CHIASMA

Investigational Product **Octreotide Capsule**
Phase **3**

MPOWERED

Maintenance of Acromegaly Patients with Octreotide Capsules Compared With Injections – Evaluation of REsponse Durability

Protocol No. **OOC-ACM-302**
Version and Date [redacted] **Protocol Version 6.0 January 16, 2020**

CLINICAL STUDY PROTOCOL

A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE CONTROLLED, MULTICENTER STUDY TO EVALUATE MAINTENANCE OF RESPONSE, SAFETY AND PATIENT REPORTED OUTCOMES IN ACROMEGALY PATIENTS TREATED WITH OCTREOTIDE CAPSULES, AND IN PATIENTS TREATED WITH STANDARD OF CARE PARENTERAL SOMATOSTATIN RECEPTOR LIGANDS WHO PREVIOUSLY TOLERATED AND DEMONSTRATED A BIOCHEMICAL CONTROL ON BOTH TREATMENTS

Sponsor: Chiasma, Inc.

[redacted]

Study Chairman: [redacted]

[redacted]

[redacted]

Protocol Number: OOC-ACM-302

Study Phase: 3

[redacted]

Version: 6.0

Protocol Date: January 16, 2020

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Protocol Signature Page

Protocol Title	A phase 3, randomized, open-label, active controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes in acromegaly patients treated with octreotide capsules, and in patients treated with standard of care parenteral somatostatin receptor ligands, who previously tolerated and demonstrated a biochemical control on both treatments
Protocol Identification	OOC-ACM-302
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 Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

[redacted]

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

[redacted]

PROTOCOL SYNOPSIS

Study Title	A phase 3, randomized, open-label, active controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes in acromegaly patients treated with octreotide capsules, and in patients treated with standard of care parenteral somatostatin receptor ligands who previously tolerated and demonstrated a biochemical control on both treatments.
Protocol No.	OOC-ACM-302
Clinical Sites	Global, Multicenter Study
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. Octreotide capsules will be administered to all eligible patients during the Run-in phase, and will be up titrated (from 40 mg to 60 mg and 80 mg/day), based on clinical and biochemical response. Patients who are biochemically controlled at the end of the Run-in phase will be randomized to either continue octreotide capsules treatment or revert to their standard of care (SOC) injectable somatostatin receptor ligand (SRL), during the randomized controlled treatment (RCT) phase. Patients entering the Study Extension phase will continue octreotide capsules for 5 years or until product marketing or termination of study by Sponsor (the earliest of which). Following the completion of the 5-year Extension phase, the Sponsor will either extend the Extension phase (via protocol amendments, for an additional year or until product marketing or study termination, the earliest of which), or consider compassionate use (if requested by the principal Investigator under compassionate use protocol); subsequently a compassionate use protocol will be prepared and submitted for regulatory approval. ***Injectable Somatostatin Receptor Ligands -- SRLs (Octreotide LAR or Lanreotide)*** Patients randomized to the active control arm in the RCT phase, will receive their SOC injectable SRL (octreotide LAR or lanreotide), according to the individual patient use prior to enrollment in the study. ***Cabergoline (for Combination phase sub-study in selected sites)*** Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D2 receptors. It is commonly used for the treatment of acromegaly as monotherapy or in combination with other agents. Patients who fail to respond to octreotide capsules 80 mg for at least two weeks therapy during the course of the Run-in, or patients ineligible to enter the RCT on

	octreotide capsules 80 mg, due to inadequate biochemical control (Insulin-like growth factor 1(IGF-1) ≥ 1.3 times upper limit of normal (ULN) to IGF-1 <2 × ULN, or IGF-1<1.3 × ULN and GH ≥ 2.5 ng/mL), will enter a Combination phase sub-study) and receive co-administration of octreotide capsules 80 mg with cabergoline [redacted]. If the patient is biochemically controlled (defined as IGF-1 < 1.3 × ULN) at the week 4 assessment (or later), based on clinical judgement, the cabergoline dose can be maintained (i.e. no further dose escalation is required). Those with IGF-1 ≥2 × ULN will revert to their injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician. During the Study Extension phase, eligible patients will continue to receive cabergoline and octreotide capsules.
Target 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 4 months and are biochemically controlled (IGF-1 < 1.3 × ULN and mean integrated growth hormone (GH) <2.5 ng/mL) as evident at screening.
Study Objectives	Core study objectives • To assess maintenance of biochemical control of octreotide capsules compared to parenteral SRLs in patients with acromegaly, who previously demonstrated biochemical control on both treatments. • To assess maintenance of biochemical control of octreotide capsules in patients with acromegaly, who previously tolerated and demonstrated biochemical control on SRL injections [redacted]. • To assess symptomatic response to octreotide capsules compared to parenteral SRLs. • To assess patient reported outcome (PRO) in patients treated with octreotide capsules compared to parenteral SRLs. • To evaluate the safety profile of octreotide capsules compared to parenteral SRLs. [redacted] Extension phase objective • To assess the long-term safety, efficacy and patient reported outcomes of octreotide capsules in acromegaly patients Combination phase sub-study (in selected sites) objective • To assess the efficacy of octreotide capsules co-administered with cabergoline in the treatment of acromegaly patients with modestly elevated IGF-1 levels (defined as 1.3 ≤ IGF-1 < 2 × ULN, or IGF-1<1.3 × ULN and GH ≥ 2.5 ng/mL)
Study design	This will be a phase 3, randomized, open-label, active controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes (PROs) in acromegaly patients treated with octreotide capsules and in patients treated with SOC parenteral SRLs, who previously tolerated and demonstrated biochemical control on both treatments. The Core study will consist of 3 phases: a Screening phase, Run-in phase and an RCT phase.

	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 up to 4 weeks Screening phase, eligible patients who are biochemically controlled (defined as IGF-1 < 1.3 × ULN and mean integrated GH <2.5 ng/mL), on parenteral SRLs will be switched to octreotide capsules for a 26-week Run-in phase. During this phase the effective dose for each patient will be determined through dose titration (see Run-in phase below). Patients whose acromegaly has been controlled biochemically on octreotide capsules at the end of the Run-in Phase will enter a 36-week open-label RCT phase where they will be randomized to continue on octreotide capsules or switch back to their injectable SRL treatment (as received prior to Screening). Following the completion of the Core study (Screening, Run-in and RCT phases), eligible patients will be offered to enter the Study Extension phase and receive octreotide capsules for 5 years or until product marketing or study termination (the earliest of which). Beyond 5 years Extension phase, the Sponsor will either extend the Extension phase (via protocol amendment for an additional year or until product marketing or study termination) or consider compassionate (if requested by the principal Investigator under compassionate use protocol). [redacted] In selected sites where the Combination phase sub-study is conducted, patients who fail to respond to octreotide capsules 80 mg for at least 2 weeks therapy during the course of the Run-in phase, or patients ineligible to enter the RCT phase on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 ≥ 1.3 × ULN to IGF-1 <2 × ULN, or IGF-1<1.3 × ULN and GH ≥ 2.5 ng/mL), will be eligible to enter the Combination phase sub-study. These patients will receive co-administration of octreotide capsules (80 mg/day) with cabergoline [redacted] for a total of 36 weeks. At the end of the Combination phase sub-study, eligible patients will be offered to enter the Study Extension phase and continue the same combined treatment regimen. Patients discontinuing early from the Combination phase sub-study or all other patients not meeting the criteria for randomization into the RCT phase or Combination phase sub-study will revert to their prior injectable SRL treatment (prior to

	Screening) or other treatment as determined by their physician, and be followed for 12 weeks after last dose. Patients who early terminate the Run-in phase for any reason in sites who do not participate in the Combination phase sub-study will revert back to their injectable SRL treatment (prior to Screening) or other treatment as determined by their physician and will be followed up for 12 weeks after last dose of study medication. *Database lock for the core study and the Combination phase sub-study will occur at the completion of both the RCT phase/End of Treatment (EOT) (last patient completes week 62) and the Combination phase sub-study, (last patient completes week 36), and will not include the Follow-up phase, [redacted] or Study Extension treatment phase. Interim analyses of the Extension Phase will be conducted periodically, after completion of the RCT phase. Data collected post RCT, phase or Combination phase sub-study will be included in the Study Extension database. Details of these analyses will be outlined in the statistical analysis plan (SAP).*
Study Phases and Procedures	**Screening Phase (≤ 4 weeks)** Following informed consent, adult patients will be screened for study eligibility by assessment of inclusion and exclusion criteria. Screening procedures will be conducted as specified in the Schedule of Activities. Eligible patients will have a confirmed diagnosis of acromegaly and have been treated with SRL injections (octreotide or lanreotide monotherapy) for at least 6 months and have been on a stable dose for the last four months. Eligible patients should be biochemically controlled (IGF-1 < 1.3 × ULN and mean integrated GH <2.5 ng/mL), as evident at any time during the Screening phase. If any of the screening samples do not qualify the patient for the study, repeat screening samples (re-assessments) may be taken once during the Screening phase. Eligibility should be determined based on the last assessment. [redacted] **Run-in Phase** The duration of the Run-in phase for each patient will be 26 weeks. The octreotide capsules dose should be escalated per Investigator's discretion, in the case of significantly increased IGF-1 levels compared to Baseline, worsening of acromegaly symptoms or both. The Sponsor recommends the following guiding rules for dose escalation:

[redacted]

- Significantly increased IGF-1 levels compared to Baseline [redacted]
- Increase in the number of symptoms or symptoms severity compared to Baseline or prior visi[redacted] clinically meaningful at the [redacted]

The dose escalation will be done in a stepwise manner from 40 mg/day (20 mg twice daily; BID) to 60 mg/day (40 mg in the morning and 20 mg in the evening/night) to 80 mg/day (40 mg BID).

During the Run-in phase, patients will return to the clinic for a site visit every four weeks (± 3 days) through week 24 and will attend an end of the Run-in phase visit at week 26 (visit window -3 days to 10 days). 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. IGF-1 will be assessed at every visit, GH will be assessed at Baseline, week 24 and end of the Run-in period (week 26)/End of treatment. Acromegaly symptoms will be collected every four weeks. Other procedures will be conducted as specified in the Schedule of Activities for the Run-in phase.

Eligibility to continue into the RCT phase will be determined at week 26, based on the biochemical results at week 24. Patients with IGF-1 <1.3 × ULN and mean integrated GH <2.5 ng/mL will be allowed to continue into the RCT phase.

Patients should be early terminated due to failure to respond to octreotide capsules in the Run-in phase if the following criterion is met:

- Patients have IGF-1 levels ≥ 1.3 × ULN and increased by at least 30% from Baseline and exacerbation of clinical symptoms (as determined by the Investigator) for 2 consecutive visits (at least 2 weeks apart) starting on week 12 (including week 12).

Patients who discontinue treatment early during the Run-in phase or who are ineligible or do not wish to continue into the RCT phase will revert back to their injectable SRL treatment (prior to Screening, non-investigational medicinal product; non-IMP) or other treatment as determined by their physician; these patients will enter the Follow-up phase and will be followed for 12 weeks after last dose of study medication.

Patients treated with octreotide capsules 80 mg for at least 2 weeks who fail to respond to octreotide capsules during the course of the Run-in phase, yet with modestly elevated IGF-1 ≥ 1.3 × ULN to IGF-1 < 2 × ULN at week 24 (as evident on week 26) will be eligible to enter a 36-week Combination phase sub-study (in selected sites) and receive co-administration of octreotide capsules 80 mg with cabergoline [redacted] – see below for description of Combination phase sub-study.

Patients who are ineligible or do not wish to enter the Combination sub-study will revert back to their injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will be followed up for 12 weeks after last dose of study medication.

Randomized Controlled Treatment Phase (RCT)

Patients meeting the eligibility RCT criteria at week 26 (based on IGF-1 and GH levels at week 24), with IGF-1 <1.3 × ULN and mean integrated GH <2.5 ng/mL,

	will be randomized at week 26 in a 3:2 ratio to one of two treatment arms: continue treatment with octreotide capsules (treatment arm 1) or switch to their prior parenteral SRL treatment (treatment arm 2) for an additional 36 weeks (starting on week 26 through week 62). The study will utilize centralized stratified randomization based on the following variables on week 24 of the Run-in phase: • IGF-1 ≤1 × ULN vs. IGF-1 > 1 × ULN to <1.3 × ULN at week 24 • Octreotide capsules treatment dose at week 24 (40 mg vs. 60 mg or 80 mg) Clinic visits during the RCT phase will be scheduled to occur every four weeks (week 26[2], 30, 34, 38, 42, 46, 50, 54, 58 and 62). Patients randomized to receive parenteral SRLs will receive their injections at the site at the same frequency and dose as received prior to screening. Patients, who received parenteral SRLs every four (or five) weeks, will receive their injections every four weeks at weeks 26, 30, 34, 38, 42, 46, 50, 54 and 58. Patients who received parenteral SRLs at an interval of once every eight weeks will be assessed every four weeks yet will receive their injection every eight weeks (weeks 26, 34,42, 50 and 58). Patients who received their parenteral SRLs injections every six (or seven) weeks will attend visit week 32 instead of visits weeks 30 and 34, visit week 44 instead of visit weeks 42 and 46 and visit week 56 instead of weeks 54 and 58. These patients will receive their injection on weeks 26, 32, 38, 44, 50 and 56. Visit window will be ±3 days. IGF-1 will be assessed on all scheduled visits during the RCT phase, GH will be assessed at week 26 (End of Run-in/beginning of RCT) and week 62/End of treatment. Acromegaly symptoms will be collected at each visit. Other procedures will be conducted as specified in the Schedule of Activities. Unscheduled visits will be allowed throughout the study for safety or management of active disease, per the Investigator discretion, throughout the RCT phase. All efforts should be made to maintain patients on their randomized treatment throughout the RCT phase up to completion of the core study. Eligible patients who have completed the RCT phase will be offered to continue into a voluntary Study Extension phase and receive octreotide capsules. Patients completing the RCT phase who are ineligible to enter the Study Extension phase (see eligibility criteria), due to inadequate control, patients who do not opt to enter the Study Extension phase or patients who discontinue treatment early during RCT, will revert back to their prior injectable SRL (prior to Screening, non-IMP), or other treatment as determined by their physician; these patients will undergo three Follow-up visits within 12 weeks (+4, +8 and +12 weeks) after their last study medication dose. **Combination phase sub-study (in selected sites)** Patients who fail to respond to octreotide capsules 80 mg for at least two weeks therapy during the course of the Run-in phase, or patients ineligible to enter the RCT on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 ≥ 1.3 × ULN to IGF-1 <2 × ULN, or IGF-1<1.3 × ULN and GH ≥ 2.5 ng/mL, will enter the Combination phase sub-study and receive co-administration of octreotide capsules 80 mg with cabergoline [redacted] for 36 weeks.

[2] Visit window for week 26 will be -3 to +10 days

Clinic visits during the Combination phase sub-study will be scheduled to occur every four weeks (±3 days). Study procedures will be conducted as specified in the Schedule of Activities. At the end of the Combination phase sub-study eligible patients will be offered to enter the Study Extension phase on the same combination treatment regimen.

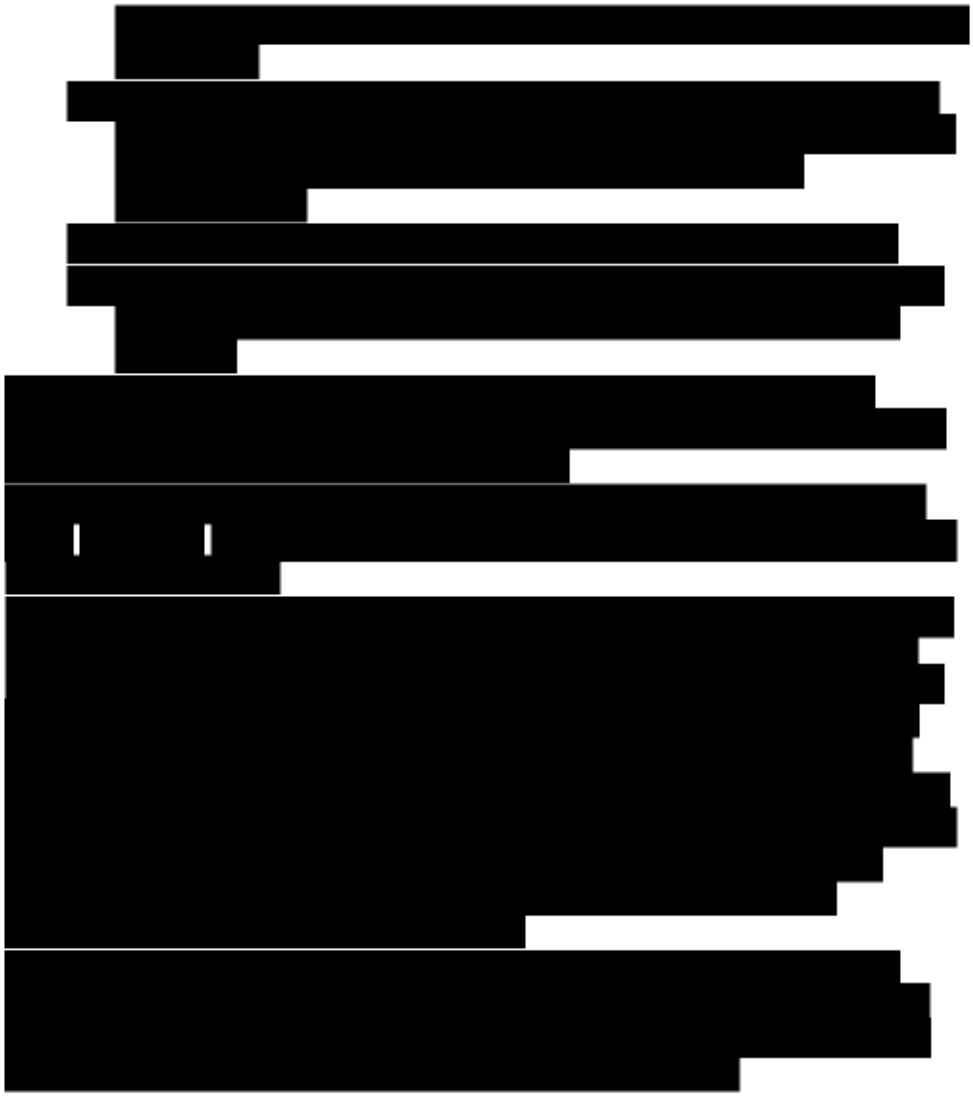
Patients who complete the Combination phase sub-study and are ineligible to enter the Study Extension phase (see eligibility criteria) or who do not opt to enter the Study Extension phase, or patients who early discontinue treatment during the Combination phase sub-study will revert to their prior SOC injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician, and will undergo three Follow-up visits within 12 weeks (+4, +8 and +12 weeks)after their last study medication dose.

