of the treatment allocation of their participating patients during the DPC period. In case a patient has maintained response on the placebo arm throughout the DPC period, the investigator, based on his clinical discretion could discontinue treatment and follow-up the patient for 12 weeks after EOT.

5.4 END OF TREATMENT (EOT) VISIT

End of Treatment (EOT) visit is scheduled for patients who discontinued study medication prematurely during DPC period and OLE period. This visit may be performed on a same day as originally scheduled visit or could be scheduled separately. Data collection for this visit should primarily be guided according to principles to protect patient safety and wellbeing.

All efforts should be made to continue and follow up, per protocol until week 36 (including all in-clinic visits and assessments as detailed in DPC Schedule of Assessments) all patients who early

[1] .For a patient with a single visit IGF-1 level ≥ 1.3 × ULN, a second sample will be obtained within two weeks of the first assessment for a total of 2 consecutive IGF-1 assessments for confirmation of disease activity.

[2] GH: Five samples collected every 30 ± 5 minutes over two hours, 2-4 hours after study medication administration in the clinic, (patients to fast 4 hours prior to and the 2 hours during GH sampling)

discontinued study medications during the DPC period for any reason.

The following procedures will be conducted at the EOT visit:

- Weight
- Vital signs
- 12-lead ECG
- Laboratory tests: hematology, biochemistry, urinalysis, TSH, free T4, and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) and HbA1c; serum pregnancy test in women of childbearing potential
- Physical examination
- Acromegaly directed and treatment directed physical examination
- AEs and concomitant medications recording
- Study medication accountability and compliance assessment
- IGF-1 and GH[1]
- Abdominal (gall bladder) ultrasound
- Complete Early discontinuation/treatment phase completion form, if applicable

Other procedures and evaluations will be completed as deemed necessary by the Investigator after consultation with the medical monitor.

5.5 FOLLOW-UP PERIOD

Patients who discontinue study medication any time during the OLE period, for any reason, or have completed the 36-week DPC period on study medication and are ineligible or opt not to continue into the OLE period, will revert to their prior injectable SRL treatment (prior to Screening period) or other treatment as determined by their physician and will be followed-up for 12 weeks consisting of an in-clinic follow-up visit 4 weeks (±5 days) after EOT and a phone call 8 weeks later (±5 days).

The following procedures will be performed at the in-clinic Follow-up visit:

- Vital signs and weight
- 12-lead ECG
- Laboratory tests: hematology and biochemistry
- Acromegaly directed and treatment directed physical examination
- AEs and concomitant medications recording
- Study medication accountability
- IGF-1 and GH[2]
- Abdominal (gall bladder) ultrasound

[1] GH: five samples will be collected every 30 ± 5 minutes over two hours. 2-4 hours after study medication administration in the clinic, (patients to fast 4 hours prior to and the 2 hours during GH sampling).

[2] GH: five samples will be collected every 30 ± 5 minutes over two hours. If octreotide capsules were taken at the clinic - 2-4 hours after octreotide capsules administration, otherwise 0-2.

The following procedures will be performed during the phone call 12 weeks after EOT:

- AE
- Concomitant medications

5.6 UNSCHEDULED VISIT

Unscheduled visits will be allowed throughout the study for safety, tolerability or management of active disease, per the Investigator discretion. If IGF-1 ≥1.3 × ULN at any visit, or upon physician assessment of exacerbation of clinical symptoms, the patient should be invited to an unscheduled visit within two weeks of the first assessment.

The following assessments are mandatory during an unscheduled visit:

- AEs and concomitant medications recording
- Vital signs

The following assessments are required on any unscheduled visit due to inadequate biochemical or clinical control of acromegaly (as determined by the investigator), in addition to the measures listed above:

- IGF-1 assessment
- Acromegaly directed and treatment directed physical examination
- Compliance assessment and drug administration instructions
- Assessment of dose titration – during DPC period or OLE period
- Other as deemed necessary by the study investigator

5.7 EFFICACY ASSESSMENTS

5.7.1 IGF-1 and GH

IGF-1 and GH levels will be assessed by a central laboratory.

IGF-1 concentration in the blood will be assessed at all study visits (single sample). GH concentration in the blood will be assessed at selected study visits (as specified in Schedule of Assessments Appendix A). Blood samples for GH will be collected every 30±5 minutes over two hours (total five samples), at screening from time 0-2 hours, baseline from time 0-2 hours, and at all other visits (Week 36 or EOT [for patients who discontinue study medication early and withdraw consent], during OLE Month 6, Month 12, annually thereafter and end of OLE period), 2-4 hours after study medication administration, if administered at the clinic, otherwise 0-2 hours. The mean integrated concentration will be calculated. A minimum of three GH samples are needed to calculate the mean integrated concentration or the data point will be considered missing. GH samples should be collected after at least 4 hours fast; the fast should be maintained during the 2 hours sampling.

5.8 SAFETY ASSESSMENTS

Safety assessments include AEs (either reported by the patient or observed by the Investigator),

concomitant medication use, vital signs, ECG, physical examination, abdominal (gall bladder) ultrasound, and laboratory assessments; these assessments will be conducted as specified in Schedule of Assessments (Appendix A).

5.8.1 Adverse Events

Adverse events (AEs) will be assessed at all study visits throughout the study from informed consent signing. Any AEs that occur throughout the study (including the follow up periods) will be recorded (Refer to Section 7). Any new AE or exacerbation of existing condition (including acromegaly symptoms, see Section 7.57.1 for details) that occur between scheduled visits should be brought to the attention of the Investigator and recorded as an AE on the appropriate eCRF page, as well as in the patient's medical file.

For list of common AEs associated with octreotide capsules, please refer to the corresponding Investigator's Brochure.

5.8.2 Medical History and Concomitant Medications

Any diseases that are ongoing at screening and before the baseline will be documented in the medical history and concomitant disease section of the eCRF. The diagnosis of concomitant disease resulting from assessment at the screening must be also documented in the medical history.

Use of concomitant medication will be recorded onto the eCRF from the patient's medical file at each study visit throughout the study. This will include trade name (generic name), strength, unit, route of administration, dosage form, frequency, indication, start and stop date(s) of administration. Refer to Section 6.10 for prohibited and allowed medications.

5.8.3 Vital Signs

Vital signs will be measured at all study visits and will include blood pressure and heart rate, at rest as per standard practice at the investigational site. Significant findings noticed after the start of study medication which meet the definition of an AE must be recorded on the AE eCRF.

5.8.4 ECG Assessment

Twelve-lead ECG will be done as specified in Schedule of Assessments (Appendix A). Any ECG abnormality determined by the Investigator to be clinically significant will be noted as an AE on the appropriate eCRF page(s). Such abnormalities will closely be monitored up to their resolution.

5.8.5 Physical Examination

Complete physical examination will be conducted on as specified in Schedule of Assessments (Appendix A).

Acromegaly directed and treatment directed physical examination (Appendix B), will be conducted as specified in Schedule of Assessments (Appendix A). It will include assessment of physical signs related to acromegaly (soft tissue swelling, facial features, signs and symptoms potentially associated with carpal tunnel syndrome, other systems -- e.g. cardiovascular, neurology, abdomen -- as necessary, per the investigator's judgment).

Significant findings made after the start of study medication which meet the definition of an AE must be recorded on the AE eCRF.

Height will be recorded at Screening and weight measurements will be recorded as specified in Schedule of Assessments (Appendix A).

5.8.6 Abdominal Ultrasound

Abdominal ultrasound will be conducted to monitor gall bladder and biliary tract disease as specified in Schedule of Assessments (Appendix A). Abdominal ultrasound may be repeated during the treatment period to comply with local guidelines. Evidence of cholelithiasis, biliary sludge, and bile duct dilatation will be documented.

5.8.7 Safety Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory (except for urine pregnancy test). Blood sampling will be done under fasting conditions (at least eight hours). Fasting conditions may be altered on a case-by-case basis, per the Investigator's clinical discretion, and a documented rationale, at visits when GH assessment following octreotide/placebo capsules administration is assessed at the clinical site as specified in Schedule of Assessments (Appendix A). Laboratory tests (hematology and serum chemistry) will be done under overnight fasting conditions at all clinic visits except Week 36/EOT as well as selected OLE visits where GH is collected and only a 4-hour fast is required.

The laboratory evaluations will include, but not limited to:

- Hematology: red blood cell count, hemoglobin (Hb), hematocrit (Htc), white blood cell (WBC) count and differential, platelets
- Serum biochemistry: glucose, total bilirubin (in case that it is found elevated direct and indirect bilirubin), albumin, sodium, potassium, calcium, creatinine, BUN, phosphorous, uric acid, GOT (AST), GPT (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), total protein (for additional assessments in case of abnormal liver functions please refer to Section 7.6).
- TSH, free T4
- HbA_{1c}.
- FPG; for diabetic patients only at Screening
- Lipid profile (total cholesterol, triglycerides, HDL, LDL)
- Urinalysis: glucose, ketones, pH, protein, specific gravity, and routine microscopy observations
- Serum pregnancy test, if applicable
- Urine pregnancy test, if applicable

6 INVESTIGATIONAL PRODUCT

6.1 IDENTITY OF INVESTIGATIONAL PRODUCT

6.1.1 Octreotide Capsules

Octreotide capsule is a novel, orally-administered formulation of the well-characterized and commercially-available parenteral drug octreotide. Octreotide capsule is a capsule filled with an oily suspension of octreotide formulated with proprietary TPE excipients. The TPE facilitates paracellular transit across the intestinal wall, primarily via transient and reversible opening of the tight junctions between cells, enabling intact octreotide to be absorbed. The capsule is enteric coated and designed to dissolve in the small intestine.