Patients meeting one of the two criteria below should be terminated early from the Combination phase sub-study due to failing to respond to treatment:

- IGF-1 levels > 1.3 × ULN for at least two consecutive visits on the maximal cabergoline dose and no decrease of at least 10% compared to entry into the Combination phase

  Or

- Worsening clinical signs and symptoms based on the Investigator's discretion for at least two consecutive visits on the maximal cabergoline dose.



Study Extension phase

Eligible patients, that is those completing the RCT phase, adequately controlled (see inclusion criteria to the Study Extension phase), or significantly benefiting from octreotide capsules treatment (as determined by the study Investigator, and agreed by the study medical monitor), may enter the Study Extension treatment phase. The Study Extension treatment phase will continue for 5 years or until the date when the study medication becomes commercially available in the applicable region or country or when the Sponsor decides to terminate the study (the earliest of which). Following the completion of the 5-year Extension phase, the Sponsor will either extend the Extension phase (via protocol amendments, for an additional one year or until product marketing or study termination) or consider compassionate use (if requested by the principal Investigator under compassionate use protocol); subsequently a compassionate use protocol will be prepared and submitted for regulatory approval.

During the Study Extension phase, eligible patients, previously treated with octreotide capsules during the RCT phase, will continue to receive their prior treatment regimen, while patient treated with long acting SRLs injections will switch to the octreotide capsules dose they were controlled on at the end of the Run-in phase.

	Patients adequately controlled on combination of octreotide capsules and cabergoline at the end of the 36 weeks Combination phase sub-study (in selected sites; see eligibility criteria) or patients significantly benefiting from the combination treatment (as determined by the study Investigator, and agreed by the study medical monitor), will also be offered to continue into the Study Extension phase on octreotide capsules and cabergoline. Patients who are not adequately controlled or significantly benefiting from octreotide capsules, at the end of the RCT phase will not be allowed to continue into the Study Extension phase and will revert to their parenteral SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will undergo three Follow-up visits within 12 weeks (+4, +8 and +12 weeks) after their last dose of study medication. Patients completing the Run-in period adequately controlled, yet completed the RCT phase on parenteral SRLs as inadequately controlled, would be allowed to enter the Study Extension phase. During the first year of the Study Extension phase, clinic visits will be scheduled to occur every 12 weeks (±10 days). Thereafter, in-clinic visits will occur every 24 weeks (±10 days), with dispensing visits every 12 weeks (±10 days). Patients from RCT phase who switch to octreotide capsules will be contacted by phone one week after initiating octreotide capsules. IGF-1 will be assessed at Month 3, Month 6 and then every six months. GH will be assessed at the beginning and end of the Study Extension phase and yearly. Acromegaly symptoms will be assessed on every scheduled in-clinic visit and patient reported outcomes will be collected at Month 3, Month 6, Month 12 and then yearly. Other procedures will be conducted as specified in the Schedule of Activities. Patients who discontinue treatment during the Study Extension phase will revert to their parenteral SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will undergo three Follow-up visits within 12 weeks (+4, +8 and +12 weeks) after their last dose of study medication. **Follow-Up Phase** Any patient early discontinuing treatment during the study (Run-in phase, RCT phase, Combination sub-study or Extension phase), or patient ineligible to enter RCT phase or Combination phase sub-study, patients ineligible or not opting into the study Extension phase, will undergo three follow-up visits over 12 weeks (+4, +8 and +12 weeks) after their last study medication dose for safety and efficacy assessments. Visit window will be ±3 days. [redacted] Procedures will be conducted as specified in the Schedule of Activities. All discontinued patients will revert to their parenteral injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician.

Study Duration and Study Phases

Core study duration: 66 weeks, composed of:

Screening phase	up to four weeks
Run-in phase (octreotide capsules)	26 weeks
Randomized Controlled Treatment (RCT) phase (octreotide capsules vs. Parenteral SRLs)	36 weeks

Combination phase sub-study (in selected sites): (octreotide capsules + cabergoline, for patients failing to respond to octreotide capsules) 36 weeks (in parallel to the RCT duration).

[redacted]

Study Extension phase: 5 years or until study medication is commercially available or Sponsor terminates the study (the earliest of which). The Extension phase may be extended (protocol amendment) or treatment may be provided under a separate Compassionate Use protocol following a specific request by the Principal Investigator.

Follow up Phase: All discontinued patients (during any study phase) or patients ineligible into the RCT phase or the Combination phase sub-study [redacted] and the Extension phase will be followed-up for 12 weeks.

Inclusion Criteria

All inclusion criteria should be met to be eligible to the study.

1. Adult subjects, aged 18 to 75 years old, inclusive, at the Screening visit.
2. Patients with acromegaly, defined as documented evidence of GH-secreting pituitary tumor that is abnormally responsive to an oral glucose tolerance test or abnormal IGF-1 levels [redacted], who are currently receiving parenteral SRLs (octreotide or lanreotide but not pasireotide) for at least 6 months with a stable dose for at least the last four months.
3. Documented biochemical control of their acromegaly on the current dose of SRL (IGF-1 < 1.3 × ULN and mean integrated GH < 2.5 ng/mL over two hours) based on Screening assessment.
4. Patients able and willing to comply with the requirements of the protocol at the time of Screening.
5. 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[3] 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.
6. Patients able to understand and sign written informed consent to participate in the study.

[3] 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 less frequently than once every eight weeks (dosing interval > 8 weeks). 2. Patients who previously participated in CH-ACM-01. 3. Symptomatic cholelithiasis. 4. Received pituitary radiotherapy within five years prior to screening (including total body, head and neck or stereotactic radiotherapy). 5. Undergone pituitary surgery within six months prior to screening or have elected surgery planned within the course of the core study. 6. High-risk pattern[4] 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 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.

[4] 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 course of the study period based on tumor growth on serial MRIs
- Metastatic pituitary carcinoma or prior chemotherapy for pituitary carcinoma

	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 12 weeks before the screening visit. 22. Treatment with dopamine agonists within 6 weeks before the screening visit. 23. Treatment with pasireotide within 12 weeks before the screening visit.
Eligibility criteria to RCT Phase	1. Patients who completed the full duration of the Run-in phase and their acromegaly is biochemically controlled (based on IGF-1 and GH levels at week 24), with IGF-1 <1.3 × ULN and mean integrated GH<2.5 ng/mL. 2. Investigator assessment that the patient's acromegaly is adequately controlled (acromegaly related clinical symptoms are maintained with no meaningful exacerbation compared to Baseline).
Eligibility Criteria to Combination phase sub-study (in selected sites):	Patients complying with all of the following criteria: 1. Patients who fail to respond to octreotide capsules 80 mg for at least two weeks during the course of the Run-in phase or patients ineligible to enter the RCT phase on octreotide capsules 80 mg due to in-adequate control of acromegaly at week 24 (as evident on week 26) with (a) IGF-1 levels between 1.3 × ULN to 2 × ULN or (b) IGF-1<1.3 × ULN and GH ≥2.5 ng/mL 2. Patient is willing and able to comply with the protocol requirements for the duration of the Combination phase sub-study. **Exclusion criteria for Combination phase sub-study (in selected sites):** A patient cannot enter the Combination phase sub-study if they meet one of the following criteria: 1. Patient is currently having study medication withheld for a study medication-related AE. 2. Patient has a clinically significant or unstable medical or surgical condition detected or worsens during the study, which would preclude safe participation and completion of the study. 3. Patient has known hypersensitivity to ergot derivatives. 4. Patient has uncontrolled hypertension (≥ 160 mmHg systolic OR ≥ 100 mmHg diastolic blood pressure). 5. Patient has history of clinically significant cardiac valve disorder or study echocardiogram (ECHO) valve disorder finding during the Run-in phase or at entry into the Combination phase sub-study (valve leaflet thickening, valve restriction, or mixed valve restriction-stenosis). 6. Patient has history of pulmonary, pericardial, or retroperitoneal fibrotic disorders. 7. Patient receives phenothiazines, butyrophenones, thioxanthenes, or metoclopramide.

[redacted]	[redacted]
Eligibility Criteria to Study Extension Phase	1. Patient completing the full duration of either one of the following treatment phases, per protocol: a. RCT phase (in any treatment arm) b. Combination phase sub-study 2. Most recently available IGF-1 level (central laboratory), within not more than six weeks (+5 days) prior to Study Extension phase eligibility assessment, is < 1.3 × ULN, and the Investigators' assessment that the patient's acromegaly is adequately controlled (on a case-by-case basis, patients who are benefiting from octreotide capsules treatment, per the Investigator assessment, could also continue into the Study Extension phase following approval of the Sponsor. This includes but not limited to patients who completed the Run-in phase adequately controlled, yet completed the RCT phase on parenteral SRLs as non-adequately controlled). 3. Patient not currently having study medication withheld for a study medication-related AE. 4. Patient did not have a clinically significant or unstable medical or surgical condition detected or worsen during the study, which would preclude safe participation and completion of the Study Extension phase (including, if relevant in selected sites participating in the Combination phase sub-study, conditions contraindicated for treatment with cabergoline). 5. Octreotide capsules are not commercially available in the applicable region or country. 6. Patient is willing and able to comply with the protocol requirements for the duration of the Study Extension phase. 7. Patient preference to continue treatment with octreotide capsules and able to understand and sign an additional written informed consent prior to entering the Study Extension phase.
Outcome Measures / Endpoints	**Efficacy Endpoints** **Primary Endpoint** [redacted] • The proportion of patients who are biochemically controlled throughout the RCT phase. A patient will be considered biochemically controlled if their IGF-1 Time Weighted Average (TWA) during the RCT phase is < 1.3 × ULN. **Additional** [redacted] **Endpoints** [redacted]

- RCT phase - Proportion of patients on octreotide capsules who are biochemically controlled at the end of the RCT phase, defined as IGF-1 <1.3 × ULN (based on the average of week 62 and week 58).

Secondary Endpoints

- The proportion of patients who are biochemically controlled throughout the RCT phase. A patient will be considered biochemically controlled if their IGF-1 TWA during the RCT phase is < 1.3 × ULN [redacted].
- [redacted]
- Proportion of patients who maintain or reduce the overall number of active acromegaly symptoms, at the end of the RCT phase (week 62/EOT), compared to week 26 (start of RCT).
- Proportion of patients who maintain or improve their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score), compared to week 26 (start of RCT)
- Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ) at the end of the RCT phase.
- Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country), who enter the Study Extension phase, overall and by treatment group.
- Change from the start of the randomized phase of the study (week 26) through the end of the RCT (week 62) for IGF-1.
- Change from the start of the randomized phase of the study (week 26) to end of the RCT (week 62) in mean integrated GH.

Exploratory Endpoints

- [redacted]
- Proportion of patients with TWA IGF-1 ≤1 × ULN during the RCT Phase in patients who started the RCT with IGF-1≤1 × ULN.
- [redacted]

	[redacted] • Proportion of patients with a reduction in the overall number of active acromegaly symptoms, at the end of the Run-in phase compared to Baseline. • Proportion of patients with improved AIS score at the end of the Run-in phase compared to Baseline. • Health economic outcomes (EQ-5D, WPAI). [redacted] **Study Extension Primary Endpoint** • The proportion of patients who are biochemically controlled at the end of each year of the Study Extension (e.g. first Extension year = Study Extension week 48, second Extension year = Study Extension week 96), out of those who entered this year as responders. A patient will be considered biochemically controlled if their end of the year IGF-1 is < 1.3 × ULN. Additional Extension endpoints will be detailed in the Study Extension statistical analysis plan. **Safety** • Frequency and severity of adverse events (AEs) and serious adverse events (SAEs). • Clinically significant laboratory abnormalities.
Planned Sample Size	Approximately 150 patients will be enrolled into the Run-in phase of the study. The total number of patients will be adjusted to ensure a minimum of 80 patients will enter the RCT phase, with approximately 48 patients assigned to octreotide capsule arm and 32 patients assigned to SRL injection arm. [redacted]

	[redacted] An assessment of NI will be made by comparing the lower bound of the two-sided 95% confidence interval (CI) for the difference in biochemical control (octreotide capsules - SRL) to a NI margin of -20%. [redacted]
Statistical Methods	**Analysis Populations** Full Analysis Set (FAS) is defined as all randomized patients to the RCT phase who receive at least one dose of study medication and have one post randomization measurement of IGF-1 and GH. This population will serve as the primary efficacy analysis population for the RCT phase of the core study. Patients will be included in the group to which they were randomized. Per-Protocol Analysis Set (PP) is defined as all patients in the FAS without a major protocol violation. Major protocol violations will include non-compliance[5] with study medication. Safety Analysis Set (SAS) is defined as all randomized patients who receive at least one dose of study medication. This population will serve as the primary safety analysis population for the RCT phase of the core study. Patients will be included in the group according to which medication they actually received. Enrolled Analysis Set (EAS) is defined as all patients who are enrolled into the Run-in phase of the core study, and receive at least one dose of study medication. This population will be used for the analysis of safety and efficacy data during the Run-in phase of the core study. Combination Analysis Set (CAS) is defined as all patients who are enrolled into Combination phase sub-study. This population will be used for the analysis of safety and efficacy data collected in the Combination arm. Extension Analysis Set (EXT-AS) is defined as all patients who are enrolled into the Study Extension phase of the study. This population will be used for the analysis of safety and efficacy data during the Study Extension phase. [redacted]

[5] Non-compliance will be defined in Study Monitoring Plan and Statistical Analysis Plan prior to database lock

Primary Efficacy Analyses

Primary efficacy analysis [redacted]:

The primary efficacy analysis will estimate the proportion of patients biochemically controlled throughout the RCT phase within each arm and the difference between arms using the FAS. A patient will be considered biochemically controlled if their TWA during the RCT phase for IGF-1 is < 1.3 x ULN. However, if a patient discontinues during the RCT phase for lack of efficacy, he/she will not be considered to be biochemically controlled, regardless of his/her TWA.

An assessment of non-inferiority will be made using an NI margin of -20%. The difference (octreotide capsules – Injectable SRLs) in response rate and two-sided 95% CI for the difference will be calculated. If the lower bound of the CI is greater than the NI margin of -20%, octreotide capsules will be declared non-inferior to injectable SRLs. The FAS will be the primary population used for this analysis, with a PP population used as a sensitivity analysis.

Additional [redacted] efficacy analysis [redacted]:

The [redacted] efficacy analysis [redacted] will be descriptive in nature. For the Run-in phase the enrolled analysis set will be the primary analysis population. For the RCT phase the FAS will be the [redacted] analysis population. The proportion of responders and associated two-sided 95% confidence intervals will be reported. If a patient discontinues, they will be considered failures for each of the endpoints. If a patient completes the study, but is missing their final assessments, their worst observation will be carried forward (WOCF) in order to determine their response.

[redacted]

Secondary Efficacy Analyses

Analysis of the secondary efficacy endpoints will be conducted without adjustment for multiplicity. Data will be summarized by treatment group using descriptive statistics and inferential analyses will be conducted to compare the two treatment groups using methods appropriate for each endpoint (details will be presented in the statistical methods section of the protocol).

Exploratory Analyses

Details of the Exploratory analyses will be presented in the statistical methods section of the protocol.

Safety Analyses

All safety endpoints will be summarized across each phase of the study using descriptive statistics. During the Run-in phase, the enrolled population will be used; during the RCT phase, the safety population will be used. The Study Extension phase will be summarized separately using the appropriate population as described above.

	At the completion of the RCT phase, data will be analyzed and reported. Patients continuing into Study Extension phase will be analyzed separately. **Sub-study Analyses for Combination phase (in selected sites)** Patients continuing into the Combination phase sub-study will be analyzed separately using the CAS population analysis.

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GLOSSARY

Subject and patient will be used interchangeably throughout this document.

Abbreviation/Term	Definition
%	Percent
AACE	American Association of Clinical Endocrinologists
ACRO-TSQ	Acromegaly Treatment Satisfaction Questionnaire
AE	Adverse Event
AESI	Advere Event of Special Interest
AIS	Acromegaly Index of Severity
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
CAS	Combination Analysis Set (sub-study in selected sites)
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CPK	Creatine Phosphokinase
CRO	Contract Research Organization
d	Day
dL	Deciliter
EAS	Enrolled Analysis Set
ECG	Electrocardiogram
ECHO	Echocardiogram
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
ENDO	Endocrine Society
EOT	End-of-Treatment
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Levels Quality of Life questionnaire
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

Abbreviation/Term	Definition
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
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 Conference on 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)
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
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MID	Minimal Important Difference
min	Minute
mL	Milliliter
mmol	Millimole
MRI	Magnetic Resonance Imaging
[redacted]	[redacted]
NDA	New Drug Application
ng	Nanogram
NI	Non-inferiority
OGTT	Oral Glucose Tolerance Test

Abbreviation/Term	Definition
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
PRO	Patient Reported Outcome
PT	Preferred Term
QA	Quality Assurance
RA	Regulatory Authority
RBC	Red Blood Cell
RCT	Randomized Controlled Treatment Phase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Steering Committee
sc (injection)	Subcutaneous
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulator
SOC (safety)	System Organ Class
SOC (treatment)	Standard of Care
SOP	Standard Operation Procedures
SPA	Special Protocol Assesment
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
[redacted]	[redacted]
WBC	White Blood Cell
WHO	World Health Organization
Wk	Week
WOCF	Worst observation carried forward
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire Specific Health Problem V2.0

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, Colao 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, Colao et al. 2009; Melmed, Kleinberg 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, Ferone et al. 2004; Chanson and Salenave 2008; Melmed 2009; Fleseriu 2014; Melmed, Kleinberg 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.

1.3.1 Nonclinical Studies

The nonclinical studies conducted with octreotide capsules include: (1) pharmacology studies characterizing the TPE technology, (2) pharmacokinetics (PK) in rats, pigs and monkeys and (3) the toxicology of repeat doses of octreotide capsules in monkeys. Overall, octreotide capsules have been shown to have bioavailability in animals of up to 10% in rats and pigs using jejunal intubation and up to 2.4% in monkeys using oral administration of enteric-coated capsules. Toxicology studies up to 9 months in duration in cynomolgus monkeys showed a lack of any signs of toxicity at daily doses of up to 20 mg of octreotide which is equivalent to a human dose of approximately 113 mg based on body surface area conversion factors between species and an average human body weight of 70 kg. The nonclinical studies with octreotide capsules have demonstrated that the GI permeability following TPE administration was limited to molecules smaller than 70 kDa in size and to 60 to 90 minutes in duration. These data indicate that use of the TPE technology will not permit absorption of intestinal pathogens that are larger than 70 kDa in size (e.g., bacteria, viruses, toxins). The GI permeability was shown to be a transient and reversible process.

More detailed information is available in the octreotide capsules Investigator's Brochure (IB).

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).

Overall, 214 subjects were exposed in 11 Phase 1 pharmacology studies (184 healthy volunteers, 18 patients with hepatic impairment, 6 patients with severe renal impairment, and 6 patients with ESRD on dialysis). Drug exposure in the pharmacology studies was typically 1 day and not more than 6 days.

Overall, 349 acromegaly patients were exposed to octreotide capsules in three Phase 3 studies (203 patients in studies CH-ACM-01 and OOC-ACM-303 including OOC-ACM-303 Extension phase and 146 patients in the current ongoing Study OOC-ACM-302. In CH-ACM-01 and OOC-ACM-303 studies 92 patients were exposed to octreotide capsules for at least 12 months.

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

1.3.2.1 Clinical Pharmacology Studies

[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, Cook 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.

1.3.2.3 Phase 3 Study OOC-ACM-303 study in Acromegaly Patients

Study OOC-ACM-303, conducted under a USA FDA Special Protocol Assessment agreement (SPA), was a 9-month, randomized, double-blind, placebo-controlled study in 56 acromegaly patients. Eligible patients were required to be responders to injectable SRLs, defined as having an average IGF-1 ≤ 1 times ULN based on the two screening assessments. The primary efficacy endpoint and all secondary efficacy endpoints for this study were met.

Primary endpoint:

- 58% of the patients on octreotide capsules maintained their IGF-1 response compared to 19% of the patients on placebo (p = 0.0079). 81% of patients randomized to placebo lost IGF-1 control while on placebo. Thus, the placebo withdrawal treatment resulted in most patients losing biochemical disease control, which confirmed that patients had active

disease. Efficacy of octreotide capsules was demonstrated by the observation that 58% of patients randomized to active therapy retained biochemical disease control.

Secondary efficacy endpoints:

- 78% of patients treated with octreotide capsules maintained their growth hormone (GH) levels below 2.5 ng/mL at the end of the core study vs 30% of patients treated with placebo ($p = 0.0007$).
- The time to loss of response (defined as IGF-1 > 1.0 times ULN on two consecutive visits) was significantly greater in the octreotide capsules group compared to the placebo group ($p < 0.0001$). The median and 75th percentile times to loss of response in the placebo group were 16.0 and 16.6 weeks, respectively, while the median and 75th percentile times to loss of response in the octreotide capsules group were not reached (i.e., > 36 weeks). Twenty-six of 28 patients (93%) in the placebo group met this loss of response criteria by the end of the study (i.e., week 36) vs 13 of 28 patients (46%) in the octreotide capsules group.
- The time to loss of response (defined as IGF-1 ≥ 1.3 times ULN on two consecutive visits) was significantly greater in the octreotide capsules group compared to the placebo group ($p < 0.0001$). The median and 75th percentile times to loss of response in the placebo group were 16.2 weeks and 29.3 weeks, respectively, while the median and 75th percentile times to loss of response in the octreotide capsules group were not reached (i.e., > 36 weeks). Twenty-two of 28 patients (79%) in the placebo group met this loss of response criteria by the end of the study (i.e., week 36) vs 9 of 28 patients (32%) in the octreotide capsules group.
- 75% of patients treated with octreotide capsules did not require rescue medication with injectable SRLs (octreotide LAR or lanreotide depot) anytime throughout the core study vs 32% of patients treated with placebo ($p = 0.0029$).

90% of patients completing therapy on octreotide capsules opted to go into the open label extension (OLE).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 AEs were similar to those reported with long-acting somatostatin analogs but with no injection site reactions.

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

1.4 OVERALL BENEFIT TO RISK ASSESSMENT

1.4.1.1 Benefits

In healthy volunteers, 20 mg octreotide capsules yielded systemic drug exposure (AUC) comparable to a 0.1-mg sc dose of octreotide (Tuvia et al, 2012). Octreotide capsules significantly inhibited both basal GH secretion and GHRH-induced GH secretion. Inhibition of GH was recorded in all healthy volunteer subjects receiving octreotide capsules.

The novel octreotide capsules TPE technology safely and successfully allowed oral delivery of a therapeutic peptide to achieve systemic endocrine effects. Twice-daily octreotide capsules appears to offer a safe option for acromegaly monotherapy.

Study OOC-ACM-303, conducted under a SPA-agreed protocol, met its primary efficacy

endpoint and all its secondary hierarchical efficacy endpoints. 58% of the patients on octreotide capsules maintained their IGF-1 response compared to 19% of the patients on placebo ($p = 0.0079$). 75% of patients treated with octreotide capsules did not require rescue medications with injectable SRLs and 75% completed the study on study drug. 93% of placebo patients lost their response at some time throughout the study. 81% of patients randomized to placebo failed to maintain their response at the end of the study. Thus, the placebo withdrawal treatment resulted in most patients losing biochemical control of their disease, thus confirming that this patient population indeed had active disease.

In Study CH-ACM-01 65% of octreotide capsules patients met the primary endpoint of response at the 7-month end of core treatment (by last observation carried forward [LOCF] imputation for non-completers), and 53% met the primary endpoint of response at end of treatment by worst observation carried forward (WOCF).

Patients on octreotide capsules therapy exhibited maintenance or reduction of acromegaly symptoms. In Study OOC-ACM-303, 15 patients (53.6%) in the octreotide capsules group and 26 patients (92.9%) in the placebo group experienced AEs of special interest (AESIs). In Study CH-ACM-01, the overall AIS symptom score showed a statistically significant reduction ($p = 0.0275$) from Baseline to End of Core Treatment in the mITT population. The individual symptom scores for swelling of extremities and joint pain also showed a statistically significant reduction between Baseline to End of Core Treatment ($p = 0.0165$, $p = 0.0382$, respectively).

1.4.1.2 Risks

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 octreotide capsules nonclinical and clinical program (Studies CH-ACM-01, OOC-ACM-303). The most commonly reported TEAEs were similar to those reported with somatostatin analogs but with no injection site reactions.

Octreotide capsules warning and precautions are similar to Sandostatin label

- Cholelithiasis and Gallbladder Sludge: Somatostatin analogs have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to echogenic gallbladder abnormalities or sludge.
- Gallbladder-related AEs have been reported in clinical trials in patients receiving octreotide capsules. Symptomatic patients should be monitored periodically.
- Hyperglycemia and Hypoglycemia: Somatostatin analogs have been shown to alter the balance between the counter-regulatory hormones (insulin, glucagon, and GH) which may result in hypoglycemia or hyperglycemia. Blood glucose levels should therefore be monitored when somatostatin analog treatment is initiated, or when the dose is altered. Antidiabetic treatment should be adjusted accordingly.
- Thyroid Function Abnormalities: Somatostatin analogs have been shown to suppress the secretion of thyroid-stimulating hormone (TSH), which may result in hypothyroidism. Baseline and periodic assessment of thyroid function (TSH, total, and/or free T4) is recommended during chronic octreotide therapy.
- Cardiac Function Abnormalities: In acromegaly patients, bradycardia, arrhythmias, and conduction abnormalities have been reported during therapy with somatostatin analogs. The relationship of these events to somatostatin analogs is not established because many of these patients have underlying cardiac disease. Other ECG changes such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave

progression, and nonspecific ST-T wave changes have been reported in patients who received somatostatin analogs. These ECG changes are not uncommon in patients with acromegaly. Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary.

- Nutrition: Depressed vitamin B12 levels and abnormal Schilling tests have been observed in some patients receiving therapy with somatostatin analogs. Monitoring of vitamin B12 levels is recommended during therapy with somatostatin analogs.

Patients could be prescribed with octreotide capsules, and those who need to revert to injectable SRLs could do so without long-term deterioration in IGF-1. In Study OOC-ACM-303 the majority of patients who were rescued following a short trial of therapy with octreotide capsules returned to their baseline values following one SRL injection. Additionally, treatment interruption is a routine practice in the treatment of acromegaly, for those within 10 years of radiotherapy—to determine ongoing need for therapy—and in pregnancy.

Administration of octreotide capsules with food decreased the extent of exposure by 82% to 92% when 20 mg octreotide capsules was administered 1 or 2 hours after a full meal or 1 hour prior to a full meal. There is a potential risk for not complying with food restrictions. However, as non-compliance translates to an immediate increase in clinical symptoms, patients will likely keep within these restrictions, and therefore it should not be regarded as an actual risk. Acromegaly patients work hard to reduce acromegaly symptoms due to their very negative impact on quality of life. Additionally, these patients are routinely monitored biochemically for their disease status, and therefore loss of control would be readily detectable.

1.4.1.3 Risk/Benefit Assesment

Overall, the results observed in the two pivotal Phase 3 studies, OOC-ACM-303 and CH-ACM-01, confirm the efficacy of octreotide capsules and the durability of its effect.

Octreotide, the active ingredient in octreotide capsules, is a well-understood active ingredient. It is the same active ingredient in both Sandostatin and Sandostatin LAR, each approved for the treatment of acromegaly, the same population studied in the octreotide capsules clinical development program.

Study OOC-ACM-303 was conducted under a SPA; the study met the primary efficacy endpoint and all secondary hierarchical efficacy endpoints.

Both Phase 3 trials were maintenance-of-response trials, where the definition of response was identical to the inclusion criterion for biochemical control at screening.

The octreotide capsules clinical program demonstrated an acceptable safety profile for octreotide capsules with no new safety signals and an absence of injection site reactions. The discontinuation rate for Study OOC-ACM-303 was lower than for Study CH-ACM-01, likely reflecting a better understanding that AEs occurring on initiation of octreotide capsules treatment generally resolved on continued treatment as had been observed in Study CH-ACM-01. There was no dose response in the reported TEAEs.

Current injectable therapies for acromegaly are suboptimal for patients for several reasons. The injections are poorly tolerated due to significant persistent pain lasting for days, nodules, hemorrhage, inflammation, and scarring.

In addition to this physical impact of injections there is also an emotional impact of frustration, anxiety, and loss of independence. Work time is lost due to scheduling and travel for injections, AEs associated with injections, and exacerbation of symptoms near the end of the injection interval. Direct and indirect costs of monthly injections for both patients and HCPs are

significant. These injection burdens are supported by expert treating physicians, patient testimonials, the literature, the FDA and WHO post-marketing AE database, the Chiasma PRO study conducted in the EU, and a PRO study conducted in the US.

The exacerbation of symptoms near the end of the injection interval deserves further mention because it would not be anticipated for daily treatment with octreotide capsules. Studies have shown that long-acting somatostatin analogs often do not provide a full month of adequate symptomatic control, with > 50% of patients reporting a wear-off effect and recurrence or worsening of symptoms near the end of the dosing interval (Strasburger et al, 2016; Geer et al, 2019). Symptom recurrence sometimes necessitates supplemental patient injections. Additionally, logistical challenges and technical difficulties can also affect proper injection preparation and administration, which, in turn, can impair effective drug delivery and symptom control.

Octreotide capsules have a short and easy titration schedule, with a single up or down dose titration. Patients can be prescribed with octreotide capsules, and those who need to revert to injectable SRLs can do so without long-term deterioration in IGF-1 control. Similar temporary treatment interruption is already routine practice in acromegaly patients, such as during the first 10 years after pituitary irradiation to assess the need for continued therapy and during pregnancy.

1.4.1.4 Conclusion

In conclusion, two adequate and well-controlled Phase 3 studies demonstrated that octreotide capsules are effective as a maintenance therapy in most acromegaly patients for whom treatment with somatostatin analog injections has been shown to be effective and tolerated.

- Octreotide capsules are effective maintenance therapy for patients previously maintained on injectable somatostatin receptor ligands.
- Efficacy is durable:
  - In Study OOC-ACM-303, 92% of the patients initially responding to octreotide capsules had a sustained or durable response to end of treatment at 9 months.
  - In Study CH-ACM-01, 86% of the patients who entered the Fixed-Dose phase as responders maintained this response at the End of Core Treatment. The observed maintenance-of-response rate for patients in both trials who were able to be controlled on octreotide capsules was consistent with that known from the literature for parenteral somatostatin receptor ligands (Sandostatin LAR PI 2019; Lancranjan 1999).
  - In Study CH-ACM-01, patients on octreotide capsules therapy exhibited a reduced prevalence of acromegaly symptoms at end of study and in Study OOC-ACM-303 patients on octreotide capsules therapy experienced fewer AESIs compared with patients on placebo.
  - Patients were satisfied with octreotide capsules treatment: In Study OOC-ACM-303, 90% of patients (21/24) completing the trial on octreotide capsules continued into the OLE and, in Study CH-ACM-01, 86% of the patients (88/102 patients) who completed the Core Treatment Period elected to continue to the 6-month Extension Treatment Period and not revert to injections.
  - The results noted are statistically significant and clinically meaningful.

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 octreotide capsules clinical program. The most commonly reported AEs were similar to those reported with long-acting somatostatin analogs but with no injection site reactions. Octreotide capsules safety is supported by the Listed Drug, sc Sandostatin IR, and published scientific literature. Overall, octreotide capsules has a favorable risk-benefit profile in the management of patients with acromegaly currently controlled by injectable somatostatin analogs.

Patients who were not controlled on octreotide capsules or who opted to revert to SRLs were able to do so at any time. This can be done without deterioration in long-term IGF-1 control.

Thus, octreotide capsules as an alternative treatment option, provides the following significant benefits over existing therapy:

1. Eliminates all injection site reactions and their consequences
2. Enables a simple and straight forward administration that is technique-insensitive
3. Allows patients to take control over their disease, without dependency on HCPs, friends, or relatives
4. Eliminates the anxiety, frustration, and lost time related to injections
5. Maintains or improves acromegaly symptoms control
6. Allows easier and faster dose titration, symptomatic control, and treatment washout (in case of pregnancy or post-surgery).

The clinical program has demonstrated that octreotide capsules have a favorable risk-benefit profile. It provides a safe and effective therapy for acromegaly patients previously managed on injectable somatostatin analogs and fulfills an important unmet need in this patient population.

1.5 STUDY RATIONALE

Pharmacologic treatment of acromegaly includes chronic therapy with parenteral SRLs, including octreotide. Chiasma has developed octreotide capsules, a new formulation that enables the oral delivery of octreotide. Octreotide capsules may offer advantages to parenteral therapy. The formulation, called TPE[3], facilitates octreotide absorption from the intestine into the systemic circulation.

Following the completion of the pivotal Phase 3 safety and efficacy, multicenter, open-label, dose-titration study in acromegaly patients, octreotide capsules will now be further assessed in a randomized, open-label, multicenter, active-controlled, Phase 3 study to evaluate response maintenance , safety and patient reported outcomes in acromegaly patients treated with octreotide capsules, and in patients treated with standard of care (SOC) parenteral SRLs, who previously demonstrated a biochemical response to both treatments.

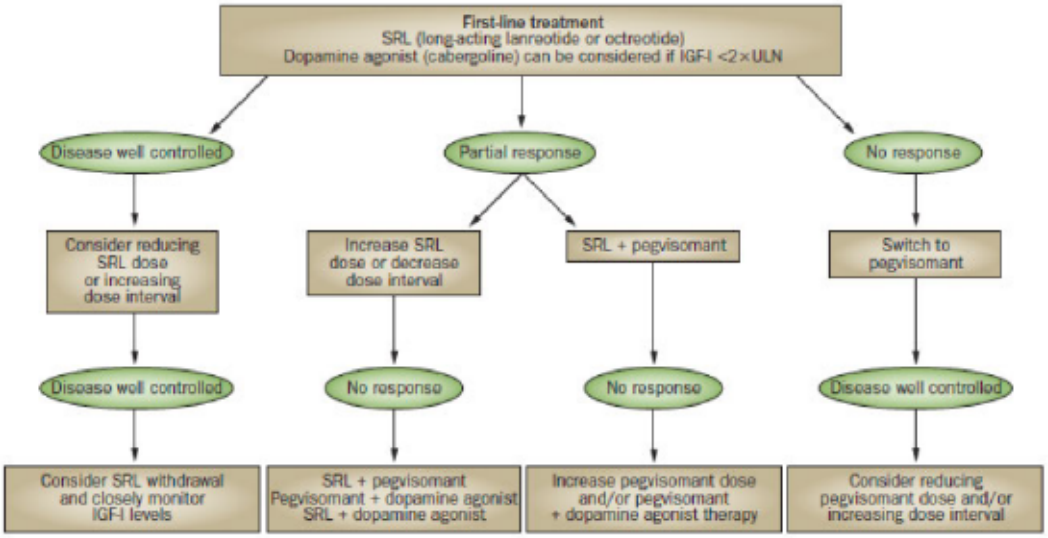
[redacted]

[3] TPE is a proprietary excipient mixture that permits oral administration; for more details, please refer to Investigator's Brochure

[redacted]

[redacted]

[redacted] [redacted]



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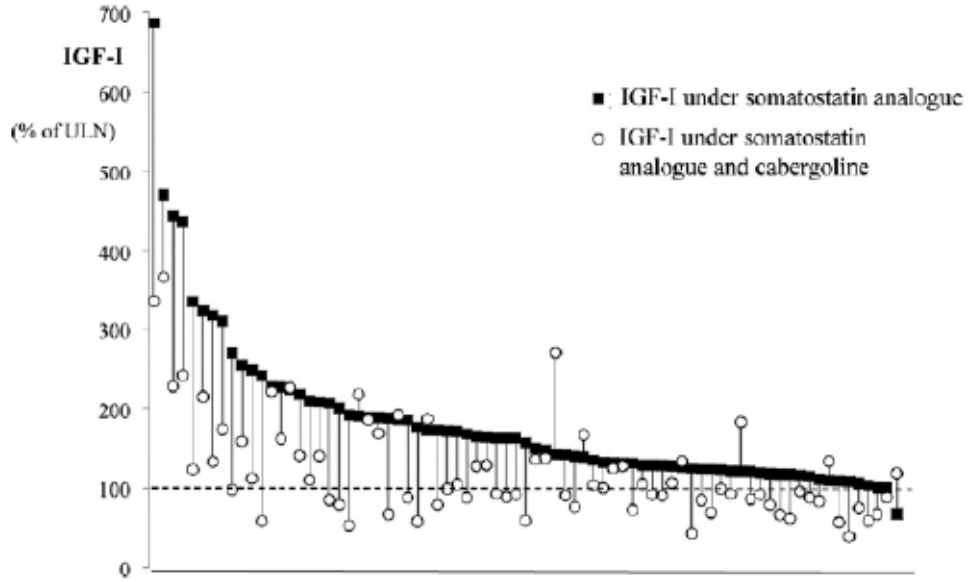

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[redacted]

[redacted]

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

Core study objectives

- To assess maintenance of biochemical control of octreotide capsules compared to parenteral SRLs in patients with acromegaly, who previously demonstrated biochemical control on both treatments.
- To assess maintenance of biochemical control of octreotide capsules in patients with acromegaly, who previously tolerated and demonstrated biochemical control on SRL injections [redacted]
- To assess symptomatic response to octreotide capsules compared to parenteral SRLs.
- To assess patient reported outcome (PRO) in patients treated with octreotide capsules compared to parenteral SRLs.
- To evaluate the safety profile of octreotide capsules compared to parenteral SRLs.