[redacted]

6.1.2 Placebo

Matching placebo capsules, identical in appearance (shape, color and markings) to octreotide capsules[redacted].

6.2 STUDY MEDICATION ADMINISTRATION

Study medication should be administered twice daily with a glass of water (240 mL) on an empty stomach, i.e. at least one hour prior to a meal or at least two hours after a meal.

Optional/recommended drug administration timing to patients:

Morning Dose

- Take the morning dose first thing in the morning and have breakfast at least one hour later OR
- Have breakfast and take the morning dose at least two hours later and at least one hour prior to lunch

Evening Dose

- Take the evening dose before going to bed, at least two hours after dinner or any other snack OR
- Take your evening dose at least 1 hour prior to dinner and at least two hours following an earlier snack/meal

During DPC period, study medication will be up-titrated up in all eligible patients from 1 capsule twice daily; 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 can be escalated any time through week 24 (including week 24); thereafter the dose must be kept stable.

The Sponsor recommends the following guiding rules for dose escalation:

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

During the OLE period, the initial octreotide capsules dose will be 60 mg for all patients. The dose can be escalated or de-escalated upon the investigator's discretion, based on either IGF-1 and/or safety and tolerability.

The Sponsor recommends the following guiding rules for dose de-escalation:

- IGF-1 decreased by at least 50% on two consecutive visits, compared to baseline (average of2 assessments within 2 weeks prior to randomization) and acromegaly signs/symptoms are adequately controlled (as determined by study investigator). OR
- IGF-1 $\leq$ 1×ULN and acromegaly signs/symptoms are adequately controlled (as determined by study investigator), for two consecutive visits (starting from week 4) and the patient was treated with 2 capsules/day (equivalent to 40 mg/day) during the DPC period. OR
- IGF-1 $\leq$ 1×ULN and acromegaly signs/symptoms are adequately controlled (as determined by study investigator), and the patient experience moderate to severe GI symptoms.

Dose escalation recommendations are similar to those in the DPC period.

6.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patients meeting the eligibility criteria will be randomized at Baseline in 1:1 ratio to one of two treatment arms:

1. Octreotide capsules
2. Matching placebo capsules

[redacted]

Randomization and drug dispensing will be done through a qualified randomization service provider (e.g., IWRS/IVRS).

6.4 BLINDING AND UNBLINDING

The study is a double-blind placebo controlled study. Treatment allocation will not be revealed before database lock, after the last patient has completed the DPC.

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a clinical supply manager as well as specified independent unblinded statistician and programmer who will have access to the randomization code for purposes of IDMC reporting, as will be specified in the IDMC charter. The randomization code will be maintained by the IWRS/IVRS. At the time of analyses, when treatment codes are revealed, the IWRS/IVRS will provide the randomization code to the statistician assigned to this study.

[1] Low dose - octreotide dose 10 mg /month or lanreotide 60 mg /month or lanreotide 120 mg/8 weeks

The unblinded study statistician or programmer will not otherwise participate in study procedures or data analysis prior to unblinding of the study data to all study related personnel.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, study personnel will use the IWRS. Access to the IWRS unblinding module requires a special password that may be obtained from the medical monitor or other designated team member. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The investigator or designee must record the date and reason for study discontinuation on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

6.5 MANUFACTURING OF STUDY MEDICATIONS

Octreotide capsule and matching placebo are manufactured for Chiasma, Inc. under good manufacturing practices (GMP) by [redacted], UK. Certain manufacturing operations have been performed by other firms.

6.6 PACKAGING AND LABELING OF STUDY MEDICATION

Octreotide capsules and matching placebo capsules will appear as enteric-coated capsules provided by the Sponsor in wallets containing 28 capsules. The wallets will be packaged and labeled in compliance with the EU GMP, Annex 13 of drugs used in clinical trials and with FDA 21 CFR Part 312.6 *Labeling of an investigational new drug*.

All study medications (octreotide capsules and matching placebo capsules) will be labeled as specified in the Study Pharmacy Manual and may include at minimum:

- Product name
- Dose
- Lot/batch number
- Expiration date
- Protocol number
- Sponsor's name
- Instructions for use and storage
- "Investigational Use Only" statement

6.7 DISTRIBUTION AND RECEIPT OF STUDY MEDICATION

For detailed information on the distribution and receipt of study medication please refer to the Study Pharmacy Manual.

The study medications will be shipped under appropriate conditions with temperature monitoring device for supplies that need to be shipped under refrigerated conditions. Upon arrival at the clinical investigation site, the study pharmacist or designated team member should examine the study medication supplies and report any discrepancies in amounts received, damaged supplies or temperature excursion immediately as outlined in the Pharmacy Manual.

Each shipment of study medication supplies for the study will be accompanied by a shipment form describing the contents of the shipment, acknowledgement of receipt and other appropriate documentation. The study staff will confirm the receipt of clinical supply and will return signed drug accountability logs as instructed in the Study Pharmacy Manual.

All study supplies should arrive at the Pharmacy/Investigational site in sufficient quantity and in time to enable dosing as scheduled. Sites must communicate individual patient status following each study visit to trigger shipments of study medication in time for the subsequent visit.

6.8 STORAGE OF STUDY MEDICATION

The pharmacist (or other authorized designee) is responsible for ensuring that the appropriate storage conditions for the investigational products are maintained in accordance with the requirements in the Study Pharmacy Manual.

Wallets containing enteric-coated octreotide capsules or matching placebo capsules should be stored at 5 ± 3°C. Temperature monitoring should be maintained by the site staff and reviewed on a regular basis by the study monitor. Any significant or extended temperature excursions need to be reported immediately as outlined in the Study Pharmacy Manual. Minor temperature excursions that may occur from opening the door of the refrigerator will be recorded but are not a cause of concern and do not need to be reported.

The study staff and monitors should also check the study medication supplies to ensure sufficient amount of study medication is on hand for active patients and that the supplies are not expired.

All study medications must be kept in a locked area with access to the study medication limited to designated study personnel. Only personnel under the supervision of either the Investigator or the local pharmacist are authorized to dispense study medication.

Further details and instructions will be provided in the Study Pharmacy Manual.

6.9 ACCOUNTABILITY AND COMPLIANCE OF STUDY MEDICATION

The Investigator or pharmacist/designee may dispense study medication(s) only to patients enrolled in the study. Individual patient accountability records must be kept by the site staff. The patient number, the date, batch number/wallet number, and quantity of study medication used or returned by the patient will be recorded on the appropriate accountability forms by the site staff. These records and the inventory of study medication on site will be verified by the study monitor for accuracy and completeness on an ongoing basis throughout the study. Unused drug supplies will be disposed of as instructed in the Study Pharmacy Manual.

Treatment compliance will be assessed at all visits during the study. It will be based on

accountability records and an inventory of used/unused supplies. Study medications compliance may be enhanced with regular telephone calls and other reminders.

At the end of the study, the monitor will conduct a final drug reconciliation for all patients and the study site overall. All records of study medication receipt, accountability records and drug disposition records will be examined and reconciled by the study monitor. Further details will be provided in the Study Pharmacy Manual.

6.10 PRIOR AND CONCOMITANT THERAPY

6.10.1 General Guidelines

All prior treatments received by the patient, e.g. general use since diagnosis (list of prior medications for acromegaly any time in the past), medications for acromegaly within the last year (including the last dose of SRL injection) and medications for other conditions – within the last 12 weeks of the initial Screening visit will be recorded on the patient's eCRF including the treatment's name, indication and the start and stop dates.

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the Investigator and recorded on the concomitant medication eCRF page.

All concomitant medications taken by the patient must be recorded on the eCRF, along with the indication and start and stop dates as well as daily dose.

6.10.2 Prohibited Prior Medications or Therapies

The following are prohibited prior medications or therapies:

- Treatment with pegvisomant within 24 weeks before the first screening visit
- Treatment with dopamine agonists within 12 weeks before the first screening visit
- Treatment with pasireotide within 24 weeks before the first screening visit
- Treatment with long-acting SRLs at a dosing frequency different than once monthly except for lanreotide 120 mg every six or eight weeks
- Conventional or stereotactic radiotherapy any time in the past
- New treatment with estrogens and/or selective estrogen receptor modulators (SERMs)

  (stable regimen of estrogens and/or SERMs will be permitted. Women who are treated with oral contraceptives for 21 days or who are treated with active (hormone containing) pills for 21 days and with non-active pills (non-hormone containing), during the monthly period should make all efforts to schedule all their clinical visits during the 21 days when active hormonal contraception is administered and preferably on the same week pre/post the monthly period).