[redacted]

Extension phase objective

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

Combination phase sub-study (in selected sites) objective

- To assess the efficacy of octreotide capsules co-administered with cabergoline in the treatment of acromegaly patients with modestly elevated IGF-1 levels

(defined as 1.3≤ IGF-1 <2 × ULN, or IGF-1<1.3 × ULN and GH ≥ 2.5 ng/mL).

2.2 STUDY ENDPOINTS/OUTCOMES

2.2.1 Efficacy Endpoints

Primary Endpoint [redacted]

- The proportion of patients who are biochemically controlled throughout the RCT phase. A patient will be considered biochemically controlled if their IGF-1 Time Weighted Average (TWA), during the RCT phase is < 1.3 × ULN.

Additional [redacted] **Endpoints** [redacted]

[redacted]

- RCT phase - Proportion of patients on octreotide capsules who are biochemically controlled at the end of the RCT phase, defined as IGF-1 <1.3 × ULN (based on the average of week 62 and week 58).

Secondary Endpoints

- The proportion of patients who are biochemically controlled throughout the RCT phase. A patient will be considered biochemically controlled if their IGF-1 TWA during the RCT phase is < 1.3 × ULN [redacted]

[redacted]

- Proportion of patients who maintain or reduce the overall number of active acromegaly symptoms, at the end of the RCT phase (week 62/EOT), compared to week 26 (start of RCT phase).
- Proportion of patients who maintain or improve their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score), compared to week 26 (start of RCT phase)
- Acromegaly treatment satisfaction questionnaire (ACRO-TSQ) at the end of the RCT phase.
- Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country), who enter the Study Extension phase, overall and by treatment group.
- Change from the start of the randomized phase of the study (week 26) through the end of the RCT (week 62) for IGF-1.
- Change from the start of the randomized phase of the study (week 26) to end of the RCT (week 62) in mean integrated GH.

Exploratory Endpoints

- Proportion of patients who maintain or improve their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score), compared to Baseline (i.e., prior to the Run-in phase).

[redacted]

- Proportion of patients with TWA IGF-1 ≤1 × ULN during the RCT Phase in patients who started the RCT with IGF-1≤1 × ULN.

[redacted]

- Proportion of patients with a reduction in the overall number of active acromegaly symptoms, at the end of the Run-in phase compared to Baseline.
- Proportion of patients with improved AIS score at the end of the Run-in phase compared to Baseline.
- Health economic outcomes (EQ-5D, WPAI).

[redacted]

2.2.3 Study Extension Phase: Primary Endpoint

- The proportion of patients who are biochemically controlled at the end of each year of the Study Extension (e.g. first Extension year = Study Extension week 48, second Extension year = Study Extension week 96), out of those who entered this year as responders. A patient will be considered biochemically controlled if their end of the year IGF-1 is < 1.3 × ULN.

Additional Extension endpoints will be detailed in the Study Extension statistical analysis plan.

2.2.4 Safety Outcomes

- Frequency and severity of AEs and serious adverse events (SAEs)
- Clinically significant laboratory abnormalities

2.2.5 Combination Phase Sub-Study Endpoints

The following exploratory endpoints will be defined for the Combination phase sub-study (in selected sites) of the study:

- Proportion of patients with the following IGF-1 and mean integrated GH values at the end of the Combination phase sub-study compared to Baseline
  - IGF-1 <1.3 × ULN and mean integrated GH < 2.5 ng/mL
  - IGF-1 < 1.0 × ULN and mean integrated GH < 1.0 ng/mL
  - IGF-1 < 1.3 × ULN
  - IGF-1 ≤ 1.0 × ULN
  - Mean integrated GH < 2.5 ng/mL
  - Mean integrated GH < 1.0 ng/mL
- Rate of change in IGF-1 (i.e., slope)
- Proportion of patients who reduced the overall number of active acromegaly symptoms, at the end of the Combination phase sub-study, compared to baseline
- Proportion of patients who improved their AIS score at the end of the Combination phase sub-study compared to baseline

3 STUDY DESIGN

This will be a Phase 3, randomized, open-label, active-controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes (PROs) in acromegaly patients treated with octreotide capsules and in patients treated with SOC parenteral SRLs, who previously tolerated and demonstrated biochemical control on both treatments.

The Core study will consist of 3 phases: a Screening phase, a Run-in phase and a RCT phase (Figure 3).

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 IDMC will act in an advisory capacity to the Sponsor to monitor patients' safety during the study.

After up to 4 weeks Screening phase, eligible patients whose acromegaly has been controlled biochemically (defined as IGF-1 < 1.3 × ULN and mean integrated GH <2.5 ng/mL) on parenteral SRLs will be switched to octreotide capsules for a 26-week Run-in phase. During this phase the effective dose for each patient will be determined through dose titration (see Section 6.2).

Patients whose acromegaly has been controlled biochemically on octreotide capsules at the end of the Run-in Phase will enter a 36-week open-label RCT phase where they will be randomized to continue on octreotide capsules or switch back to their SOC injectable SRL (as received prior to Screening).

Following the completion of the Core study (Screening, Run-in and RCT phases), eligible patients will be offered to enter the Study Extension phase and receive octreotide capsules for 5 years or until product marketing or study termination (the earliest of which). Beyond 5-years

Extension phase, the Sponsor will either extend the Study Extension phase (via protocol amendments, for an additional year or until product marketing or study termination) or consider compassionate use (if requested by the principal Investigator under compassionate use protocol); subsequently a compassionate use protocol will be prepared and submitted for regulatory approval.

[redacted]

In selected sites where the Combination phase sub-study is conducted, patients who fail to respond to octreotide capsules 80 mg for at least two weeks therapy during the course of the Run-in phase, or patients ineligible to enter the RCT phase on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 $\geq$ 1.3 $\times$ ULN), will be eligible to enter the Combination phase sub-study. These patients will receive co-administration of octreotide capsules (80 mg/day) with cabergoline [redacted] for a total of 36 weeks. At the end of the Combination phase sub-study, eligible patients will be offered to enter the Study Extension phase and continue the same combined treatment regimen. Patients discontinuing early from the Combination phase sub-study or all other patients not meeting the criteria for randomization into the RCT phase or Combination phase sub-study will revert to their prior injectable SRL (prior to Screening, non-investigational medicinal product; non-IMP) or other treatment as determined by their physician and be followed for 12 weeks after last dose.

Patients who early terminate the Run-in phase for any reason in sites who do not participate in the Combination phase sub-study will revert back to their injectable SRL treatment (prior to Screening) and will be followed up for 12 weeks after last dose of study medication.

Database lock for the core study and the Combination phase sub-study will occur at the completion of both the RCT phase/End of Treatment (EOT) (last patient completes week 62) and the Combination phase sub-study (last patient completes week 36), and will not include the Follow-up phase, [redacted] *or Study Extension treatment phase. Interim analyses of the Extension Phase will be conducted periodically, after completion of the RCT phase. Data collected post-RCT phase or Combination phase sub-study will be included in the Study Extension database. Details of these analyses will be outlined in the statistical analysis plan (SAP).* For Study Decision Tree please refer to Appendix A.

Core study duration will be 66 weeks, comprised of:

Phase	Duration	Visit window

Screening phase:	**up to four weeks**	
Run-in phase (octreotide capsules):	**26 weeks**	**±3 days***
Randomized Controlled Treatment (RCT) phase (octreotide capsules vs. Parenteral SRLs):	**36 weeks**	**±3 days**

* At week 26, the visit window will be – 3 days to 10 days

Duration of other study phases will be as follows:

Combination phase sub-study (in selected sites) (octreotide capsules + cabergoline, for patients failing to respond to octreotide capsules): 36 weeks (in parallel to the core study durations). Visit window ±3 days.

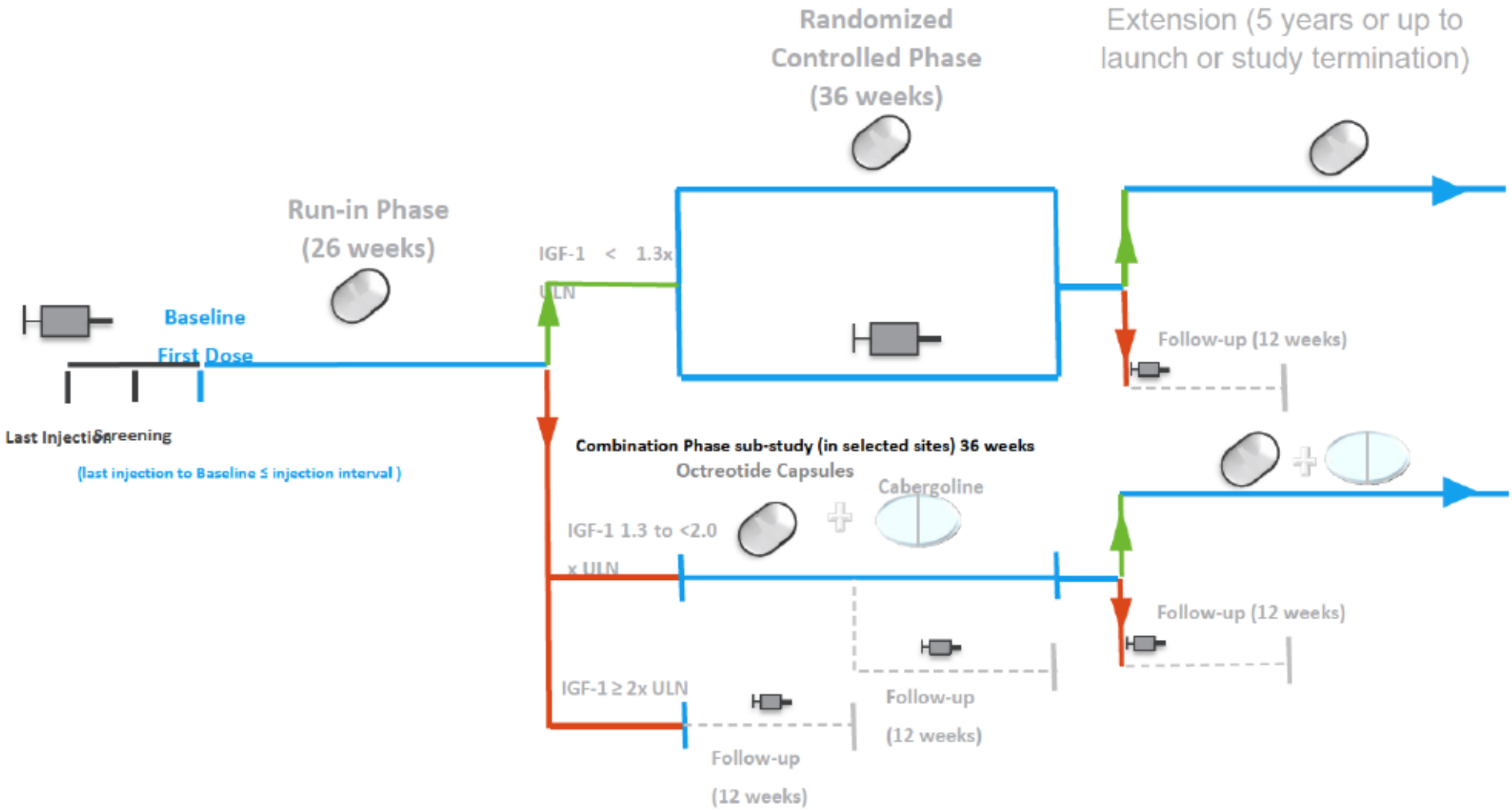
[redacted]

Study Extension phase: 5 years or until study medication is commercially available or Sponsor terminates the study (the earliest of which). The Study Extension phase may be extended (protocol amendment) or treatment may be provided under a separate Compassionate Use protocol following specific request by the Principal Investigator. Visit window ±10 days.

Follow-up Phase:

All discontinued patients (during any study phase) or patients ineligible to enter the RCT phase or the Combination phase sub-study or patients ineligible or not opting to continue into [redacted] the Extension phase will be followed-up for 12 weeks.

Figure 3 Study Overview



[redacted]

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 4 months and are biochemically controlled (IGF-1 < 1.3 × ULN and mean integrated GH <2.5 ng/mL) as evident at screening are eligible to participate in the study.

4.1 INCLUSION CRITERIA

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

1. Adult subjects, aged 18 to 75 years old, inclusive, at the Screening visit.
2. Patients with acromegaly, defined as documented evidence of GH-secreting pituitary tumor that is abnormally responsive to an oral glucose tolerance test or abnormal IGF-1 levels [redacted] who are currently receiving parenteral SRLs (octreotide or lanreotide but not pasireotide) for at least 6 months with a stable dose for at least the last four months.
3. Documented biochemical control of their acromegaly on the current dose of SRL (IGF-1 < 1.3 × ULN and mean integrated GH < 2.5 ng/mL over two hours), based on Screening assessment.
4. Patients able and willing to comply with the requirements of the protocol at the time of Screening.
5. 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.
6. 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 less frequently than once every eight weeks (dosing interval > 8 weeks).
2. Patients who previously participated in CH-ACM-01.
3. Symptomatic cholelithiasis.
4. Received pituitary radiotherapy within five years prior to screening (including total body, head and neck or stereotactic radiotherapy).
5. Undergone pituitary surgery within six months prior to screening or have elected surgery 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 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 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 12 weeks before the screening visit.
22. Treatment with dopamine agonists within 6 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 course of the study period based on tumor growth on serial MRIs
- Metastatic pituitary carcinoma or prior chemotherapy for pituitary carcinoma

23. Treatment with pasireotide within 12 weeks before the screening visit.

4.3 ELIGIBILITY CRITERIA TO RCT PHASE

1. Completed the full duration of the Run-in phase and biochemically controlled (based on IGF-1 and GH levels at week 24), with IGF-1 <1.3 × ULN and mean integrated GH <2.5 ng/mL.
2. Investigator assessment that the patient's acromegaly is adequately controlled (acromegaly related clinical symptoms are maintained with no meaningful exacerbation compared to Baseline).

4.4 ELIGIBILITY CRITERIA TO COMBINATION PHASE SUB-STUDY (IN SELECTED SITES)

Patients complying with all of the following criteria:

1. Patients who fail to respond to octreotide capsules 80 mg for at least two weeks during the course of the Run-in phase or patients ineligible to enter the RCT phase on octreotide capsules 80 mg due to in-adequate control of acromegaly at week 24 (as evident on week 26) with (a) modestly elevated IGF-1 levels between 1.3 × ULN to <2 × ULN or (b) IGF-1<1.3 × ULN and GH ≥2.5 ng/mL.
2. Patient is willing and able to comply with the protocol requirements for the duration of the Combination phase sub-study.

Exclusion criteria for Combination phase sub-study:

A patient cannot enter the Combination phase sub-study if they meet one of the following criteria:

1. Patient is currently having study medication withheld for a study medication-related AE.
2. Patient has a clinically significant or unstable medical or surgical condition detected or worsened during the study, which would preclude safe participation and/or completion of the study.
3. Patient has a known hypersensitivity to ergot derivatives.
4. Patient has uncontrolled hypertension (≥ 160 mmHg systolic OR ≥ 100 mmHg diastolic blood pressure).
5. Patient has history of clinically significant cardiac valve disorder or study ECHO valve disorder finding during the Run-in phase or at entry into the Combination phase sub-study (valve leaflet thickening, valve restriction, or mixed valve restriction-stenosis).
6. History of pulmonary, pericardial, or retroperitoneal fibrotic disorders.
7. Patient receives phenothiazines, butyrophenones, thioxanthenes, or metoclopramide.

[redacted]

[redacted]

4.6 ELIGIBILITY CRITERIA TO STUDY EXTENSION PHASE

1. Patient completing the full duration of either one of the following treatment phases, per protocol:
2. RCT phase (in any treatment arm)
3. Combination phase sub-study
4. Most recently available IGF-1 level (central laboratory), within not more than six weeks (+5 days) prior to Study Extension phase eligibility assessment is $< 1.3 \times$ ULN, and the Investigators' assessment that the patient's acromegaly is adequately controlled. (On a case-by-case basis, patients who are benefiting from octreotide capsules treatment, per the Investigator assessment, could also continue into the Study Extension following approval of the Sponsor. This includes but not limited to patients who completed the Run-in phase adequately controlled, yet completed the RCT phase on parenteral SRLs as non-adequately controlled).
5. Patient not currently having study medication withheld for a study medication-related AE.
6. Patient did not have a clinically significant or unstable medical or surgical condition detected or worsen during the study, which would preclude safe participation and completion of the Study Extension phase (including, if relevant in selected sites participating in the Combination phase sub-study, conditions contraindicated for treatment with cabergoline).
7. Octreotide capsules are not commercially available in the applicable region or country.
8. Patient is willing and able to comply with the protocol requirements for the duration of the Study Extension phase.
9. Patient preference to continue treatment with octreotide capsules and able to understand and sign an additional written informed consent prior to entering the Study Extension phase.

4.7 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.

4.8 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 SOC (not as study medication) as practiced at that particular site. Screen failures will not count towards the total enrolled and evaluable patients. [redacted]

[redacted]

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

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

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

The patient's participation in this study may be discontinued 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)

4.9.1 Early Termination during the Run-In Phase

Patients should be discontinued if they fail to respond to octreotide capsules in the Run-in phase if they meet the following criterion:

- Patients have IGF-1 levels $\geq 1.3 \times$ ULN and increased by at least 30% from Baseline and exacerbation of clinical symptoms (as determined by the Investigator) for 2 consecutive visits (at least 2 weeks apart) starting on week 12 (including week 12).

Patients who discontinue treatment early during the Run-in phase or who are ineligible or do not wish to continue into the RCT phase, will revert back to their parenteral SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician; these patients will enter the Follow-up phase and will be followed for 12 weeks after last dose of study medication.

In selected sites participating in the Combination phase sub-study, patients who are ineligible or do not wish to enter the Combination sub-study will revert back to their injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will be followed up for 12 weeks after last dose of study medication.

Patients who discontinue treatment early during the Run-in phase, who are eligible and continue into the Combination phase sub-study, will complete the Early discontinuation/Treatment phase completion form.

Patients who have completed the Run-in phase and are ineligible to continue into the RCT phase are not considered Early Terminations, but should complete the Early discontinuation/Treatment phase completion form (including those continuing into the Combination phase sub-study).

4.9.2 Early Termination from RCT Phase

All efforts should be made to maintain patients on their randomized treatment throughout the RCT phase up to completion of the core study.

Early treatment discontinuation during the RCT phase, patients completing the RCT phase who are ineligible to enter the Study Extension phase due to inadequate control of their acromegaly (see eligibility criteria in Section 4.5), or patients who opt not to enter the Study Extension phase, will revert back to their prior SOC injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will be followed up for 12 weeks after their last study medication dose (see Section 5.8).

Patients who have completed the RCT phase and are ineligible or do not wish to continue into the Extension phase are not considered Early Terminations, but should complete the Early discontinuation/Treatment phase completion form.

4.9.3 Early Termination from Combination Phase sub-study (in selected sites)

Patients should be discontinued from the Combination phase sub-study if they fail to respond to combination treatment and meet one of the following criteria from week 6 of the Combination phase sub-study onwards:

1. IGF-1 levels > 1.3 × ULN for at least two consecutive visits on the maximal cabergoline dose and no decrease of at least 10% compared to entry into the Combination phase Or
2. Worsening clinical signs and symptoms based on Investigator's discretion for at least two consecutive visits on the maximal cabergoline dose.

Patients who early discontinue treatment during the Combination phase sub-study will revert to their prior injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will be followed for 12 weeks post last dose.

Patients who discontinue treatment early during the Combination phase sub-study will complete the Early discontinuation/ Treatment phase completion form.

Patients completing the Combination phase sub-study who are ineligible to enter the Study Extension phase (see eligibility criteria in Section 4.5) or patients who opt not to go into the Study Extension phase, could revert to their prior SOC injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician, and will be followed up for 12 weeks (+4, +8 and +12 weeks), after their last study medication dose.

Patients who have completed the Combination phase sub-study and are ineligible to enter the Study Extension phase (see eligibility criteria in Section 4.5) or patients who opt not to go into the Study Extension phase are not considered Early Terminations, but should complete the Early discontinuation/Treatment phase completion form.

[redacted]

[redacted]

4.9.5 Early Termination from Study Extension Phase and for Patients Not Opting into the Study Extension Phase

Patients who discontinue treatment during the Study Extension phase will undergo three follow-up visits within 12 weeks (+4, +8 and +12 weeks) after their last study medication dose (Section 5.8).

4.10 Handling of Withdrawals

If a patient is withdrawn from the study, every effort should be made to determine the reason. This information will be recorded on the patient's eCRF. All patients who withdraw from the study prematurely, regardless of cause, should undergo all early termination assessments as specified in Section 5.7, preferably within not more than three days from the last study medication dose. Follow-up visits will be scheduled, per protocol.

4.11 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.

Patients entering the Study Extension phase will continue receiving octreotide capsules for 5 years or until product marketing or Sponsor's decision to terminate the study (the earliest of which). Following the completion of the 5-year Extension phase, the Sponsor will either extend the Extension phase (via protocol amendments, for an additional year or until product marketing or study termination (the earliest of which)) or consider compassionate use (if requested by the principal Investigator under compassionate use protocol); subsequently a compassionate use protocol will be prepared and submitted for regulatory approval.

5 STUDY PROCEDURES AND ASSESSMENTS

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

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.

All efforts should be made that 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 Phase (≤4 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 and have been treated with SRL injections (octreotide or lanreotide monotherapy) for at least six months and have been on a stable dose for at least the last four months. Eligible patients should have their acromegaly biochemically controlled (IGF-1 $< 1.3 \times$ ULN and mean integrated GH <2.5 ng/mL), as evident at any time during the Screening phase. If screening samples do not qualify the patient for the study, repeat screening samples (re-assessments) may be taken once during the Screening phase. Eligibility should be determined based on the last assessment.

[redacted]

The following evaluations should be done at the Screening visit:

- Informed consent signature
- Inclusion and exclusion criteria review
- ACRO-TSQ
- EuroQol – 5 Dimensions – 5 Levels quality of life questionnaire (EQ-5D-5L)
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- Verify the availability of a recent MRI image and/or report[1]. In case of surgery a post-surgical MRI is required. A CT scan can be done in place of an MRI if the MRI is contraindicated.
- Acromegaly history – date of diagnosis, basis for diagnosis (positive oral glucose tolerance test (OGTT) prior to surgery, elevated IGF-1 prior to surgery, pathology report, positive OGTT following surgery, elevated IGF-1 following surgery), previous surgery, previous radiotherapy, most recently documented MRI/CT findings – prior to surgery, following surgery.
- Medical history and demographic data; 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.
- Previous and concomitant medications recording – medications for acromegaly within the last year (with start and stop dates) and general use since diagnosis (list of prior medications for acromegaly any time in the past), medications for other conditions – within the last 12 weeks. Last dose of SRL injection should be recorded.
- Height and weight measurements
- Vital signs (blood pressure, heart rate, respiration rate)
- 12-lead ECG
- Safety laboratory tests: hematology, chemistry, urinalysis, HbA1c, fasting plasma glucose (FPG; for diabetic patients only) and serum pregnancy test, if

[1] MRI available within 12 months prior to screening is acceptable. If remnants were not visible or less than 5mm at last MRI, the MRI done with 2 years is also acceptable. Data from the MRI image/report will be captured in the eCRF (date of pituitary MRI, tumor size, tumor location, other). If specific data is missing an updated MRI will be required. A CT scan can be done in place of an MRI if the MRI is contraindicated.

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[1]
- Acromegaly directed physical examination
- AIS
- Abdominal (gall bladder) ultrasound

5.2 RUN-IN PHASE (26 WEEKS)

At the Run-in phase, all eligible patients will receive octreotide capsules for 26 weeks. Octreotide capsules dose should be escalated per Investigator's discretion in the case of significantly increased IGF-1 levels compared to baseline, worsening of acromegaly symptoms or both (for dose-escalation rules refer to Section 6.2). The dose escalation will be done in a stepwise manner from 40 mg/day (20 mg BID) to 60 mg/day (40 mg in the morning and 20 mg in the evening/night) to 80 mg/day (40 mg BID).

Determination of eligibility to continue into the RCT phase will be done at week 26, based on biochemical results at week 24.

5.2.1 Baseline Visit

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

- ACRO-TSQ
- EQ-5D-5L
- WPAI
- Inclusion and exclusion criteria review and confirmation
- Vital signs
- 12-Lead ECG
- Weight
- Safety laboratory tests: hematology, biochemistry, urinalysis, TSH, free T4, and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density 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 and GH[3]
- Acromegaly directed physical examination (including skin reactive lesions,

[1] Acromegaly related signs and symptoms should be captured under the acromegaly symptoms assessment. Other signs and symptoms not captured in the acromegaly symptoms assessment should be captured in the medical condition form.

[2] Time from last dose should not exceed injection interval +3 days

[3] GH: At Baseline, five samples will be collected every 30 ± 5 minutes for two hours, from 0-2 hours, before octreotide capsules administration

potentially associated with injections)

- AIS
- AEs and concomitant medications recording
- Dispense study medication (call IVRS/IWRS)
- Octreotide capsules administration at the site
- Drug administration instructions: apply food habits questionnaire, and adjust octreotide capsules 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 octreotide capsules 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.

Only at selected sites participating in the Combination phase sub-study, an ECHO should be performed for all patients enrolling into the Combination sub-study. For those sites who cannot perform an ECHO from the time frame between week 25 (availability of week 24 IGF-1 and GH results) and week 26 (enrollment into the Combination sub-study phase), the ECHO may be performed, within the initial 12 weeks of the Run-in phase, so that results are available prior to study entry into the Combination phase sub-study.

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 (±3 days):

- AEs recording
- AIS
- Compliance assessment and drug administration instructions
- Address any potential questions the patient may have with the new treatment

5.2.2 Run-In Treatment Visits (Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24)

During the Run-in phase, patients will return to the clinic for a site visit every 4 weeks (± 3 days) through week 24 and will attend an end of the Run-in visit at week 26.

The following assessments and procedures will be performed every four weeks (week 4, week 8, week 12, week 16, week 20 and week 24):

- Octreotide capsules administration at the site – weeks 24 only

- Weight
- Vital signs
- Safety laboratory tests: hematology and biochemistry
- IGF-1
- GH[1] - week 24 only
- Cardiac ECHO (in selected sites participating in the Combination phase sub-study, ECHO will be done once, prior to enrollment into the Combination sub-study. If a site cannot perform an ECHO from the time frame between week 25 (availability of week 24 IGF-1 and GH results) and week 26 (enrollment into the Combination phase), then the ECHO can be performed at any time within the initial 12 weeks of the Run-in phase, so that results are available for entry into the Combination phase sub-study
- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording
- Dispense study medication (call IVRS/IWRS)
- Compliance assessment and drug administration instructions - weeks 4 and 12
- Study medication accountability
- Dose titration (Section 6.2): The Sponsor recommends the following guiding rules for dose escalation relying on IGF-1 increase and/or exacerbation of symptoms:
  - Significantly increased IGF-1 levels compared to Baseline [redacted]
  - Increase in the number of symptoms or symptoms severity compared to Baseline or prior visit [redacted]

5.2.3 Randomization to Randomized Controlled Treatment (RCT) Phase (Week 26)

Patients will be assessed for eligibility to enter RCT phase, (see Section 4.3) based on week 24 IGF-1 and GH levels, with IGF-1 <1.3 × ULN and mean integrated GH <2.5 ng/mL. Pre-randomization will occur at week 25 (not an in-clinic study visit; i.e. patients will not be required to come to the clinic). The patient will be pre-assigned a randomization number and a treatment arm to allow medication to be on site for the randomization visit. The patient will be randomized at week 26 using an Interactive Web / Voice Response System (IWRS/IVRS). If the patient chooses not to continue to the RCT phase, the pre-assigned record will be released and replaced and used by another patient.

Eligible patients will be randomized in a 3:2 ratio to one of two treatment arms: continue same treatment with octreotide capsules (treatment arm 1) or switch to their prior parenteral SRL treatment (treatment arm 2) for an additional 36 weeks (starting on week 26 through week 62).

[1] GH: 5 samples will be collected every 30 ± 5 minutes for 2 hours, starting 2-4 hours after octreotide capsules administration

The study will utilize centralized stratified randomization based on the following variables on week 24 of the Run-in phase:

- IGF-1 ≤1 × ULN vs. IGF-1 > 1 × ULN to <1.3 × ULN
- Octreotide capsules treatment dose at week 24 (40 mg vs. 60 mg or 80 mg)

5.2.4 End of Run-in Visit (Week 26)

The visit window for week 26 is -3 to + 10 days to allow sufficient time to supply the study drug following week 25 pre-randomization.

The following assessments and procedures will be performed at week 26/End of Run-In:

- ACRO-TSQ
- EQ-5D-5L
- WPAI
- Safety laboratory tests: hematology, biochemistry, urinalysis, TSH, free T4, lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein), HbA1c, and serum pregnancy test, if applicable for women of childbearing potential
- Weight
- Vital signs
- 12-lead ECG
- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording
- Abdominal (gall bladder) ultrasound
- IGF-1 and GH[1]
- Verify availability of recent cardiac ECHO within the last six months
- Inclusion and exclusion criteria review for eligibility into RCT phase or Combination phase sub-study
- Dispense study medication (call IVRS/IWRS)
- Study medication administration and instructions
  - in RCT phase, octreotide capsules for those randomized to oral arm and SRL injections to those randomized to the injectable arm – same dose as administered prior to screening.
  - in Combination phase sub-study, octreotide capsules + cabergoline
- Compliance assessment
- Study medication accountability
- Complete treatment phase completion form

[1] GH: five samples will be collected every 30 ± 5 minutes over two hours, 2 to 4 hours after octreotide capsules administration

5.3 RANDOMIZED CONTROLLED TREATMENT (RCT) PHASE

Clinic visits during the RCT phase will be scheduled to occur every four weeks (weeks 26, 30, 34, 38, 42, 46, 50, 54, 58 and 62/EOT). Patients who received parenteral SRLs every 6 weeks will attend visits on weeks 26, 32, 38, 44, 50 and 56 (week 62 study procedures are described in Section 5.3.1). Visit window from week 30 onward will be ±3 days.

The week 26 procedures (RCT baseline) will be the same as performed at the end of the Run-in (see Section 5.2.4).

All efforts should be made to maintain patients on their randomized treatment throughout the RCT phase up to completion of the core study.

The following procedures and assessments will be conducted during RCT phase visits:

- ACRO-TSQ (weeks 38 and 50 only)
- EQ-5D-5L (weeks 38 and 50 only)
- WPAI
- Weight
- Vital signs
- Safety laboratory tests: hematology and biochemistry
- IGF-1
- Acromegaly directed physical examination (including skin reactive lesions, potentially associated with injections)
- AIS
- AEs including GI and injection site reactions
- Concomitant medications recording
- Dispense study medication (call IVRS/IWRS)
- Study medication administration per randomization assignment[1]
- Drug administration instructions (weeks 38 and 50 only)
- Study medication accountability
- Compliance assessment (weeks 38 and 50 only)

5.3.1 RCT: End of Treatment Visit (Week 62)

The following procedures will be done at week 62/EOT[2] visit of RCT phase:

- ACRO-TSQ
- EQ-5D-5L
- WPAI

[1] Patients randomized to receive parenteral SRLs will receive their injections at the site at the same frequency and dose as received prior to Screening. Patients, who received parenteral SRLs every four or five weeks, will receive their injections every four weeks at weeks 26, 30, 34, 38, 42,46, 50, 54 and 58. Patients who received parenteral SRLs at an interval of once every eight weeks will be assessed every four weeks yet will receive their injection every eight weeks (weeks 26, 34,42, 50 and 58). Patients who received SRL injections every six or seven weeks will attend visit week 32 instead of visit weeks 30 and 34, visit week 44 instead of visit weeks 42 and 46 and visit 56 instead of visit weeks 54 and 58; these patients will receive their injection on weeks 26, 32, 38, 44, 50 and 60.

[2] EOT procedures will also be performed in any case of early treatment discontinuation

- Weight
- Vital signs
- 12-lead ECG
- Safety laboratory tests: hematology, biochemistry, urinalysis, TSH, free T4, lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein), HbA1c, and serum pregnancy test, if applicable in women with childbearing potential.
- IGF-1
- Acromegaly directed physical examination (including skin reactive lesions, potentially associated with injections
- AIS
- AEs including GI and injection site reactions
- Concomitant medications recording
- GH[1]
- Abdominal (gall bladder) ultrasound
- Assess eligibility to continue into Study Extension phase (see Section 4.5) and if eligible obtain informed consent signature [redacted]
- [redacted]
- Dispense and administer study medication (octreotide capsules) to those patients eligible to continue into the Study Extension phase (*note, parenteral SRL injections will not be administered at Week 62/EOT*) (call IVRS/IWRS). [redacted]
- Drug administration instructions
- [redacted]
- Compliance assessment and drug administration instructions for those switching from SRLs to octreotide capsules in Study Extension phase
- Study medication accountability
- Complete treatment phase completion form

Patients completing the RCT phase who are ineligible to enter the Study Extension phase due to inadequate control, patients who fail to respond to octreotide capsules treatment during RCT phase, or patients who opt not to enter into the Study Extension phase will revert back to their

[1] GH: five samples will be collected every 30 ± 5 minutes over two hours, starting 2 to 4 hours after octreotide capsules administration and prior to the administration of the next (non-IMP) injection in those on the injection arm.

prior SOC injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will be followed for 12 weeks (see Section 5.8).

5.4 COMBINATION PHASE SUB-STUDY (IN SELECTED SITES)

Patients who fail to respond to octreotide capsules 80 mg for at least two weeks therapy during the course of the Run-in, or patients ineligible to enter the RCT on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 $\geq$ 1.3 × ULN to IGF-1 <2 × ULN, or IGF-1<1.3 × ULN and GH $\geq$ 2.5 ng/mL will enter the Combination phase sub-study and receive co-administration of octreotide capsules 80 mg with cabergoline [redacted] for 36 weeks (see eligibility criteria to Combination phase sub-study, Section 4.4).

[redacted]

End of Run-in phase will be considered Day 0 of the Combination phase sub-study. All procedures of end of Run-in phase (week 26) should be completed on Day 0 (see Section 5.2.4). Cabergoline dose titration instructions to be done by Day 0 and cardiac ECHO should be performed by Day 0 or between week 25 and week 26 (Day 0) or any time prior to week 25 during the Run-in phase if the latter are not feasible.

Clinic visits during the Combination phase sub-study will be scheduled to occur every four weeks (±3 days). Pre-scheduled telephone call will occur at week 2 and week 6.

The following assessments will be conducted during Week 2 and 6 telephone calls:

- AEs and concomitant medications recording
- Cabergoline dose titration instructions
- Compliance assessment

The following procedures and assessments will be conducted on Combination phase sub-study week 4, week 8, week 12, week 16, week 20, week 24, week 28, and week 32:

- Vital signs
- Weight
- Cardiac ECHO (week 12 and week 24 only)
- Cabergoline dose titration instructions
- Safety laboratory tests: hematology and biochemistry
- IGF-1

- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording
- Dispense study medication (call IVRS/IWRS)
- Study medication accountability

The following procedures will be done at Combination phase sub-study week 36/End of combination treatment[1] visit:

- Octreotide capsules administration at the site
- ACRO-TSQ
- EQ-5D-5L
- WPAI
- Safety laboratory tests: hematology, biochemistry, urinalysis, TSH, free T4, and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein), HbA1c and serum pregnancy test, if applicable
- Weight
- Vital signs
- 12-lead ECG
- Cardiac ECHO
- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording
- Abdominal (gall bladder) ultrasound
- Study medication accountability
- IGF-1 and GH[2]
- Assess eligibility to continue into Study Extension phase (see Section 4.5) and if eligible obtain informed consent signature and dispense study medication (call IVRS/IWRS)
- Complete treatment phase completion form

At the end of the Combination phase sub-study eligible patients will be offered to enter the Study Extension phase on the same combination treatment regimen.

Patients who early discontinue treatment during the Combination phase sub-study will revert to their prior injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician and will be followed for 12 weeks post last dose. Refer to Section 4.9.3 for Early Termination criteria from Combination phase sub-study.

Patients who complete the Combination phase sub-study and are ineligible to enter the Study Extension phase (see eligibility criteria in Section 4.5) or patients who opt not to enter the Study Extension phase, will revert to their prior SOC injectable SRL treatment (prior to Screening,

[1] EOT procedures will also be performed in any case of early treatment discontinuation
[2] GH: Five samples will be collected every 30 ± 5 minutes over two hours, 2 to 4 hours after octreotide capsules administration

non-IMP) or other treatment as determined by their physician, and will be followed for 12 weeks.