6.10.3 Allowed Medications

Other than the investigational medicinal drugs, concomitant medications allowed to be used in this study are those used at screening to control existing medical condition, and/or those taken during the study to treat possible AEs. Per the Investigator discretion, new/worsening acromegaly clinical

signs or symptoms could be medically treated (e.g. with analgesics, antidiabetic or antihypertensive medications) while the patient remains in the study.

Concomitant administration of octreotide capsules and thyroid hormone replacement therapy (HRT) is permitted on an empty stomach after an overnight fast or two hours after breakfast. PPIs and H_2 blockers are advised to be taken at least 30-60 minutes prior to meals and at least 1 hour after octreotide capsule administration. Anti-acid is advised to be taken with food or just prior to meals. Timing of octreotide capsules intake in patients taking anti-diabetic medications should be discussed with the study investigator/study nurse.

Loperamide is allowed to treat GI symptoms.

Acute steroid use should be documented on the appropriate eCRF page.

All concomitant medications used to treat AEs will be recorded in the patient's medical file and on the appropriate eCRF page.

If intake of a new systemic prescription drug should become necessary for any reason during the course of the study, the patient is required to inform the Investigator immediately, who will record the drug, the dose and the time of administration in the patient's eCRF.

6.10.4 Prohibited Concomitant Medication

Women taking oral contraception containing levonorgestrel are advised to switch to another oral contraceptive or barrier method.

Investigational therapy for the treatment of acromegaly are prohibited during the course of the study.

Parenteral SRLs or dopamine agonists, GH antagonists are prohibited while the patient is treated with study medication (octreotide capsules/placebo).

7 SAFETY AND PHARMACOVIGILANCE

7.1 ADVERSE EVENT

The FDA defines an AE as "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (US Department of Health and Human Services Food and Drug Administration December 2012).

An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it fulfills one or more of the following:

- Results in patient's withdrawal by the Investigator
- Is associated with clinical signs or symptoms
- Results in change in study medication schedule or in concomitant medication

- Is considered by the Investigator to be of clinical significance (a laboratory abnormality that is not clinically significant will not be considered an AE)

A new condition or the worsening of a pre-existing condition will be considered an AE.

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction is "any AE for which there is a reasonable possibility that the drug caused the adverse event."

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to study entry and do not worsen during the study.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at baseline.
- Overdose of either study medication or concomitant medication without any signs or symptoms unless the patient is hospitalized for observation.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred).
- Pregnancy will not be considered an AE, but if occurs, will be reported on pregnancy form.

AEs will be assessed at all study visits throughout the study from informed consent signing. AEs reported prior to dosing on Baseline Day will be captured and considered non-treatment emergent AEs. Treatment Emergent AEs (TEAEs) will be considered all AEs that occurred from Baseline (following study medication administration) to end of core study (i.e. end of DPC period). AEs reported after termination/completion of the core study, during the Follow-up period will be reported separately. AEs reported during the OLE period will be reported separately and together with the core study. The final safety analysis will be detailed in the Statistical Analysis Plan (SAP). The date and time of each AE occurrence will be recorded.

All AEs, whether observed by the Investigator or designee or volunteered by the patient, should be recorded individually on an AE eCRF page with the following information: the specific event or condition, whether the event was present pre-study (and if so, should be captured in the medical history eCRF page), the dates and times (using the 24 hour clock, where midnight is 00:00 and noon is 12:00) of occurrence, duration, severity, relationship to study medication, specific countermeasures, outcome, and whether considered non-serious or serious, drug-related or not. AEs will be recorded from the time a patient has signed the informed consent form (ICF) and throughout the study, including the Core study, Follow-up and OLE period. Severity of the AE will be assessed by the Investigator in accordance with the definitions below. An SAE must fulfill the requirements listed in the Section 7.2.

Three definitions only should be used by the investigating physician to describe the severity of the AE (Table 1). Only one severity (the worst severity) definition should be used for each AE (e.g., "mild/moderate" is not acceptable).

Table 1 Definition of Adverse Events Severity

INTENSITY	DEFINITION
MILD	A mild adverse event is one where the symptoms are barely noticeable to the patient. It does not influence the performance or prevent the patient from carrying on with normal life activities.
MODERATE	A moderate adverse event is one where the symptoms make a patient uncomfortable and cause some impairment to normal life activities. Treatment for symptom(s) may be required.
SEVERE	A severe adverse event is one where the symptoms cause severe discomfort to the patient and severely limit the patient's normal daily activities. Treatment for symptom(s) is given. Note that serious and severe are not synonymous. A serious adverse event must fulfill the requirements listed in the Section 7.2.

The Investigator will document in his/her opinion the relationship of the AE to the study medication using the criteria outlined in Table 2. Causality assessment will be done for each of the IMP assessed in the study (octreotide capsules or placebo).

Table 2 Definition of Adverse Events Causality

CAUSALITY	ASSESSMENT CRITERIA (all points should be reasonably complied with)
Not related	• An AE with sufficient evidence to accept that there is improbable relationship to IMP administration (e.g., no temporal relationship to drug administration) and the disease, other drugs or other events provide plausible explanation)
Possibly related	• An AE with a reasonable time sequence to administration of the IMP, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related	• An AE occurring in a plausible time relationship to IMP administration, and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (de-challenge) and rechallenge (if necessary), are clinically reasonable

Outcome to Date are classified as follows:

- Fatal
- Not-Recovered/Not Resolved (ongoing) - AE is not recovered/resolved
- Recovered/Resolved – The patient has fully recovered from the AE with no residual effects observable
- Recovered/Resolved with sequelae – The patient has recovered from the AE with residual effects observable
- Unknown

AEs will be coded by data management using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary, Version 18 or later.

Follow-up Reports for Non-Serious AEs

All AEs, that do not meet any of the criteria for serious, should be regarded as non-SAEs and will be recorded on the AE eCRF. Severity and relationship to study medication will be assigned by the Investigator. Follow-up of AEs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

7.1.1 Adverse Events of Special Interest

New or worsening acromegaly signs and/or symptoms will be recorded as adverse events of special interest (AESI) and are headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia or hypertension or other signs that in view of the Investigator are related to acromegaly.

Worsening of symptoms will be any new sign/symptom or shift in severity (e.g. mild to moderate or moderate to severe). Severity will be defined according to Table 1.

Worsening of dysglycemia is a shift in the severity criteria as defined in common terminology criteria for adverse events (CTCAE) v4.03 and shown in Table 3.

Worsening of hypertension is defined as a shift in severity as defined in CTCAE v4.03 and shown in Table 4.

Table 3 Dysglycemia Severity criteria

Dysglycemia	**1 (mild)**	**2 (moderate)**	**3 (severe)**	**4 (life threatening)**	**5 Death**
Hyperglycaemia Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance	Fasting glucose value: >ULN -160 mg/dL; >ULN - 8.9 mmol/L	Fasting glucose value: >160 - 250 mg/dL; >8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L Hospitalization indicated	> 500 mg/dL > 27.8 mmol/L life-threatening consequences	Death
Hypoglycaemia Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood	<LLN - 55 mg/dL <LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L Life-threatening consequences; seizures	Death

Table 4 Hypertension Severity criteria

Severity	**Hypertension** Definition: A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mm Hg.
1 (mild)	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)
2 (moderate)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (≥24 hrs) BP >ULN; monotherapy indicated
3 (severe)	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.
4 (life threatening)	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
5 (death)	Death

7.2 SERIOUS ADVERSE EVENTS

An SAE is any AE occurring at any dose that suggest a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to the study medication and that result in, but may not be limited to, any of the following outcomes:

- Death (regardless of the cause)
- A life-threatening AE or suspected adverse reaction
- Inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- A persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be **serious** when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and optional hospitalizations not associated with a clinical AE (e.g., elective cosmetic surgery) are not considered SAEs.

Important medical events are those which may not be immediately life-threatening, but may jeopardize the patient and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an AE will normally be considered serious by this criterion.

A **life-threatening** adverse drug experience is any AE that places the patient, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

7.3 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

An **unexpected** adverse event is any AE, the specificity or severity of which is not consistent with information in the clinical protocol or current Investigator's Brochure for an unapproved study medication or package insert/summary of product characteristics for an approved product (package inserts are available separately at the participating center). Evaluation will be assessed separately for each of the IMPs in the study.

Serious Unexpected Suspected Adverse Reaction (SUSAR) is a serious adverse reaction assessed as unexpected by the Sponsor and that is judged by either the reporting Investigator or the Sponsor to have a reasonable causal relationship to a medical product.

7.4 NOTIFICATION OF SERIOUS UNEXPECTED SUSPECTED ADVERSE EVENT

The Investigator is responsible for identifying, documenting, evaluating and reporting SAEs in accordance with the protocol, 21CFR312.32, 21CFR312.64, International Council for Harmonisation (ICH) guidelines, and all other applicable regulations.

Initial Notification

Upon identification, all SAEs will be reported by the site within 24 hours using the Initial SAE Report Form. The Initial SAE Report Form should be submitted to the contract research organization (CRO), Pharm-Olam within 24 hours either by e-mail (preferable) or by fax using the contact information provided below.

For regulatory purposes, the initial SAE reports should include:

a) a suspected investigational medicinal product

b) an identifiable patient (e.g., study patient code number)

c) an AE with seriousness reason and the Investigator's assessment of the relationship to study medication

d) an identifiable reporting source (Investigator contact details)

SAEs should also be reported to the IRB/IEC according to local regulations.