[redacted]

- [redacted]

[redacted]

Investigator's decision to terminate the study:

- Vital signs
- IGF-1
- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording
- [redacted]

Investigator's decision that the patient will receive octreotide capsules as part of the Study Extension phase:

- Re-verify patient consent for Study Extension phase
- Vital signs
- IGF-1
- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording
- Dispense study medication (octreotide capsules) (call IVRS/IWRS)
- Drug administration instructions
- [redacted]

5.6 STUDY EXTENSION PHASE

Patients who completed the RCT phase and had adequately controlled IGF-1 (see eligibility criteria to the Study Extension phase, Section 4.5), or who benefited significantly from octreotide capsules treatment (as determined by the study Investigator, and agreed by the study medical monitor), may enter the Study Extension phase. Eligible patients, previously treated with octreotide capsules during the RCT phase, will continue to receive octreotide capsules regimen, while patients treated with long acting SRLs injections during the RCT phase will switch to the octreotide capsules dose they were controlled on at the end of the Run-in phase. Patients must sign a Study Extension informed consent prior to enrolling into the Study Extension phase. The Study Extension phase will continue for 5 years or until the date when the study medication (octreotide capsules) becomes commercially available in the applicable region or country or when the Sponsor decides to terminate the study. Following the completion of the 5-year Study Extension phase, the Sponsor will either extend the Study Extension phase (via protocol amendments, for an additional year or until product marketing or study termination) or consider compassionate use (if requested by the principal Investigator under compassionate use protocol); subsequently a compassionate use protocol will be prepared and submitted for regulatory approval.

In addition, patients adequately controlled on the combination of octreotide capsules and cabergoline at the end of the 36-week Combination phase sub-study (see eligibility criteria, Section 4.5) or patients significantly benefiting from the combination treatment (as determined

by the study Investigator, and agreed by the study medical monitor) will also be offered to continue into the Study Extension phase on octreotide capsules and cabergoline.

During the first year of the Study Extension phase, clinic visits will be scheduled to occur every 12 weeks (±10 days). Thereafter, in-clinic visits will occur every 24 weeks (±10 days), with dispensing visits every 12 weeks (±10 days). Patients from RCT phase who switch to octreotide capsules will be contacted by phone one week after initiating octreotide capsules.

The following assessments will be done on the telephone call one week into the Study Extension (in patients who were randomized to SRL injections during the RCT phase):

- AEs and concomitant medication recording
- Assessments of acromegaly symptoms
- Compliance assessment

The following procedures will be done on pre-scheduled in-clinic visits during the Study Extension phase (that are not dispensing visits only - M3, M6, M9, M12 and every 6 Months thereafter):

- Octreotide capsules administration at the site (every 12 M, when GH is assessed)
- ACRO-TSQ (Months 3, 6 and 12 followed by every 12 months)
- EQ-5D-5L (Months 3, 6 and 12 followed by every 12 months)
- WPAI (Months 3, 6 and 12 followed by every 12 months)
- Safety laboratory tests:
  - hematology, biochemistry, urinalysis,
  - TSH, free T4, and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) (Months 6 and 12 followed by every 12 months)
  - HbA1c (Months 6 and 12 followed by every 12 months)
- Serum pregnancy test, if applicable, every 6 months
- Weight
- Vital signs
- 12-lead ECG (Months 6 and 12)
- Cardiac ECHO (Months 6 and 12 and every 12 months for patients on combination treatment)
- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording
- Dispense study medication (call IVRS/IWRS). [redacted]
- Drug administration instructions
- Study medication accountability
- Compliance assessment

- IGF-1 (Months 3 and 6 followed by every 6 months)
- GH[1] (annually and end of Study Extension phase).
- [redacted]
- [redacted]
- [redacted]

The following procedures will be done on pre-scheduled dispensing visits only during the Study Extension phase (every 6 M starting on Month 3 of the 2nd Extension year):

- Dispense study medication (call IVRS/IWRS)
- Study medication accountability

Patients who discontinue treatment during the Study Extension phase will to their prior SOC injectable SRL treatment (prior to Screening, non-IMP) or other treatment as determined by their physician, and will be followed for a further two weeks (Section 5.8).

5.7 EARLY DISCONTINUATION STUDY VISIT

Early termination visits are scheduled for patients who terminate the study prematurely. These visits may be performed on a same day as originally scheduled visit or could be scheduled separately. Data collection for these visits should primarily be guided according to principles to protect patient safety and wellbeing.

If a patient discontinues prematurely from the study for the reasons specified in Section 4.9, the following procedures should be completed preferably within not more than three days from the last study medication dose:

- ACRO-TSQ
- EQ-5D-5L
- WPAI
- 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 every 6 months
- Acromegaly directed physical examination
- AIS
- AEs and concomitant medications recording

[1] GH: 5 samples will be collected every 30 ± 5 minutes for 2 hours, 2-4 hours after octreotide capsules administration

- Study medication accountability
- IGF-1 and GH[1]
- Abdominal (gall bladder) ultrasound
- ECHO (for patients who discontinue the Combination phase sub-study in selected sites)
- Complete Early discontinuation/treatment phase completion form

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

5.8 FOLLOW-UP PHASE

Any patient early discontinuing treatment during the study (Run-in phase, RCT, Combination phase sub-study or Extension phase), or patients ineligible to enter the RCT phase or Combination phase sub-study patients ineligible or not opting into [redacted] the Study Extension phase, will undergo three follow-up visits over 12 weeks (+4, +8 and +12 weeks) after their last study medication dose for safety and efficacy assessments. Visit window will be ±3 days.

[redacted]

[redacted] UNSCHEDULED VISIT

An unscheduled visit may be performed throughout the study at the patient's request or as deemed necessary by the Investigator.

[1] 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 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 physical examination
- AIS
- Compliance assessment and drug administration instructions
- Dose titration – during Run-in phase, dose adjustment during the Combination phase sub-study
- Other as deemed necessary by the study Investigator

5.10 EFFICACY ASSESSMENTS

5.10.1 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 B through Appendix E). Blood samples for GH will be collected every 30±5 minutes over two hours (total five samples), at screening from time 0-2 hours, at Baseline before octreotide capsules administration from 0-2 hours, at all other visits (visit week 24, visit week 26/EOT, visit week 62/EOT, annually during the Study Extension phase and at the end of Study Extension), 2-4 hours after octreotide capsules administration; for patients randomized to the SRL injection arm, GH at week 62/EOT will be assess based on blood samples collected every 30 ± 5 minutes for two hours, prior to the administration of the next (non-IMP) injection. 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.

5.10.2 Oral Glucose Tolerance Test (OGTT)

OGTT is the gold standard for diagnosis of acromegaly and confirmation of disease activity. At time zero blood sample is drawn and the patient is then given 75 gram of glucose solution to drink within a 5-minute time frame. Blood is drawn at 30 minutes intervals for measurement of glucose and GH levels (30, 60, 90 and 120 minutes post glucose load). Failure to suppress nadir GH levels below 1 ng/ml (Katznelson, Laws et al. 2014), is considered a positive test, confirming disease activity in acromegaly. OGTT will be conducted as specified in Appendix E

Preparation:

- Unrestricted carbohydrate diet for 3 days prior to the test;
- Overnight fast (at least 8 hours) – (e.g. fast from 24:00 hours the previous night), water is allowed

Patient aspects of test:

- Patient should attend the in-clinic visit on morning time, and procedure is explained
- Patient should be seated throughout test – smoking is not permitted;
- Discontinue test if any glucose is lost by vomiting;
- Breakfast is given when test has been completed;

Technical details of test:

- place IV cannula for sample collection
- time 0 - take blood for growth hormone, IGF-1, glucose and any other safety labs;
- patient then consumes 75 gram of glucose solution to drink within a 5-minute time frame
- times +30 +60 +90 +120 minutes – take blood for growth hormone and glucose;
- samples including baseline bloods are sent to central laboratory on completion of test.

If OGTT is contraindicated (e.g. in a patient with severe uncontrolled diabetes as determined by the study investigator), 7 GH samples, taken within 3 hours (time zero, 30, 60, 90, 120, 150, 180 minutes), will be done instead. Average GH levels ≥ 2.5 ng/ml will confirm evidence of active disease.

5.10.3 Acromegaly Symptoms Assessment – Index of Severity (AIS)

Acromegaly symptoms are routinely assessed in clinical trials (Lancranjan and Atkinson 1999; Trainer, Drake et al. 2000; Caron, Beckers et al. 2002; Chanson and Salenave 2008; Petersenn, Schopohl et al. 2010; Chieffo, Cook et al. 2013; Colao, Bronstein et al. 2014; Petersenn, Farrall et al. 2014). Although some variability exists between studies in the severity scoring system (0-3, 0-4, 0-8), similar symptoms are routinely assessed in all studies. According to the consensus guidelines, acromegaly symptoms are considered a core clinical outcome (Giustina, Chanson et al. 2014) that should be incorporated into prospective clinical trials for evaluating new treatments.

AIS will be assessed throughout the study as specified in Schedule of Assessments (Appendix B through Appendix E). At each visit the following symptoms will be assessed: Headache, Swelling of extremities, Joint pain, Sweating and Fatigue. Each symptom will be graded from no symptoms (score 0), to mild symptoms (1), moderate (2) or severe symptoms (3) (Appendix J).

5.11 PATIENT REPORTED OUTCOME AND HEALTH ECONOMICS QUESTIONNAIRES

5.11.1 Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ)

A treatment satisfaction questionnaire for adult patients with acromegaly, developed by Chiasma, will be used in this study and is intended to be completed by the patient (i.e. PRO).

The questionnaire was developed according to best practices for PRO development. It was validated in a stand-alone study using data from 79 acromegaly patients enrolled from 14 clinical practices in the US and Europe and the Acromegaly Community. Its measurement properties, including internal consistency reliability, test-retest reliability, construct validity and known groups validity were evaluated and found to be acceptable. Items related to Emotional Impact and injection site reactions were revised based on these results, and, together with responsiveness to change and minimal important difference (MID) for all scales, will be evaluated using data from the run-in phase of the current study.

The questionnaire has several versions available for use at different time points throughout the study, each with minor modifications (specifically the recall period of interest). Week 62/end of treatment version of the ACRO-TSQ, is attached in Appendix G.

This questionnaire is expected to generate balanced information on the advantages and disadvantages of both treatment options for acromegaly (octreotide capsules and parenteral SRLs). The results of the ACRO-TSQ will provide a comprehensive assessment pertaining to treatment satisfaction, including treatment preference, related to mode of administration.

The ACRO-TSQ is focused on the following aspects:

- Acromegaly Symptoms
- Treatment-related Gastrointestinal side effects
- Injection Site Reactions
- Treatment Administration Bother
- Treatment Convenience
- Emotional Impact
- Treatment Satisfaction
-

The questionnaire will be assessed as specified in the Schedule of Assessments (Appendix B through Appendix E).

5.11.2 EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L)

EQ-5D-5L (five severity levels EQ-5D), developed by the EuroQoL, is a standardized instrument to be completed by the patient for use as a measure of health outcome applicable to a wide range of health conditions (Herdman, Gudex et al. 2011). It comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. Based on qualitative and quantitative studies conducted by the EuroQol Group, there are five options (levels) under each domain: 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to/extreme problems' (Appendix H). The responses to all five dimensions, can be converted to a single summary index, utility (range: 0-1), by using value sets. Higher index values represent better health states.

5.11.3 Work Productivity and Activity Impairment Questionnaire Specific Health Problem V2.0 (WPAI:SHP)

Work Productivity and Activity Impairment Questionnaire Specific Health Problem V2.0 (WPAI:SHP) is a standardized and validated tool to measure health outcomes in clinical trial settings (Reilly, Zbrozek et al. 1993). Specifically, this self-administered tool measures time missed from work, impairment of work and regular activities due to overall health and symptoms, relative to measures of general health perceptions, role (physical), role (emotional), pain, symptom severity and global measures of work and interference with regular activity (Appendix I).

5.12 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, cardiac ECHO, and laboratory assessments; these assessments will be conducted as specified in Schedule of Assessments (Appendix B through Appendix E).

5.12.1 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 7.1 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.

5.12.2 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.

5.12.3 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.

5.12.4 ECG Assessment

Twelve-lead ECG will be done as specified in Schedule of Assessments (Appendix B through Appendix E). 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.

5.12.5 Physical Examination

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

Acromegaly directed physical examination, will be conducted as specified in Schedule of Assessments (Appendix B through Appendix E). It will include assessment of physical signs related to acromegaly (swelling of extremities, 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) and treatment related signs and symptoms (presence of injection site reactions e.g. erythema, nodules, hematoma, inflammation, atrophy, or other).

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 B through Appendix E).

Positive acromegaly related signs that are also captured on the AIS should be captured on the corresponding AIS eCRF and not reported as an AE.

5.12.6 Abdominal Ultrasound

Abdominal ultrasound will be conducted to monitor gall bladder and biliary tract disease as specified in Schedule of Assessments (Appendix B through Appendix E). 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.

5.12.7 Echocardiogram

In selected sites participating in the Combination phase sub-study, cardiac ECHO will be performed to assess the potential presence of valvular disease (valvular regurgitation, valvular restriction or valve leaflet thickening). It will be done as specified in Schedule of Assessments (Appendix B through Appendix E) in all patients receiving combination treatment of octreotide capsules + cabergoline.

5.12.8 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 capsules administration is assessed at the clinical site as specified in Schedule of Assessments (Appendix B through Appendix E). Laboratory tests (hematology and serum chemistry) will be done under overnight fasting conditions at all clinic visits except week 24/26, end of RCT (week 62)/ end of Combination phase (week 36); these are 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 Reference Therapy: Injectable Somatostatin Receptor Ligands -- SRLs (Octreotide LAR or Lanreotide)

Patients randomized to the active control arm in the RCT phase will receive their SOC injectable SRL (octreotide LAR or lanreotide), according to the individual patient use prior to enrollment in the study. SRLs are provided as injectable suspension.

6.1.3 Cabergoline (for Combination phase sub-study in selected sites)

Cabergoline tablet is an orally-administered a long-acting dopamine receptor agonist with a high affinity for D2 receptors. It is commonly used for the treatment of acromegaly as monotherapy or in combination with other agents. It will be provided together with octreotide capsules in the Combination phase sub-study and the Study Extension phase.

6.2 STUDY MEDICATION ADMINISTRATION

6.2.1 Octreotide capsules

Octreotide capsules (each capsule is 20 mg strength) 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*

Octreotide capsules will be up-titrated in all eligible patients during the initial Run-in phase from 40 mg to 60 mg and 80 mg/day, based on clinical and biochemical response.

The Sponsor recommends the following guiding rules for dose escalation relying on IGF-1 increase and/or exacerbation of symptoms:

- Significantly increased IGF-1 levels compared to Baseline, [redacted]
- [redacted]

Patients who are biochemically controlled at the end of the Run-in phase will be randomized to either continue octreotide capsules treatment or revert to their SOC injectable SRL during the RCT phase.

Patients entering the Study Extension phase will continue octreotide capsules for 5 years or until product marketing or termination of study by Sponsor (the earliest of which). Following the completion of the 5-year Study Extension phase, the Sponsor will either extend the Study Extension phase (via protocol amendments, for an additional year or until product marketing or study termination (the earliest of which), or consider compassionate use (if requested by the principal Investigator under compassionate use protocol); subsequently a compassionate use protocol will be prepared and submitted for regulatory approval.

6.2.2 SRL injections

In the RCT phase, for patients randomized to the active control arm, SRLs will be injected sc at site visits at the same dose and administration frequency as received prior to study entry.

For this study, the dose ranges allowed for Octreotide or Lanreotide are any dose used on the market (Octreotide 10, 20 and 30 mg and Lanreotide 60, 90 and 120 mg) as long as the dosing interval does not exceed once every 8 weeks (e.g. dosing intervals of every 4, 5, 6, 7 or 8 weeks are allowed). Dosing every 2 weeks is not allowed unless the patient was stabilized for 4 months on a monthly dosing regimen.

Label information for SRLs used in this study (Octreotide, Lanreotide) should be strictly followed, with specific attention paid to Contraindications, Warnings and Precautions and to Drug-Drug Interactions sections (see US label and SmPC in Appendix F).

6.2.3 Cabergoline (for Combination phase sub-study in selected sites)

Patients entering the Combination phase sub-study will receive co-administration of octreotide capsules 80 mg with cabergoline [redacted]

[redacted]

During the Study Extension phase, eligible patients who receive cabergoline and octreotide capsules will continue to receive octreotide capsules and cabergoline for 5 years or until octreotide capsules marketing or termination of study by Sponsor (the earliest of which). Following the completion of the 5-year Study Extension phase, the Sponsor will either extend the Study Extension phase (via protocol amendments, for an additional year or until product marketing or study termination (the earliest of which)), or consider compassionate use (if requested by the principal Investigator under compassionate use protocol); subsequently a compassionate use protocol will be prepared and submitted for regulatory approval.

6.3 Method of Assigning Patients to Treatment Group

Patients meeting the eligibility RCT criteria (see Section 4.3) at week 24 will be randomized in a 3:2 ratio to receive octreotide capsules or SRL. The study will utilize centralized stratified randomization based on the following variables on week 24 of the Run-in phase:

- IGF-1 $\leq 1 \times$ ULN vs. IGF-1 $> 1 \times$ ULN to $< 1.3 \times$ ULN.
- Octreotide capsules treatment dose at week 24 (40 mg vs. 60 mg or 80 mg).

Randomization and drug dispensing will be done using IVRS/IWRS.

6.4 Blinding

To maintain the blinding to key efficacy data, Chiasma will ensure that none of the study efficacy outcome measures (e.g., IGF-1 and GH levels, acromegaly symptoms or ACRO-TSQ) will be tabulated or summarized during the study to be able to reflect the potential efficacy of octreotide capsules in the enrolled acromegaly subject population. Only the IDMC, on its closed sessions and per request will be able to see such tabulated data.

To maintain the blinding of efficacy data the following individuals will be the only recipients of individual patients' efficacy data during the study; the data provided should be presented by patient (i.e. listings) and not grouped or aggregated:

- IDMC members (as described in the IDMC charter)
- Investigators to enable clinical decisions and dose titration as per protocol (through laboratory results data)
- A highly selective group of senior Chiasma Representatives (Chief medical officer, VP Clinical Development, Head of Clinical Operations and Medical Monitor) responsible for overall patient safety and study oversight
- Study team members that interact directly with investigators (i.e., Clinical Research Associates)

It is important to note that these individuals would not see aggregate or grouped data.

6.5 Manufacturing of Study Medications

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

Marketed long acting octreotide and lanreotide injections as well as cabergoline tablets 0.5 mg will be procured by the Sponsor, re-labeled and distributed to participating sites. Details will be provided in the Study Pharmacy manual.