Once reported, the SAE form and accompanying documentation should be placed in the Investigator's site file.

In addition, all AEs / SAEs / SUSARs will be reported by the Sponsor to the IDMC, IRB/IEC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Follow-up of SAEs / SUSARs

Follow-up of SAEs / SUSARs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

When supplementary information is available, a follow-up SAE Report Form must be completed by the site (marked as "follow-up report"). The contact report information for follow-up SAE reporting is the same as for initial SAE reports (see above section).

If supplementary information on a SAE has to be sent, the SAE form has to be used marked as "follow-up report" and should be placed in the SAE section of the Investigator's site file.

Accompanying documentation, such as copies of hospital case reports, autopsy report, and other

documents when applicable, should be sent as soon as they are available.

Patients who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAEs after treatment is discontinued or the patient has completed the study that is considered to be related to the study medication or study participation should be recorded and reported immediately to Pharm-Olam using the contact information as described above.

The Investigator will add the information on the SAE on the AE eCRF page and any other relevant eCRF. Particular attention will be made to ensure no discrepancies between the AE eCRF and the SAE form (i.e., outcome, severity, relationship must be consistent).

7.5 ANTICIPATED ADVERSE EVENTS

Previous human experience and known AEs of octreotide are detailed in the corresponding IB.

7.6 OCTREOTIDE SAFETY GUIDANCE

Below is the Sponsor's safety guidance for using octreotide in case of common GI adverse events, elevated liver function tests (LFTs) and/or blood sugar disorder. These guidelines should be used to guide treatment, however, in any case, should not replace clinical judgment.

Common Gastrointestinal Adverse Events

In the previous Phase 3 Study (CH-ACM-01), GI symptoms were among the most commonly reported AEs. These AEs were generally transient and declined with time (median duration was 13 days). Most were mild to moderate in intensity, and occurred during the first two months. There was no dose relationship and most resolved with treatment continuation.

In patients who develop abdominal symptoms (e.g., nausea, vomiting, abdominal pain or diarrhea), common GI illnesses should be excluded (e.g., gastroenteritis, cholestasis, etc.), and treated accordingly. If symptoms are mild to moderate in intensity and patient is able to tolerate oral medications, consideration should be given to treating the patient symptomatically with anti-emetics or anti-diarrheals to determine if patient's GI symptoms will resolve on therapy. Patients who have severe or persistent symptoms or who cannot tolerate food/fluids should be discontinued.

Of note, a phase 1 study showed no interaction between loperamide and oral octreotide capsules.

Liver Dysfunction

Somatostatin analogs including octreotide have been associated with liver function abnormalities, as well as sporadic post-marketing reports of acute hepatitis with or without cholestasis, jaundice and cholestatic jaundice.

Octreotide inhibits secretion of cholecystokinin, resulting in reduced contractility of the gallbladder and an increased risk of sludge and stone formation. Biliary disease is the most common reasons for liver dysfunction in acromegaly patients.

Liver function tests (ALT, AST and Bilirubin), will be monitored routinely at all scheduled visits during all periods of the study. Liver function tests could also be assessed at any unscheduled study visit, as clinically indicated.

Patients who develop liver function abnormalities (elevated transaminases to >3 × ULN) during the study should be evaluated for common causes of hepatitis such as cholestasis, alcoholic liver disease, non-alcoholic steatohepatitis, environmental exposures, other drug/herbal supplement exposures, viral or autoimmune hepatitis. The diagnostic work up of liver dysfunction should be guided by the patient's medical history and physical exam, and local practice, at the investigator discretion.

Patients with asymptomatic liver dysfunction (i.e., ALT or AST >3 × ULN and < 5 × ULN and total bilirubin < 2 × ULN), may continue to receive study drug (Figure 2). Liver function tests must be repeated in 7 days. In case of continued transaminase elevation, periodical follow up visits should be considered, per the investigator discretion up to resolution/return to baseline. Follow up should include monitoring of symptoms potentially associated with acute hepatitis (new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia), or with complications of cholestasis (e.g. cholangitis). In case of symptoms suggestive of cholestasis, a follow up abdominal ultrasound should be considered. Local assessment of INR could be added to the liver function tests, based on the investigator discretion.

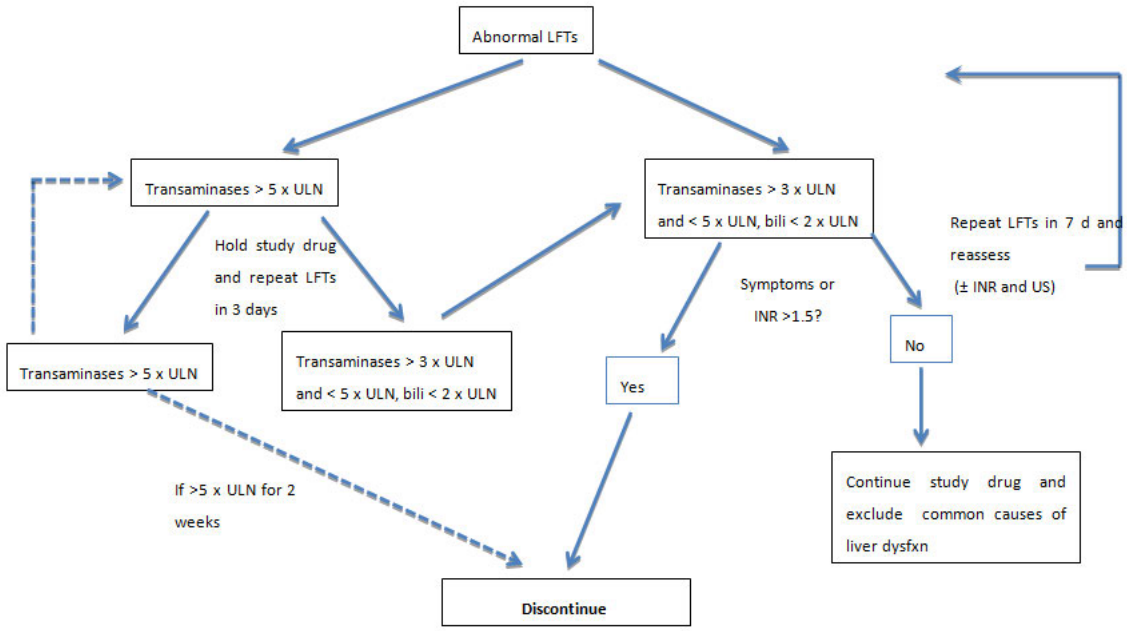
All patients who develop significant liver dysfunction (ALT or AST ≥ 5 × ULN) should have study drug held and be followed up within 3 days and every 3-4 days thereafter up to resolution/return to baseline. In case ALT/AST remains above 5 × ULN, study drug should be discontinued. If ALT/AST has fallen to >3 × ULN and < 5 × ULN, patients should be managed as described in the previous paragraph.

If liver function tests normalize or return to baseline, while study drug has been held, the decision to resume study drug must be discussed with the study medical monitor.

If no alternative etiology exists study drug should be discontinued in the following scenarios:

- ALT or AST >5 × ULN for at least 2 weeks
- ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5 × ULN)
- ALT or AST >3 × ULN with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Figure 2 Decision Tree for Abnormal Liver Function Tests



Glucose Metabolism

Because of its inhibitory action on growth hormone, glucagon, and insulin, octreotide may affect glucose regulation. Post-prandial glucose tolerance may be impaired and, in some instances, persistent hyperglycemia may be induced as a result of chronic administration. Hypoglycemia has also been reported.

Insulin requirements of patients with type I diabetes mellitus therapy may be reduced by administration of octreotide. In non-diabetics and type II diabetics with partially intact insulin reserves, octreotide administration can result in post-prandial increases in glycaemia. Hence, serum glucose will be monitored during all scheduled study visits, and as clinically indicated at unscheduled visits. Diabetic patients should be advised to report any significant increases/decreases in their blood glucose levels, or insulin requirements.

The management of impaired glucose metabolism associated with oral octreotide should be similar to other somatostatin analogs (i.e. octreotide or lanreotide), in conjunction with clinical judgment. As with octreotide or lanreotide, dose adjustments of insulin and antidiabetic medicinal products may be required with oral octreotide.

In patients in whom somatostatin analogs therapy worsens glucose control, reduction of the somatostatin analogs dose, or diabetes management with glucose-lowering agents should be considered.

A complete description of the options for managing impaired glucose tolerance is beyond the scope of the protocol. Patients who develop refractory or labile glucose metabolism should be considered for discontinuation from the study.

8 STATISTICAL ANALYSIS PLAN

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

The statistical analysis of the data obtained from this study will be the responsibility of the designee of the Sponsor.

Database lock for the core study will occur at the completion of DPC period, and will not include the OLE period. Interim analyses of the OLE period will be conducted periodically, after completion of the DPC period. Data collected post DPC period (week 36) will be included in the OLE database. Details of these analyses will be outlined in the SAP.

8.1 SAMPLE SIZE CONSIDERATION

Approximately 50 patients will be randomized into the DPC period of the study in a 1:1 ratio on either octreotide capsules or matching placebo.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

8.2 ANALYZED POPULATIONS

8.2.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) is defined as all randomized patients. This population will serve as the primary efficacy analysis population for the DPC period of the study. Patients will be included in the group to which they were randomized.

8.2.2 Per-Protocol Analysis Set (PP)

The Per-Protocol Analysis Set (PP) is defined as all patients in the FAS who were compliant with study medication and do not have any major protocol violation. Major protocol violations will be identified prior to breaking the blind. This analysis set will provide supportive to the primary analysis with the FAS set.

8.2.3 Safety Analysis Set

The safety set will consist of all randomized subjects who received any amount of study medication. Assuming no dosing errors, the safety set will be the same as the FAS. The safety set will be used for all safety analyses. Subjects will be assigned to a treatment group based on the treatment they received. Therefore, if a subject received octreotide at anytime during the DPC period, they will be included in the octreotide group for safety analyses.

8.2.4 Open Label Extension Analysis Set

For the OLE phase, a number of different analysis sets will be defined.

1. The open label extension (OLE) set will consist of all patients enrolled into the OLE phase of the study who receive at least one dose of open label study drug.
2. Octreotide capsules patients from the DPC period who enrolled into the OLE phase and received at least one dose of open label study drug (OLE-OCT)
3. Octreotide capsules patients from the DPC period, who were classified as treatment responders based on the primary endpoint, at the end of the DPC period, and who enrolled into the OLE phase and received at least one dose of open label study drug (OLE-OCT-RESP)

8.3 ENDPOINTS

For a description of the endpoints refer to Section 2.2. For a description of the assessment tools, refer to Sections 5.7 and 5.8.

8.4 STATISTICAL ANALYSIS

8.4.1 General Considerations

Descriptive statistics and graphical presentations will be used to provide an overview of the study results. For categorical parameters, the number and percentage of patients in each category will be presented. The denominator for percentages will be based on the number of patients appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will generally include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum.

Given the small number of patients, data will be pooled across all sites for reporting purposes. However, the primary endpoint will also be summarized by region (US vs. non-US), age, gender and race.

As there is a single primary endpoint, with a single primary hypothesis test, no adjustment for multiplicity is needed for the primary endpoint/hypothesis test.

To adjust for multiplicity among the secondary endpoints, a fixed testing order will be used. The secondary endpoints will be tested in the pre-specified order as outlined in section 5.1.2, if the primary endpoint is found to statistically significant. Testing will proceed to the next endpoint if the preceding endpoint is found to be statistically significant at the 5% (two-sided) level. The moment and endpoint is found not to be significant at the 5% (two-sided) level, all remaining endpoints will be considered exploratory, instead of confirmatory. No adjustment for multiplicity will be made for the exploratory endpoints.

No adjustment for multiplicity will be made for the endpoints in the OLE period, as these are all

considered exploratory.

8.4.2 Demographics and Baseline

Demographic and baseline characteristics will be summarized by treatment group for the FAS set and the OLE set, by treatment group and overall, using descriptive statistics. If the FAS and safety set are different, then summaries will also be presented for the safety analysis set. No statistical hypothesis tests will be performed.

8.4.3 Primary Efficacy Analysis

The primary efficacy analysis will estimate the proportion of responders, based on the primary endpoint, at the end of the DPC period, within the octreotide capsules and placebo arms. An assessment of superiority will be made using an exact logistic regression model, with covariates for treatment, baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median). If the two-sided p-value is < 0.05, octreotide capsules will be declared superior to placebo. The odds ratio and two-sided 95% confidence interval (CI) will be reported. The FAS will be the primary population used for this analysis, with the PP population used as a supportive analysis.

To assess the impact of missing data on the primary endpoint, sensitivity analyses will be conducted using multiple imputation. Further details will be provided in the SAP.

The primary endpoint analysis results will also be reported by sub-groups (region, age, gender and race). The same statistical methodology applied to the primary endpoint analysis will be used for analyzing the primary endpoint by each sub-group.

Randomization, in theory, should provide balance of all baseline characteristics, between the two treatment groups. At the conclusion of the study, if there is an imbalance in any baseline characteristics felt to be clinically meaningful, the effect of this imbalance on the primary endpoint will be evaluated through inclusion of covariates for these characteristics into the primary model above. These analyses will be considered sensitivity analyses to investigate the robustness of the primary analysis.

8.4.4 Secondary Efficacy Analysis

The secondary endpoint defined as the proportion of patients who maintain GH response will utilize the same methods as outlined above for the primary endpoint. Analyses will be presented using both the FAS and the PP analysis set. For the analysis of the proportion of responders based on mean GH, only patients with a screening mean GH value of < 2.5 ng/mL will be included in the analysis. The time to loss of response will be summarized using the Kaplan-Meier method, and treatment groups will be compared using a Log-Rank test. The proportion of patients who begin rescue treatment prior to and including week 36 will be compared using Fisher's exact test. The denominator for each group will be all patients randomized to that group. The numerator will be those who start rescue treatment prior to and including week 36.

After the study is completed, if there is an imbalance in any baseline characteristics felt to be clinically meaningful, the effect of this imbalance on the secondary endpoints will be evaluated through inclusion of covariates for these characteristics into the models described above. These analyses will be considered sensitivity analyses to investigate the robustness of the primary analyses for the secondary endpoints.

8.4.5 Descriptive Endpoint Analysis

The change from baseline for both GH and IGF-1 will be summarized within each treatment group separately, using descriptive statistics. No between group statistical testing will be conducted.

8.4.6 Exploratory Efficacy Analysis

The exploratory endpoints that are defined as proportions will utilize the same methods as outlined above for the primary endpoint. Analyses will be presented using both the FAS and the PP analysis set.

To help with the interpretation of the primary outcomes, an exploratory supportive analysis will be conducted to examine the relationship between the duration of treatment (i.e., time to discontinuation) and final dropout status. Results will be presented by treatment group using descriptive statistics.

An exploratory analysis will also be conducted to examine the relationship between the time from baseline to dose stabilization, and the patients' final outcome status (i.e., responder, non-responder as determined by the primary endpoint). Results will be presented by treatment group using descriptive statistics.

8.4.7 OLE Period

For all OLE endpoints which are defined as a proportion, the proportion and 2-sided 95% confidence interval (using the Wilson score method, without continuity correction) for the proportion will be reported.

For OLE shift analyses, data will be tabulated using descriptive statistics only.

For OLE endpoints defined as a relative change, the relative change from baseline will be analyzed on the log scale and back transformed for reporting. The relative change and 2-sided 95% CI will be reported.

8.4.8 Safety Analysis

All safety analyses for data collected during the DPC period will be presented using the safety set. All safety analyses for data collected during the OLE will be presented using the OLE set (summaries by treatment group will be based on the treatment group in the DPC period). Safety analyses for the DPC period will only use data collected during the DPC period. Safety analyses for the OLE will include data collected during the OLE. No formal hypothesis testing will be conducted. Data will be summarized using appropriate descriptive statistics. Missing data will be maintained as missing, unless indicated.

8.4.8.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 18.1 or higher).

All AEs that occur after randomization (i.e., date of onset is on or after the date of randomization) and on or before the end of treatment (last dose of blinded study drug) in the DPC period will be considered Treatment Emergent Adverse Events (TEAEs) for the purpose of reporting in the DPC period, and will be summarized using frequency counts and percentages. Summaries will be presented by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo) and overall for the safety set.

Summaries of TEAEs will be presented using the MedDRA level hierarchy (system organ class, high level group term, high level term, and preferred term) as follows:

- Overall (i.e., regardless of intensity or relationship to treatment)
- By intensity grade (mild, moderate, severe)
- By relationship to study medication (potential relationship to study treatment or unlikely/no relationship to study treatment)

TEAEs leading to premature discontinuation of study drug and serious TEAEs (SAEs) will also be summarized by treatment group and relationship. TEAEs leading to premature discontinuation of study drug will be defined as any TEAEs with an action taken regarding study medication equal to "permanently discontinued."

The incidence of patients reporting a new or worsening Adverse event of special interest will summarize overall and by intensity grade. In addition, the incidence of patients reporting a new or worsening AESI's leading to premature discontinuation of study drug will also be summarized overall and by severity).

AEs will be considered treatment emergent for the purpose of reporting in the OLE if they meet any of the following criteria:

- AE onset date is after the end of treatment in the DPC period (i.e., date of onset greater than the end of treatment date in the DPC period)
- AE is ongoing, and the severity worsens during the OLE (i.e., date of severity worsening is greater than the end of treatment date in the DPC period)

All summaries will be presented by final dose group (i.e., 40, 60 or 80) and overall for the OLE set.

Summaries of TEAEs overall, by relationship, leading to premature discontinuation and serious TEAEs will also be presented by sub-groups (region, age, gender and race) using descriptive statistics. .

8.4.8.2 Laboratory Assessments

Descriptive summary statistics for chemistry and hematology data at each post randomization time point (both absolute and change) will be presented by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo). Summaries will be provided for the DPC period and for the OLE period. In calculating the change from baseline for both the DPC and for the OLE, the baseline for the DPC period will be used.