6.6 PACKAGING AND LABELING OF STUDY MEDICATION

Octreotide 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, comparator SRLs and cabergoline[1]) will be labeled as specified in the Study Pharmacy Manual and may include at minimum:

- Product name
- Dose
- Lot/batch number
- Date of manufacture
- Retest date
- 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.

[1] For Combination phase sub-study in selected sites

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 should be stored at 5 ± 3°C. Daily 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 within 30 days 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 Medication or Therapies

- Treatment with pegvisomant within 12 weeks before the screening visit
- Treatment with dopamine agonists within 6 weeks before the screening visit
- Treatment with pasireotide within 12 weeks before the 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
- Pituitary radiotherapy within five years prior to screening
- 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 and specifically Screening, Baseline, week 24, week 26 and week 62, and end of treatment phase, 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.

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.

Parenteral SRLs or dopamine agonists other than the investigational medical products allowed during the study, GH antagonists, or any other investigational therapy for the treatment of acromegaly are prohibited during the course of the study.

Phenothiazines, butyrophenones, thioxanthenes, or metoclopramide are prohibited in the Combination Phase sub-study.

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 RCT phase). AEs reported after termination/completion of the core study, during the Follow-up phase, as well as AEs that occurred within the Combination phase sub-study will be reported separately. AEs reported during the Study Extension phase 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.

Normal fluctuations of existing acromegaly symptoms, as assessed by the acromegaly index of severity score (AIS), do not need to be reported as AEs unless they are judged to be clinically significant or are reported by the patient spontaneously during the clinic visit in an unsolicited manner.

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, Combination phase sub-study and Study Extension phase. 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, SRLs injection and cabergoline[1]).

[1] Applicable only to patients participating in the Combination phase sub-study (in selected sites)

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.

All AEs, serious and not serious, will be recorded on the AE eCRF page. Severity and relationship to study medication will be assessed by the Investigator as described in the section above.

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 Conference on 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 appropriate eCRF. If eCRFs are not available, SAEs should be reported to the contract research organization (CRO), Pharm-Olam within 24 hours using the contact information provided below. In case of emergency, a 24-hour country-specific Toll-Free number is available in the Study Binder.

[redacted]

[redacted]

These preliminary reports will be followed within 24 hours by more detailed descriptions that will include a completed SAE form, copies of hospital case reports (i.e., hospital progress notes,

results of applicable diagnostic tests, lab results and biopsy results), autopsy reports, and other documents, when requested and applicable.

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)

Once reported, the SAE form and accompanying documentation should be placed in the SAE section of 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

Information to Include on SAE Form

The following information should be provided in the SAE form to accurately and completely record the event:

- Investigator name and site number (if applicable), site address
- Patient study identification number
- Patient's initials (if applicable)
- Patient's demographics (gender; date of birth or age, as appropriate; weight; height)
- Clinical Event:
  - Description
  - Date and time of onset, stop date, or duration
  - Severity
  - Treatment (including hospitalization)
  - Relationship to study medication (causality)
  - Action taken regarding study medication
  - Information on recovery and any sequelae
  - If the AE resulted in death
  - Cause of death (whether or not the death was related to study medication)
  - Autopsy findings (if available)
  - Medical History case report form (copy)
  - Concomitant Medication case report form (copy)

- Any relevant reports (laboratory, discharge, etc.)

For more details, refer to Pharm-Olam Safety Plan.

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.

Subsequent additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site to the Sponsor representative and study monitor within 24 hours of the information becoming available.

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

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 [redacted].

The Investigator will fill out the AE eCRF page and if relevant, the Concomitant Medications Record in the eCRF. A particular attention will be made to ensure no discrepancies between the AE and the SAE form (i.e., outcome, severity, relationship must be consistent).

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 Record in the eCRF and if relevant, the Concomitant Medications Record in the eCRF. Severity and relationship to study medication will be assigned by the Investigator as described in the section above. 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.

7.5 ANTICIPATED ADVERSE EVENTS

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

7.6 OCTREOTIDE SAFETY GUIDANCE

Below are 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. For patients who are enrolled in the Combination phase sub-study (participating sites only), as noted in Section 6.10.4, D2-antagonists (e.g., phenothiazines, butyrophenones, thioxanthenes, or metoclopramide) should not be administered concurrently with cabergoline for the treatment of GI symptoms or any other AE.

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 phases 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's 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 5). 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's 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's discretion.

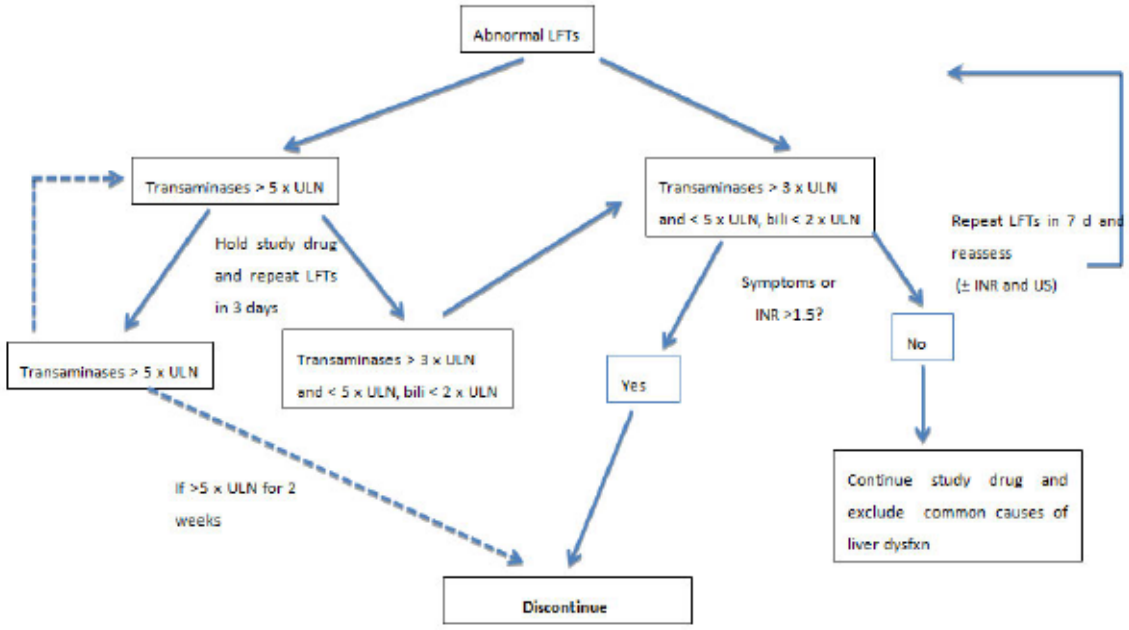
All patients who develop significant liver dysfunction (ALT or AST ≥ 5 × ULN) should have study drug held and be followed up within 3 days and every 3-4 days thereafter up to resolution/return to baseline. In case ALT/AST remains above 5 × ULN, study drug should be discontinued. If ALT/AST has fallen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

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), which will be finalized prior to the first patient randomized. As the study is open-label, early finalization will prevent the introduction of bias.

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 and the Combination phase sub-study will occur at the completion of both the RCT phase/End of Treatment (EOT) (last patient completes week 62) and the Combination phase sub-study (last patient completes week 36), and will not include the Follow up phase, [redacted] or Study Extension treatment phases. Interim analyses of the Extension Phase will be conducted periodically, after completion of the RCT phase. Data collected post RCT or Combination phases will be included in the Study Extension database. Details of these analyses will be outlined in the SAP.

8.1 SAMPLE SIZE CONSIDERATION

Approximately 150 patients will be enrolled into the Run-in phase of the study. The total number of patients will be adjusted to ensure a minimum of 80 patients will enter the RCT phase, with approximately 48 patients assigned to octreotide capsule arm and 32 patients assigned to SRL injection arm.

[redacted]

An assessment of NI will be made by comparing the lower bound of the two-sided 95% confidence interval (CI) for the difference in biochemical control (octreotide capsules - SRL) to a NI margin of -20%. The margin was based upon the use by CHMP of a 20% margin for another orphan oral product Cerdelga (eliglustat) compared to an injectable in an NI design trial (European Medicines Agency 2014).

With the pre-defined primary endpoint, a response rate of approximately 95% was observed in a previous CH-ACM 01 trial in those patients who initially responded to octreotide capsules.

[redacted]

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

8.2 ANALYZED POPULATIONS

8.2.1 Full Analysis Set (FAS)

FAS is defined as all randomized patients to the RCT phase who receive at least one dose of study medication and have one post randomization measurement of IGF-1 and GH. This population will serve as the primary efficacy analysis population for the RCT phase of the core study. Patients will be included in the group to which they were randomized.

8.2.2 Per-Protocol Analysis Set (PP)

Per-Protocol Analysis Set (PP) is defined as all patients in the FAS without a major protocol violation. Major protocol violations will include non-compliance[1] with study medication.

8.2.3 Safety Analysis Set (SAS)

SAS is defined as all randomized patients who receive at least one dose of study medication. This population will serve as the primary safety analysis population for the RCT phase of the core study. Patients will be included in the group according to which medication they actually received.

8.2.4 Enrolled Analysis Set (EAS)

EAS is defined as all patients who are enrolled into the Run-in phase of the core study, and receive at least one dose of study medication. This population will be used for the analysis of safety and efficacy data during the Run-in phase of the core study.

8.2.5 Combination Analysis Set (CAS)

CAS is defined as all patients who are enrolled into Combination phase sub-study. This population will be used for the analysis of safety and efficacy data collected in the combination arm.

8.2.6 Extension Analysis Set (EXT-AS)

EXT-AS is defined as all patients who are enrolled into the Study Extension phase of the study. This population will be used for the analysis of safety and efficacy data during the Study Extension phase.

[redacted]

8.3 ENDPOINTS

For a description of the endpoints refer to Section 2.2. For a description of the assessment tools, refer to Sections 5.10 and 5.12.

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

[1] Non-compliance will be defined in Study Monitoring Plan and Statistical Analysis Plan prior to database lock

statistics will generally include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum.

Baseline for the Run-in phase will be defined as the last value prior to the Run-in phase. The week 26 value will be used as the baseline value for the RCT phase.

Given the small number of patients, data will be pooled across all sites for reporting purposes.

8.4.2 Demographics and Baseline

Demographic data, baseline characteristics, medical history and concomitant medications will be summarized using descriptive statistics. Data will be presented by treatment group, and overall, for the FAS and SAS, and overall for the EAS and CAS.

8.4.3 Primary Efficacy Analysis [redacted]

The primary efficacy analysis will estimate the proportion of patients biochemically controlled throughout the RCT phase within each treatment arm. A patient will be considered biochemically controlled if his/her TWA, during the RCT phase, for IGF-1 is < 1.3 x ULN. The use of TWA response over time is a simple longitudinal data analysis approach intended to minimize the number of missing patients from a primary effectiveness analysis and to account for natural variation among the measure of interest that may be observed over the time period of monitoring. The TWA response, over the treatment period represents an integrated measure of efficacy across time. It is derived as the area under the curve (AUC) divided by the total amount of time under observation. All measurements will be used, including data collected at "Discontinuation" visits and "Unscheduled" visits. Every effort will be made to follow patients to completion of the RCT phase. The dropout rate is expected to be minimal, but should patient's dropout, all data collected up to that point and including the time of discontinuation will be included in the primary analysis. Given this approach for calculating the TWA response for an endpoint, no missing value will be imputed. However, if a patient discontinues during the RCT phase for lack of efficacy, he/she will be considered to be NOT biochemically controlled, regardless of their TWA. The unadjusted difference between arms and the adjusted difference between arms will be reported. The adjusted difference will be obtained by calculating the weighted average of the stratum specific differences (where the stratum are defined in the randomization process) using the inverse of the variance weighting strategy (Yan and Su 2010). An assessment of non-inferiority will be made using an NI margin of -20%. The difference (octreotide capsules – Injectable SRLs) in response rate and two-sided 95% CI for the difference will be calculated. If the lower bound of the CI is greater than the NI margin of -20%, octreotide capsules will be declared non-inferior to injectable SRLs. The FAS will be the primary population used for this analysis, with a PP population used as a sensitivity analysis. Additional sensitivity analyses may be conducted to examine the impact of missing data. Further details will be provided in the SAP.

8.4.4 Additional Primary Efficacy Analysis [redacted]

Primary efficacy analyses [redacted] will be conducted for both the Run-in phase and for the RCT phase as follows:

- Run-in phase - Proportion of patients biochemically controlled at the end of the Run-in phase defined as IGF-1 <1.3 × ULN (based on the average of week 24 and week 26)
- RCT phase - Proportion of patients on octreotide capsules who are biochemically controlled at the end of the RCT phase, defined as IGF-1

<1.3 × ULN (based on the average of week 62 and week 58).

The primary efficacy analysis [redacted] will be descriptive in nature. For the Run-in phase the enrolled analysis set will be the primary analysis population. For the RCT phase the FAS will be the primary analysis population. The proportion of responders and associated two-sided 95% confidence intervals will be reported for each endpoint. For each endpoint, if a patient discontinues during the study phase, they will be considered failures for the respective endpoint. For each endpoint, if a patient completes the phase, but is missing their final assessments, their worst observation will be carried forward (WOCF) in order to determine their response for the respective phase.

[redacted]

8.4.5 Secondary Efficacy Analysis

Analysis of the secondary efficacy endpoints will be conducted without adjustment for multiplicity using the FAS. Analyses of the change from the start of RCT phase (week 26) through the end of the RCT phase (week 62/EOT) for IGF-1 and the change from the start (week 26) to the end of the RCT phase (week 62/EOT) in mean integrated GH will be conducted using an analysis of covariance (ANCOVA) to adjust for baseline (IGF-1 and GH, respectively). The adjusted mean ratio (i.e., relative change), and associated 95% CIs will be reported. Data will be analyzed on the log scale and back transformed for reporting. The change through the end of the RCT phase for IGF-1 will be derived as a time weighted average change (it is derived as the area under the curve (AUC) divided by the total amount of time under observation), starting with the first observed value following randomization (i.e., week 26), and using the week 26 value as the baseline value to calculate the change at each visit. All measurements will be used, including data collected at "Discontinuation" visits and "Unscheduled" visits. Given this approach for calculating the TWA response for an endpoint, no missing value will be imputed. For each secondary endpoint that is defined as "the proportion of patients…", the proportions will be reported within each treatment arm, and both the unadjusted difference between arms and the adjusted difference between arms, will be reported. The adjusted difference between arms and the 95% CI for the adjusted difference will be estimated using the same approach as described above for the primary endpoint (Yan and Su 2010).

Analysis of secondary endpoint of the PRO will be conducted without adjustment for multiplicity using the FAS. Descriptive statistics will be used to summarize results within each treatment arm and between treatment groups, across time. Details of the analysis methodology will be provided in the SAP.

Analysis of the secondary endpoint "Proportion of patients (of those in the RCT phase) who enter the Study Extension" will be summarized using the FAS. The proportion and two-sided 95% CI of the proportion will be reported overall and by treatment group, no comparison of the two treatment groups will be made.

8.4.6 Exploratory Efficacy Analysis

Analysis of the exploratory efficacy endpoints based on the run-in phase will be summarized using the EAS. For each exploratory endpoint that is defined as "the proportion of patients…", the proportion and two-sided 95% CI of the proportion will be reported. If a patient did not withdraw, but is missing data at week 24, the last observation carried forward (LOCF) approach will be used to impute these values, prior to determining the patients' response status. Patients, who withdraw during the Run-in phase, will be treated as non-responders. To enter the RCT phase, patients will be required to have a week 24 value, so the occurrence of this scenario is expected to be minimal if at all. Additionally, at each post baseline visit during the run-in phase, shift tables will be produced based on the following categories (IGF-1 <1, IGF-1 between 1 and 1.3, IGF-1 ≥ 1.3). A shift table summarizing GH (<1.0, 1.0 – 2.5, >2.5) from baseline to the end of the un-in will also be presented.

Additional exploratory analyses of the RCT phase will be conducted to further understand how patients IGF-1 and GH data changes from the start of the RCT phase to the end of the RCT phase. At each post baseline visit during the RCT phase, shift tables, by treatment group, will be produced based on the following categories (IGF-1 <1, IGF-1 between 1 and 1.3, IGF 1 ≥ 1.3). A shift table, by treatment group, summarizing GH (<1.0, 1.0 – 2.5, >2.5) from baseline to week 62/EOT will be presented.

In order to identify characteristics of patients on SRL treatments that would be predictive for a successful switch to oral treatment, if such exist, exploratory analyses will be conducted using all patients enrolled into the dose titration phase. Univariate and multivariate models will be explored to identify baseline characteristics associated with biochemical response at the end of the dose titration phase. In a previous study (CH-ACM-01), baseline IGF-1 level and dose of injection were shown to be predictive and these baseline characteristics will be looked at in addition to others. In addition, baseline characteristics of those patients who entered the RCT phase and those patients who did not enter the RCT phase, will be presented using descriptive statistics. Further details will be provided in the SAP.

[redacted]

8.4.8 Combination Phase Sub-study (in selected sites)

Each endpoint will be summarized at the end of the Combination phase sub-study using the CAS. The proportion and two-sided 95% CI of the proportion will be reported for each endpoint. If a patient is missing data, the LOCF approach will be used to impute these values, prior to determining the patients' response status. At each post baseline visit during the Combination sub-study, where baseline is the start of the Combination phase sub-study, shift tables will be produced based on the following categories (IGF-1 <1, IGF-1 between 1 and 1.3, IGF-1 ≥1.3). Additionally, the rate of change for IGF-1 will be estimated using a repeated

measures mixed effects model (without imputation of missing data). PRO and health economics outcomes collected in the Combination phase sub-study will be summarized over time. Further details of the analysis methodology for the Combination phase sub-study will be provided in the SAP.

8.4.9 Study Extension Phase

Data collected in the Study Extension phase will be summarized by time point using descriptive statistics. Analyses will be based on the EXT-AS. Missing data will be maintained as missing. Further details of the analysis methodology for the Study Extension phase will be provided in the SAP.

8.4.10 Health Economics Analyses

A stand-alone analysis plan will be developed for the exploratory health economic analyses. These analyses will be conducted outside of the main clinical study analysis in support of reimbursement submissions in various countries.

8.4.11 Safety Analysis

All safety endpoints will be summarized across each phase of the study separately using descriptive statistics. For the Run-in phase, the EAS will be used, for the RCT phase, the SAS will be used, for the Combination phase sub-study, the CAS will be used and for the Study Extension phase the EXT-AS will be used. Data in the Run-in phase and Combination phase sub-study will be summarized overall. Data in the RCT phase will be summarized by treatment arm and overall. Data in the Study Extension phase will be summarized overall and by group; (1) those on octreotide capsules and, (2) those on both octreotide capsules and cabergoline (Combination phase sub-study in selected sites).