Shift tables, summarizing individual subject changes from baseline to end of treatment will be presented for each laboratory parameter, by treatment group, using the normal ranges from the central laboratory. Summaries will be provided for both the DPC period and OLE period. For both the DPC period and the OLE period summaries, baseline will be the baseline defined for the

start of the DPC period.

Subjects with clinically significant abnormalities (based on investigator's assessment) will be identified in listings

8.4.8.3 Vital Signs and Body Weight

Descriptive statistics of vital sign (systolic blood pressure, diastolic blood pressure, heart rate, body weight) data at each post randomization time point (both absolute and change) will be presented by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo). Summaries will be provided for the DPC period and for the OLE period. In calculating the change from baseline for both the DPC and for the OLE, the baseline for the DPC period will be used.

Additionally, shift tables, summarizing individual subject changes from baseline to end of treatment will be presented for heart rate, diastolic and systolic blood pressure, by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo). These will be presented for both the DPC period and OLE period. For both the DPC period and the OLE period, shifts from baseline will use the baseline defined for the start of the DPC period.

8.4.8.4 ECG, Ultrasound

All 12-Lead ECGs will be read by a central lab. 12-Lead ECG parameters will be summarized at each time point using descriptive statistics by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo). Both absolute and change from baseline will be provided for each continuous 12-Lead ECG parameter. Summaries will be provided for the DPC period and for the OLE period. In calculating the change from baseline for both the DPC and for the OLE, the baseline for the DPC period will be used. Additionally, the numbers and percentages of patients with ECG abnormalities (as determined by the central laboratory) at each visit will be presented for both the DPC and for the OLE.

Shift tables will be used to show the changes from baseline to each post baseline time point based on pre-defined abnormality criteria for both the DPC and for the OLE periods. For both the DPC period and the OLE period, shifts from baseline will use the baseline defined for the start of the DPC period.

The following information will be summarized at baseline and end of treatment for the DPC period using shift tables, by final dose group and treatment group:

- Ultrasound Normality (Normal=Yes reported on eCRF; Abnormal = No)
- Biliary Sludge (Normal=No reported on eCRF; Abnormal =Yes)
- Wall Thickening (Normal=No reported on eCRF; Abnormal =Yes)
- Dilation of Common Bile Duct (Normal=No reported on eCRF; Abnormal =Yes)

For the OLE period, shift tables will also be provided to show shifts from baseline of the DPC period to each assessment in the OLE period.

8.4.9 Interim Analyses

No interim analysis is planned; however, data will be periodically reviewed by the IDMC for safety purposes. Interim analyses of the OLE period may be conducted periodically for regulatory reporting purposes. These analyses will be conducted by the Sponsor, or its designee.

9 ETHICS

9.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

Prior to initiation of the study, the Investigator will submit the study protocol and amendments, sample ICF, and any other documents that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. The Investigator will not begin the study until the protocol and ICF have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening conditions, or death.

9.2 ETHICAL CONDUCT OF THE STUDY

All clinical work conducted under this protocol is subject to GCP guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with the following guidelines:

- ICH-GCP: Consolidated Guideline (International Council for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Brazil, 2013 (Appendix C)
- US Code of Federal Regulations (Title 21, CFR Part 11, 50, 54, 56 and 312) and/or EU Directives; and/or local country regulations and guidelines.

9.3 PATIENT INFORMATION AND CONSENT

Prior to screening for the study, each patient will be informed in detail about the study medications to be administered and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. The patients will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Written consent will be obtained from each patient to be involved in the clinical trial by using the IRB/IEC-approved ICF prior to the conduct of any study-related activity. Each patient will be given a copy of the written ICF, and each patient's chart will include the signed ICF for study participation. The original patient signed and dated ICFs will be maintained by the site for as long as specified in ICH GCP[1].

Patients will be required to sign an additional ICF to participate in the OLE period.

[1] Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.4 PATIENT INSURANCE

A product liability insurance policy to cover against any injury and damages arising from the use of products in this project is provided by Chiasma for the total duration of the study covering the patients and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's site file or can be made available to the Investigator and to the IRB/IEC upon request.

Where applicable, patients will be insured through contract between an insurance company and the Sponsor.

9.5 PERSONAL DATA PROTECTION

The study will be conducted in accordance with the data protection laws that apply in a particular country and jurisdiction.

Chiasma complies with the principle of patient's right to protection against invasion of privacy. Throughout this trial, all patient data will be identified only by a patient identification number. The personal data will be blinded in all data analyses. The patient must be informed and consent as required that authorized personnel of Chiasma such as study monitor, auditor etc. and relevant health regulatory agency will have direct access to personal medical data to assure a high-quality standard of the study.

At the patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Personal physician will be notified by site personnel of patient participation in the study.

9.6 STUDY COMMITTEES

9.6.1 Steering Committee

A Steering Committee (SC) will act in an advisory capacity to the Sponsor to provide oversight to the trial conduct and to support its successful completion. The SC will also ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules.

9.6.2 Independent Data Monitoring Committee

An IDMC will be assigned by the Sponsor prior to the beginning of the study. The IDMC will act in an advisory capacity to the Sponsor to monitor patient safety of octreotide capsules in acromegaly patients who participate in the study. The IDMC responsibilities are to:

- Review the plans for data safety and monitoring
- Evaluate the progress of the trial, study data quality, timeliness, patient recruitment, accrual and retention, patients' risk versus benefit, and other factors that could affect the study outcome
- Perform interim reviews of key safety and efficacy data at regular intervals during the course of the study
- IDMC will review the data from the OLE period at regular intervals to ensure the

safety of participating subjects

- Consider relevant information that may have an impact on the safety of the participants or the ethics of the study
- Protect the safety of the study participants
- Make recommendations to the Sponsor concerning continuation, termination or other modifications of the study based on their observations of the safety of the study

For each IDMC meeting, pre-specified reports will be provided by the data management group. In addition, the IDMC Chair will be provided with or have access to periodical safety reports as specified in the IDMC charter. The IDMC Chair may share these reports with the IDMC or convene additional meetings of the IDMC at his/her discretion. The IDMC Chair may request additional data based on the review of study data.

Further details regarding data safety monitoring guidelines will be included in the IDMC Charter, which is the governing document that supersedes this section of the protocol.

9.7 PROTOCOL EXCEPTIONS AND DEVIATIONS

No protocol deviations are anticipated as it is expected that patients will meet all eligibility criteria. Departures from the protocol should be avoided, unless required for the safety of the patient. Protocol deviations, and if possible the reason for occurrence, will be documented by the study monitor. Should any protocol deviations occur, the Investigator must report the deviation to the Sponsor, and if required, to the IRB/IEC, in accordance with local regulations, within reasonable time.

9.8 PROTOCOL AMENDMENTS

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/IEC in accordance with local requirements and, if required, to the Regulatory Authority, either as an amendment or a notification. Approval for amendments must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study patients, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

10 QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted according to GCP as outlined by ICH Topic E6 step 5 guidelines. The Sponsor and/or designated CRO maintains a quality assurance system with written standard operating procedures (SOPs) to ensure that clinical trials are conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

10.1 AUDITS AND INSPECTIONS

The study may be audited according to the Sponsor's quality assurance (QA) inspection program. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with study protocol and ICH-GCP guideline. Audit visit(s) will be arranged in advance with site personnel at a mutually acceptable time.

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor quality assurance or its designees or to regulatory authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

10.2 STUDY MONITORING

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO or a contract monitor. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements.

Before study initiation, at a site initiation visit or at an Investigator's meeting, a CRO representative will review the protocol and eCRF with the Investigator and his staff.

Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRF will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and will periodically request review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Periodically, some or all of the facilities used in the study (e.g., local laboratory, pharmacy) may be reviewed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review eCRF and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection, and respond to inquiries.

The Investigator will ensure that the study participants are aware of and consent that personal information may be scrutinized during the data verification process as part of study-related monitoring and auditing by properly authorized persons associated with Chiasma or inspection by domestic and/or foreign regulatory authority(ies). However, participation and personal information should be treated as strictly confidential to the extent that the applicable law permits and not be publicly available.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.3 QUALITY LABORATORY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local institution laboratory and central laboratories.

Before the study begins, the laboratories to be used in the study will provide a list of the reference ranges for all laboratory tests to be undertaken and details of the method used for quality control.

These will be held in the Investigator file and the trial master file. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, references, values, etc. during the study must be notified promptly to the Sponsor.

10.4 STUDY DOCUMENTATION

Study documents will include the following:

- Signed ICFs
- Source documents (e.g., patient files, medical notes, study worksheets)
- Investigator copies of the eCRFs and SAE reports
- Investigator site file + contents
- Study Manuals (including laboratory manual, pharmacy manual and reference manual)
- Investigator meeting binder and or other training materials

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.4.1 Source Document

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, ultrasound images, and laboratory results, ECG printouts, pharmacy records, care records, completed scales for each study participant and/or worksheets. Source documents should be kept in a secure and limited access area. All source documents should be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc, etc.). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Study worksheets may be used to supplement study data not recorded in the patient's medical record.

Source data for patients registered to the study should indicate date ICF was signed, participation in clinical protocol, treatment number, evidence that inclusion/exclusion criteria have been met.

10.4.2 Recording of Data on Electronic Case Report Form (eCRF)

No data will be directly entered into the eCRF without source documentation.

Only a patient identification number will be used to identify the patient in the eCRF. The Investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers).

The protocol will use an Internet-Based Electronic Case Report Form eCRF, primarily to collect clinical trial data at the investigational sites. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The design of the eCRF computerized system complies with 21 CFR Part 11. Electronic signatures will be used in conformance with 21 CFR Part 11.

10.4.3 Investigator Site File

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory agencies.

10.5 CLINICAL TRIAL SUPPLIES

The Sponsor or its vendors will be responsible for providing study supplies and for ensuring that they are used, managed and accounted for properly. Accurate and timely records of the disposition and accountability of all study drugs must be maintained by the site and reviewed by the Sponsor representative monitor. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study, the Investigator will keep the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. **Under no circumstances will the Investigator allow the study medications to be used other than as directed by this protocol.**

Upon completion or termination of the study, all study supplies will be disposed of per instructions from the Sponsor and/or its vendors (CRO).

Clinical trial supplies include, however, not limited to: eCRF, study worksheets, lab supplies and study medications.

10.6 DATA MANAGEMENT

Data Management services will be provided by the CRO. After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity, and validity of the database. These edit checks may include:

- Missing value checks
- Range checks
- Consistency checks
- Sequence checks
- Probabilistic checks
- Protocol adherence checks

Queries generated from these checks will be sent to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

For details on data management processes, please refer to the Study Data Management Plan.

11 STUDY ADMINISTRATION

11.1 PARTICIPATING CENTERS

This will be a multicenter, worldwide study (including US sites).

11.2 REQUIRED DOCUMENTS PRIOR TO STUDY INITIATION

Prior to the release of study medication to a site, all essential study documents must be collected, reviewed and approved. These may include:

- Appropriate local health authority documentation properly signed and dated by the required Investigator (i.e., the submission package)
- Signed copy (original) of the approved protocol
- Completed and signed statement of Investigator
- A signed Clinical Trial Agreement
- Curriculum vitae for the Investigator and sub-Investigator (can be collected at site initiation visit)
- IRB/IEC name and address; and membership list (can be collected at site initiation visit)
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number) and ICF (identified by protocol title and number)
- Copy of the IRB/IEC-approved written ICF to be used in the study (that has also been approved by the Sponsor)
- Provisions for direct access to source/data documents if necessary for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, as well as a copy of the laboratory certificate and list of normal laboratory values (can be collected at site initiation visit)

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided.

Upon satisfactory receipt of all required regulatory documents, Sponsor will arrange that study medications be delivered to the study site. Supply of all other study materials will be the responsibility of Chiasma and/or designee. Patient entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation visit has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of study protocol, instructions for eCRF completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee (study monitor) will prepare an Investigator's site file. This file should be used for all trial related documents. The Investigator will be responsible for keeping the Investigator's site file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

11.3 STUDY COMPLETION

This study is expected to end when all required patients have been enrolled and the last patient has completed the study and query resolution has been completed.

Data and materials that are required before the study can be considered complete and/or terminated are:

- Laboratory findings, clinical data, and all special test results from screening through the end of the follow-up period
- eCRF (including correction forms) properly completed by appropriate study personnel and electronically signed by the Investigator

- Completed Drug Accountability Records
- Statement of outcome for each SAE reported
- Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable)

11.4 CLINICAL STUDY REPORT

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

11.5 RETENTION OF STUDY RECORDS

The Investigator will retain copies of the approved protocol, completed eCRF, ICFs, relevant source documents, and all other supporting documentation related to the project for as long as specified in ICH GCP[1]. in a secure and safe facility with limited access If the Investigator is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed of the individual who will be assuming this responsibility.

Further retention, if required, will be negotiated at the end of this period. In that case, Chiasma will notify, in writing, the Investigator when the clinical study data may be discarded. The Investigator will take measures to prevent accidental or premature destruction of these documents.

These files must be made available for inspection upon reasonable request by authorized representatives of Sponsor and/or the relevant regulatory agencies.

11.6 CONFIDENTIALITY AND PUBLICATION OF STUDY DATA

All information supplied by Chiasma in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, the protocol, eCRFs, and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain sole property of Chiasma, shall not be disclosed to others without the written consent of Chiasma, and shall not be used except in the performance of this study.

Data cannot be used for publication or reporting outside of this study until the study is completed or discontinued by Chiasma. This is necessary since dissemination of preliminary information may inappropriately affect the objectivity of this study. For this reason, Chiasma, study Investigators or other parties will not be allowed to perform subset analyses at any point before the conclusion of this study. Violation of this will result in automatic expulsion from this study.

Chiasma recognizes the importance of timely communication of medical research and scientific data and its obligations to patients enrolled in the study. The object of the study will be to publish the results of the complete study in an appropriate peer-reviewed journal after the conclusion. A formal publication of data collected as a result of the study is planned and will be considered a

[1] Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

joint publication by the Investigators and the appropriate Chiasma personnel. Authorship will be determined by mutual agreement. In general, the Investigators who have made the most substantial contributions to the study will be considered lead and/or senior authors. Review and comment by Chiasma on draft abstracts and manuscripts is required prior to publication. Authors should submit draft publications to Chiasma no fewer than sixty (60) days prior to submission to any journal, publisher and/or third party. This requirement should not be construed as a means of restricting publication, but is intended solely (a) to ensure concurrence regarding data, evaluations, and conclusions, (b) to provide an opportunity to share with the Investigator any new or unpublished information of which he or she may be unaware and (c) to ensure that no Chiasma confidential information has been included. If the Sponsor believes that such publication or disclosure contains confidential information, the Investigator/author agrees to remove such confidential information from the proposed publication or disclosure.

The information developed during the conduct of this study is also considered confidential, and will used by Chiasma. This information may be disclosed as deemed necessary by Chiasma. To allow the use of this information derived from this study, the Investigator is obliged to provide Chiasma with complete test results and all data collected and developed in this study.

12 REFERENCES

Ben-Shlomo, A. and S. Melmed (2008). "Acromegaly." Endocrinol Metab Clin North Am **37**(1): 101-122, viii.

Caron, P., A. Beckers, et al. (2002). "Efficacy of the new long-acting formulation of lanreotide (lanreotide Autogel) in the management of acromegaly." The Journal of clinical endocrinology and metabolism **87**(1): 99-104.

Chanson, P. and S. Salenave (2008). "Acromegaly." Orphanet J Rare Dis **3**: 17.

Chieffo, C., D. Cook, et al. (2013). "Efficacy and safety of an octreotide implant in the treatment of patients with acromegaly." The Journal of clinical endocrinology and metabolism **98**(10): 4047-4054.

Colao, A., M. D. Bronstein, et al. (2014). "Pasireotide versus octreotide in acromegaly: a head-to-head superiority study." The Journal of clinical endocrinology and metabolism **99**(3): 791-799.

Colao, A., D. Ferone, et al. (2004). "Systemic Complications of Acromegaly: Epidemiology, Pathogenesis, and Management." Endocr Rev **25**(1): 102-152.

Fleseriu, M. (2014). "Advances in the pharmacotherapy of patients with acromegaly." Discovery medicine **17**(96): 329-338.

Giustina, A., P. Chanson, et al. (2014). "Expert consensus document: A consensus on the medical treatment of acromegaly." Nature reviews. Endocrinology **10**(4): 243-248.

Holdaway, I. M. and C. Rajasoorya (1999). "Epidemiology of acromegaly." Pituitary **2**(1): 29-41.

Katznelson, L., J. L. Atkinson, et al. (2011). "American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Acromegaly--2011 update: executive summary." Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **17**(4): 636-646.

Lancranjan, I. and A. B. Atkinson (1999). "Results of a European multicentre study with Sandostatin LAR in acromegalic patients. Sandostatin LAR Group." Pituitary **1**(2): 105-114.

Lorcy, Y., S. Dejager, et al. (2000). "Time course of GH and IGF-1 levels following withdrawal of long-acting octreotide in acromegaly." Pituitary **3**(3): 193-197.

Melmed, S. (2009). "Acromegaly pathogenesis and treatment." J Clin Invest **119**(11): 3189-3202.

Melmed, S., A. Colao, et al. (2009). "Guidelines for acromegaly management: an update." J Clin Endocrinol Metab **94**(5): 1509-1517.

Melmed, S., D. L. Kleinberg, et al. (2014). "Acromegaly: assessing the disorder and navigating therapeutic options for treatment." Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **20 Suppl 1**: 7-17; quiz 18-20.

Milani, D., J. D. Carmichael, et al. (2004). "Variability and reliability of single serum IGF-I

measurements: impact on determining predictability of risk ratios in disease development." The Journal of clinical endocrinology and metabolism **89**(5): 2271-2274.

Novartis (2012). Sandostatin (octreotide acetate) for Injection – US Prescribing Information.

Petersenn, S., A. J. Farrall, et al. (2014). "Long-term efficacy and safety of subcutaneous pasireotide in acromegaly: results from an open-ended, multicenter, Phase II extension study." Pituitary **17**(2): 132-140.

Petersenn, S., J. Schopohl, et al. (2010). "Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial." The Journal of clinical endocrinology and metabolism **95**(6): 2781-2789.

Ramirez, C., G. Vargas, et al. (2012). "Discontinuation of octreotide LAR after long term, successful treatment of patients with acromegaly: is it worth trying?" European journal of endocrinology / European Federation of Endocrine Societies **166**(1): 21-26.

Ronchi, C. L., E. Rizzo, et al. (2008). "Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal." European journal of endocrinology / European Federation of Endocrine Societies **158**(1): 19-25.

Stewart, P. M., S. E. Stewart, et al. (1999). "Clinical and biochemical response following withdrawal of a long-acting, depot injection form of octreotide (Sandostatin-LAR)." Clinical endocrinology **50**(3): 295-299.

Trainer, P. J., W. M. Drake, et al. (2000). "Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant." The New England journal of medicine **342**(16): 1171-1177.

US Department of Health and Human Services Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (draft guidance) (December 2012)

Vilar, L., M. Fleseriu, et al. (2014). "Can we predict long-term remission after somatostatin analog withdrawal in patients with acromegaly? Results from a multicenter prospective trial." Endocrine **46**(3): 577-584.

13 APPENDICES

Appendix A Schedule of Activities

Assessment	Screening		Double-Blind Placebo-Controlled (DPC) Period[1]													Open-label Extension (OLE) Period[2]		End of Study Treatment (EOT)[3]	Follow-up[4]	
	S1	S2[5]		Week												Week			Weeks after last dose	
Study Week/Month	≤ -8 weeks		Baseline[6]	1 ☎	2 ☎	4	8	12	16	20	24	28	32	34	36	OLE 2 ☎			4	12 ☎
Visit Window (days)	± 3 days		± 3 days			± 5 days														
Signed informed consent	X														X[13]					
Inclusion/exclusion criteria	X		X												X[13]					
Magnetic Resonance Imaging (MRI) [7]	X																			
Medical & acromegaly history/demographics and height	X																			
Weight	X		X			X	X	X	X	X	X	X	X	X	X		X	X	X	
Hematology[8] and chemistry[9]	X		X			X	X	X	X	X	X	X	X	X	X		X	X		
Fasting Plasma Glucose (FPG)[10]	X																			
Hemoglobin A_{1c} (HbA_{1c})	X														X		Every 6 M	X		
Thyroid-stimulating hormone (TSH), free T4			X												X		X	X		
Lipid profile[11]			X												X		X	X		
Urinalysis	X																			
Serum pregnancy for women with childbearing potential	X		X[12]												X		Every 6 M	X		

[1] Patients who discontinue study medication early during DPC, will be asked to continue to be followed-up per protocol through week 36; patients meeting the pre-defined withdrawal criteria will be rescued with injectable SRL treatment used prior to Screening).

[2] OLE scheduled to occur every 4 weeks (±5 days) for the initial 24 weeks, at weeks 36, 46 and 48 and every 12 weeks (±10 days) thereafter; the first OLE visit is also DPC Week 36.

[3] EOT is applicable for patients who discontinue study medication during DPC and/or OLE. Every effort will be made to follow-up patients in DPC per protocol through week 36.

[4] Relevant only for patients who complete the DPC period on study medication and are ineligible or do not opt to enter the OLE period or patients who early discontinue OLE period on study medications

[5] Screening 2 should be scheduled within 2 weeks prior to randomization to determine baseline IGF-1 levels for efficacy analyses.

[6] Baseline visit (first dose), should be scheduled within ± 3 days of the intended routine dosing interval following the last injection

[7] MRI available within 12 months prior to screening is acceptable. If remnants are not visible or less than 5 mm at last MRI, MRI done within 2 years is also acceptable. A CT can be done in place of an MRI if the MRI is contraindicated.

[8] Hematology: RBC, Hb, Htc, platelets, WBC and differential count

[9] Chemistry: glucose, total bilirubin (in case total bilirubin is elevated, perform direct and indirect bilirubin), albumin, Na, K, Ca, creatinine, BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; in case of abnormal liver function additional safety assessment may be done. Blood sampling will be done under overnight fasting conditions at all visits except week 36/EOT and at months 6, 12, every 12 months and the last visit of the OLE Period where only a four-hour fast is required.

[10] For diabetic patients only must be collected under fasting conditions.

[11] Lipid profile = total cholesterol, triglycerides, HDL and LDL

[12] Serum pregnancy is only applicable for women patients with positive urine pregnancy test at Baseline.

Assessment	Screening		Double-Blind Placebo-Controlled (DPC) Period[1]												Open-label Extension (OLE) Period[2]		End of Study Treatment (EOT)[3]	Follow-up[4]	
	S1	S2[5]		Week											Week			Weeks after last dose	
Study Week/Month	≤ -8 weeks		Baseline[6]	1 ☎	2 ☎	4	8	12	16	20	24	28	32	34	36	OLE 2 ☎			4	12 ☎
Urine pregnancy test for women with childbearing potential			X																
Growth Hormone (GH, mean integrated)[13]	X		X												X		Months 6, 12, every 12 M & last visit	X	X	
Insulin-like growth factor 1 (IGF-1)	X	X	X			X	X	X	X	X	X	X	X	X	X		Months 3, 6 and every 6 M and Week 46	X	X	
Assess IGF-1 levels and schedule an unscheduled visit if IGF-1 ≥1.3×ULN			X			X	X	X	X	X	X	X	X	X	X		X			
Assess Loss of Biochemical Control / Pre-defined withdrawal criteria[14]						X	X	X	X	X	X	X	X	X	X					
Abdominal (gall bladder) ultrasound	X														X		Every 6 M[15]	X	X	
Complete physical examination	X														X					
Acromegaly and treatment directed physical examination	X		X			X	X	X	X	X	X	X	X	X	X			X		
Vital signs	X		X			X	X	X	X	X	X	X	X	X	X			X		
12-lead electrocardiogram (ECG)	X														X			X	X	
Concomitant medication	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse events (AE) and AEs of special interest	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization (call IVRS/IWRS)			X																	
Dispense study medication (call IVRS/IWRS)			X			X	X	X	X	X	X	X	X		X[16]		X			
Study medication administration at the site			X												X		Months 6, 12, every 12 M & last visit			

[13] GH: Five samples collected every 30 ± 5 minutes over two hours. At the first screening visit from time 0-2 hours (prior to SOC SRL administration, if planned), at baseline from time 0-2 hours (prior to study medication), at Week 36/EOT and at all other visits in OLE, 2-4 hours after study medication administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and throughout the 2 hours of GH sampling)

[14] Loss of biochemical control is defined IGF-1 increased by at least 30% compared to Baseline (average of 2 assessments within 2 weeks prior to randomization) to a level > 1× ULN, for 2 consecutive visits, at least 1 week apart after the patient is treated for at least 2 weeks with 4 capsules per day; pre-defined withdrawal criteria is defined as IGF-1 ≥1.3×ULN AND exacerbation of acromegaly clinical signs or symptoms) for 2 consecutive visits, while the patient is treated for at least two weeks with 4 capsules per day of study medication

[15] Abdominal (gall bladder) ultrasound will be done every 6 months to week 48 and annually thereafter or as clinically indicated.

[16] For patients entering the OLE period

Assessment	**Screening**		**Double-Blind Placebo-Controlled (DPC) Period[1]**												**Open-label Extension (OLE) Period[2]**		**End of Study Treatment (EOT)[3]**	**Follow-up[4]**	
	S1	S2[5]		**Week**											**Week**			**Weeks after last dose**	
Study Week/Month	≤ -8 weeks		Baseline[6]	1 ☎	2 ☎	4	8	12	16	20	24	28	32	34	36	OLE 2 ☎			4	12 ☎
Dose titration[17]				X	X	X	X	X	X	X	X					X	X			
Study administration instructions			X	X	X	X	X	X	X	X	X	X	X		X[12]	X	X			
Compliance assessment			X			X	X	X	X	X	X	X	X		X		X			
Study medication accountability						X	X	X	X	X	X	X	X		X		X	X		
DPC Period Completion form															X					

[17] Assess the need to escalate dose cased on pre-defined criteria of biochemical response and symptomatic control

Appendix B Acromegaly and Treatment Directed Physical Examination

ACROMEGALY and TREATMENT DIRECTED PHYSICAL EXAMINATION					
Assess physical signs related to acromegaly, and acromegaly treatment. Report any new or worsening Physical Examination findings on the Adverse Events form.					
Assessment	Not Done	Normal	Abnormal	Clinically Significant	Specify Abnormalities & Clinically Significant Findings
Soft tissue welling	☐	☐	☐	☐	
Facial Features	☐	☐	☐	☐	
Carpal Tunnel Syndrome (signs and symptoms)	☐	☐	☐	☐	
Musculoskeletal (joints' swelling, Arthralgia on palpitation/movement)	☐	☐	☐	☐	
Lungs	☐	☐	☐	☐	
Abdomen	☐	☐	☐	☐	
Back and Extremities	☐	☐	☐	☐	
General Neurological System	☐	☐	☐	☐	
Skin (including sweating, injection site reactions)	☐	☐	☐	☐	
Cardiovascular	☐	☐	☐	☐	
Other, specify:	☐	☐	☐	☐	
Exams were performed by: _____ _____ Name Date					

Appendix C Declaration of Helsinki (2013)

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased

likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed

consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.