8.4.11.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of patients reporting TEAEs, SAEs, TEAEs considered related to study medication and TEAEs leading to discontinuation from study medication will be reported by System Organ Class (SOC) and preferred term (PT). The TEAEs by maximum severity will also be reported by SOC and PT.

8.4.11.2 Laboratory Assessments

Descriptive statistics will be used to summarize the observed values and changes from baseline at each scheduled visit. A shift table (abnormal low, normal, abnormal high) will be provided for selected laboratory tests, to show changes from baseline.

8.4.11.3 Vital Signs

Descriptive statistics will be used to summarize the observed values and changes from baseline at each scheduled visit.

8.4.11.4 ECG, ECHO, Ultrasound and Physical Examination

Descriptive statistics will be used to summarize data at each scheduled visit. Shift tables will be used to show changes from baseline.

8.4.12 Interim Analyses

No interim analysis is planned, for the RCT phase and the Combination phase sub-study; however, data will be periodically reviewed by the IDMC for safety purposes. Interim analyses

of the Study Extension phase may be conducted for regulatory reporting purposes. These analyses will be conducted by the Sponsor, or its designee. As the Study Extension phase is an open label, single treatment phase of the study, to allow long-term safety data collection, no adjustments for multiplicity will be required. See Section 9.6.2

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:

- GCP: Consolidated Guideline (International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Brazil, 2013 (Appendix K)
- 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].

[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.

Patients will be required to sign an additional ICF to participate in the Study Extension phase.

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 data at regular intervals during the course of the study
- IDMC will review the data from the Combination phase sub-study (in selected sites) at regular intervals to ensure the safety of participating subjects
- IDMC will review the data from the Study Extension phase 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 awaited 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 eCRFs 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 eCRFs 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 provided by the Sponsor. 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). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for patients registered to the study should indicate date ICF was signed, participation in clinical protocol number and title, 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.

The study worksheets provided by the Sponsor may be used to capture all study data not recorded in the patient's medical record. Alternatively, the site may create and use their own study worksheets. Only a patient identification number will be used to identify the patient. 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 Remote Data Entry System, 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 system was configured based on requirements from the Sponsor. Paper source documents are to be retained to enable a reconstruction and evaluation of the study. No original observations will be entered directly into the computerized system. Source documents include the clinic or hospital patient files and study worksheets provided by the Sponsor. Data will be recorded in the study worksheets as appropriate to complete and/or clarify source data.

The design of a computerized system complies with all applicable regulatory requirements for record keeping and record retention in clinical trials (21 CFR Part 11 and ICH E6 Good Clinical Practice) to the same degree of confidence as is provided with paper systems. Clinical

Investigators must retain either the original or a copy of all source documents sent to a Sponsor or CRO, including query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly provides a means to locate and read the prior information. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). 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.

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

[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.

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 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.

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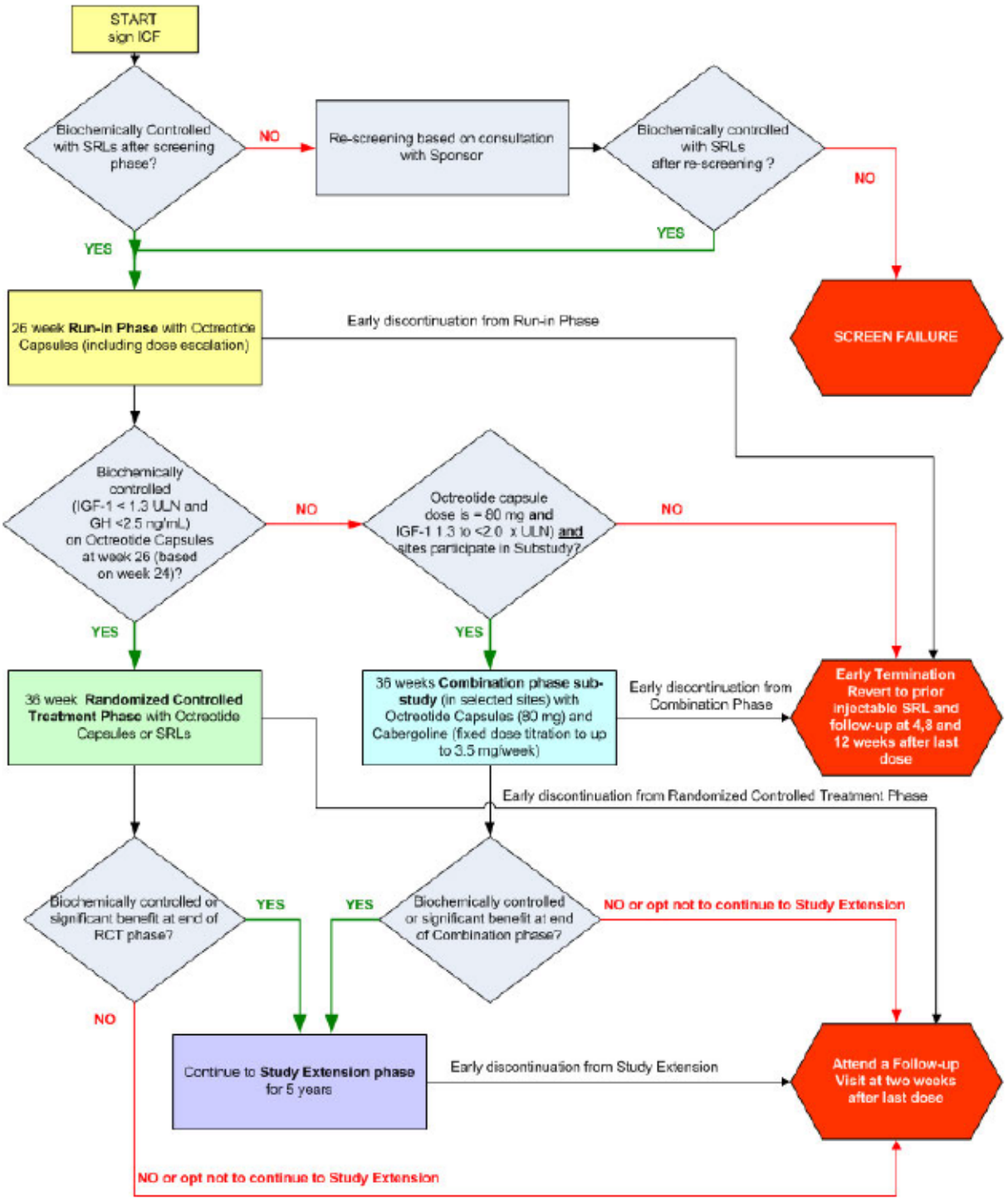
13 APPENDICES

Appendix A Study Decision Tree



Appendix B Schedule of Activities - Core Study – Screening and Run-in Phase

Parameter	Screening	Run-in Phase with octreotide capsules										
Study Week/Month	≥-28 days	Baseline[1]	Wk 1 ☎	Wk 2 ☎	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24[2]	Wk 25	Wk 26/End of Run-In
Visit Window (days)			±3	±3	±3	±3	±3	±3	±3	±3		-3 to +10
Signed informed consent	X											
Inclusion/exclusion criteria	X	X										X
Magnetic Resonance Imaging (MRI)[3]	X											
Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ)	X	X										X
EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L)	X	X										X
Work productivity questionnaire (WPAI)	X	X										X
Medical history/demographics and height	X											
Weight	X	X			X	X	X	X	X	X		X
Hematology[4] and chemistry[5]	X	X			X	X	X	X	X	X		X
Fasting Plasma Glucose (FPG)[6]	X											
Hemoglobin A_{1c} (HbA_{1c})	X											X
Thyroid-stimulating hormone (TSH), free T4		X										X
Lipid profile[7]		X										X
Urinalysis	X	X										X
Serum pregnancy for women with childbearing potential	X	X[8]										X
Urine pregnancy test for women with childbearing potential		X										
Growth Hormone (GH, mean integrated)[9]	X	X								X		X
Insulin-like growth factor 1 (IGF-1)	X	X			X	X	X	X	X	X		X
Abdominal (Gall bladder) ultrasound	X											X
Complete physical examination	X											
Acromegaly directed physical examination	X	X			X	X	X	X	X	X		X
Acromegaly symptoms - Index of Severity (AIS)	X	X	X	X	X	X	X	X	X	X		X

[1] Time from last dose should not exceed injection interval +3 days

[2] Week 24 biochemical response (IGF-1 and GH), will be used to determine response and inclusion into Randomized Controlled Treatment

[3] 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.

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

[5] Chemistry: glucose, total bilirubin (in case elevated direct and indirect bilirubin), albumin, Na, K, Ca, creatinine, BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; for additional safety assessment in case of abnormal liver function, see Section 7.6. Blood sampling will be done under overnight fasting conditions at all visits except week 24/26, where only a four-hour fast is required.

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

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

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

[9] GH: Five samples collected every 30 ± 5 minutes over two hours. At screening from time 0-2 hours (prior to SOC SRL administration, if planned), at Baseline before octreotide capsules administration from 0-2 hours, at all other visits 2-4 hours after octreotide capsules administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and the 2 hours after GH sampling)

Parameter	Screening	Run-in Phase with octreotide capsules										
Study Week/Month	≥-28 days	Baseline[1]	Wk 1 ☎	Wk 2 ☎	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24[2]	Wk 25	Wk 26/End of Run-In
Visit Window (days)			±3	±3	±3	±3	±3	±3	±3	±3		-3 to +10
Vital signs	X	X			X	X	X	X	X	X		X
12-lead electrocardiogram (ECG)	X	X										X
Echocardiogram (ECHO) - Verify availability within the last 6 months		X[10]										X[11]
Concomitant medication	X	X			X	X	X	X	X	X		X
Adverse events		X	X	X	X	X	X	X	X	X		X
Pre-randomization (not a site visit by patient)											X	
Randomization (call IVRS/IWRS)												X
Dispense study medication (call IVRS/IWRS)		X			X	X	X	X	X	X		X[12]
Study medication administration at the site		X								X		X
Dose titration[13]					X	X	X	X	X	X		
Drug administration instructions		X			X		X					X
Compliance assessment			X	X	X		X					X
Study medication accountability					X	X	X	X	X	X		X
Treatment Phase Completion form												X (Run-in)

[10] Only at selected sites participating in the Combination phase sub-study, an ECHO should be performed for all patients enrolling into the Combination sub-study. For those sites who cannot perform an ECHO from the time frame between week 25 (availability of week 24 IGF-1 and GH results) and week 26 (enrollment into the Combination sub-study phase), the ECHO may be performed, within the initial 12 weeks of the Run-in phase, so that results are available prior to study entry into the Combination phase sub-study

[11] Verify availability of Echocardiogram within the last six months for patients continuing to Combination phase sub-study (in selected sites).

[12] If patients are eligible to enter RCT phase, depending on randomization scheme, they can either receive octreotide capsules or SRL injections; if patients eligible to enter Combination phase sub-study (in selected sites), they will receive octreotide capsules + cabergoline

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

Appendix C Schedule of Activities – Core Study - Randomized Controlled Treatment (RCT) Phase

Parameter	Randomized Controlled Treatment (RCT) Phase												
Study Week/Month	Wk 26 (BL RCT[1])	Wk 30[2]	Wk 32[3]	Wk 34[2]	Wk 38	Wk 42[2]	Wk 44[3]	Wk 46[2]	Wk 50	Wk 54[2]	Wk 56[3]	Wk 58[2]	Wk 62/ EOT[4]
Visit Window (days)	-3 to +10	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Inclusion/exclusion criteria	X												X
Signed informed consent for Study Extension													X
ACRO-TSQ	X				X				X				X
EQ-5D-5L	X				X				X				X
WPAI	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[5] and chemistry[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin A_{1c}	X												X
TSH, free T4	X												X
Lipid profile[7]	X												X
Urinalysis	X												X
Serum pregnancy test if applicable	X												X
GH (mean integrated)[8]	X												X
IGF-1	X	X	X	X	X	X	X	X	X	X	X	X	X
Abdominal (Gall bladder) ultrasound	X												X
Acromegaly directed PE	X	X	X	X	X	X	X	X	X	X	X	X	X
AIS	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
Dispense study medication (call IVRS/IWRS)	X	X	X	X	X	X	X	X	X	X	X	X	X[9]
SRL at the site[10]	every 4,6,8 wks	every 4 wks	every 6 wks	every 4,8 wks	every 4,6 wks	every 4,8 wks	every 6 wks	every 4 wks	every 4,6, 8 wks	every 4 wks	every 6 wks	every 4, 8 wks	
Octreotide capsules at the site	X												X

[1] This visit can be week 26 of Run-in, visit window will be -3 to +10 days.
[2] These visits are not applicable to patients who receive their SRL injections every 6 weeks
[3] These visits are only applicable to patients with SRL injections every 6 weeks; they will attend visit week 32 instead of weeks 30 and 34, visit week 44 instead of weeks 42 and 46, and visit 56 instead of visit weeks 54 and 58)
[4] EOT procedures will also be performed in any case of Early treatment discontinuation
[5] Hematology: RBC, Hb, Htc, platelets, WBC and differential count
[6] Chemistry: glucose, total bilirubin (in case elevated direct and indirect bilirubin), albumin, Na, K, Ca, creatinine, BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; for additional safety assessment in case of abnormal liver function, see Section 7.6. Blood sampling will be done under overnight fasting conditions at all visits except week 62.
[7] Lipid profile = total cholesterol, triglycerides, HDL and LDL
[8] GH: Five samples collected every 30 ± 5 minutes over two hours, 2 to 4 hours after octreotide capsules administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and the 2 hours after GH sampling)
[9] Only to patients eligible to enter Study Extension phase. [redacted]
[10] For patients assigned to SRL arm, SRL injection frequency will vary. Patients who received SRL injections prior to screening every 4 or 5 weeks, will receive SRL injections every 4 weeks, patients who received injections every 6 or 7 weeks, will receive injections every 6 weeks and patients who received injections every 8 weeks will maintain injection frequency.

Parameter	Randomized Controlled Treatment (RCT) Phase												
Study Week/Month	Wk 26 (BL RCT[1])	Wk 30[2]	Wk 32[3]	Wk 34[2]	Wk 38	Wk 42[2]	Wk 44[3]	Wk 46[2]	Wk 50	Wk 54[2]	Wk 56[3]	Wk 58[2]	Wk 62/ EOT[4]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance assessment	X				X				X				X
Drug administration instructions	X				X				X				X[11]
Study medication accountability	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Phase Completion form	X (Run-in)												X (RCT)
[redacted]													[redacted]

ACRO-TSQ= Acromegaly Treatment Satisfaction Questionnaire; AIS = acromegaly symptoms - index of severity; BL= Baseline; EQ-5D-5L = EuroQol – 5 Dimensions – 5 Levels; EOT = end of treatment; GH = growth hormone; IGF-1 = insulin-like growth factor 1; IVRS/IWRS – Interactive voice/web response system; PE = physical exam; SRL = somatostatin receptor ligands; TSH = thyroid-stimulating hormone; Wk = week; WPAI = Work productivity questionnaire

[11] For patients assigned to SRL arm in RCT who are eligible to enter Study Extension and receive octreotide capsules

Appendix D Schedule of Activities – Combination Phase sub-study (in selected sites)

Parameter		Combination Phase sub-study (in selected sites)[1]										
Study Week/Month	Day 0[2]	Wk 2 ☎	Wk 4	Wk 6 ☎	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36/EOT[3]
Site visit window (days)			±3		±3	±3	±3	±3	±3	±3	±3	
Inclusion/exclusion criteria	X											X
Signed informed consent for Study Extension												X
ACRO-TSQ	X											X
EQ-5D-5L	X											X
WPAI	X											X
Weight	X		X		X	X	X	X	X	X	X	X
Hematology[4] and chemistry[5]	X		X		X	X	X	X	X	X	X	X
Hemoglobin A_{1c}	X											X
TSH, free T4	X											X
Lipid profile[6]	X											X
Urinalysis	X											X
Serum pregnancy (if applicable)	X											X
GH (mean integrated)[7]	X											X
IGF-1	X		X		X	X	X	X	X	X	X	X
Echocardiogram (ECHO)	X					X			X			X
Abdominal (Gall bladder) ultrasound	X											X
Vital signs	X		X		X	X	X	X	X	X	X	X
Acromegaly directed physical examination	X		X		X	X	X	X	X	X	X	X
AIS	X		X		X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X											X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication (call IVRS/IWRS)	X		X		X	X	X	X	X	X	X	
Cabergoline dose titration instructions[8]	X	X	X	X	X	X	X	X	X	X	X	

[1] In selected sites where the Combination phase sub-study is conducted, patients who fail to respond to octreotide capsules 80 mg for at least two weeks therapy during the course of the Run-in phase, or patients ineligible to enter the RCT phase on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 ≥ 1.3 × ULN) will be eligible to enter the Combination phase sub-study. These patients will receive co-administration of octreotide capsules 80 mg with cabergoline [redacted] for 36 weeks. The 36 weeks will parallel RCT duration.

[2] This visit is either week 26 for subjects not eligible to enter the RCT and eligible for Combination phase sub-study (based on week 24 biochemical response) or any earlier visit for subjects who discontinued treatment in the Run-in phase due to treatment failure as defined in the protocol. Visit window will be -3 to +10 days.

[3] EOT procedures will also be performed for patients who early discontinue treatment.

[4] Hematology: RBC, Hb, Htc, platelets and differential count.

[5] Chemistry glucose, total bilirubin (in case elevated direct and indirect bilirubin), albumin, Na, K, Ca, creatinine BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; for additional safety assessment in case of abnormal liver function, see Section 7.6. Blood sampling will be done under overnight fasting conditions at all visits except week 36.

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

[7] GH: Five samples collected every 30 ± 5 minutes over two hours. 2 to 4 hours after octreotide capsules administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and during the 2 hours sampling)

[8] Cabergoline should be taken at dinner; dose escalation every two weeks per protocol.

Parameter		Combination Phase sub-study (in selected sites)[1]									
Study Week/Month	Day 0[2]	Wk 2 ☎	Wk 4	Wk 6 ☎	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36/EOT[3]
Site visit window (days)			±3		±3	±3	±3	±3	±3	±3	±3	
Octreotide capsules at the site	X											X
Study medication accountability	X		X		X	X	X	X	X	X	X	X
Compliance assessment		X		X								
Acromegaly symptoms by phone												
Treatment Phase Completion form												X (Combination)

ACRO-TSQ= Acromegaly Treatment Satisfaction Questionnaire; AIS = acromegaly symptoms - index of severity; EQ-5D-5L = EuroQol – 5 Dimensions – 5 Levels; EOT = end of treatment; GH = growth hormone; IGF-1 = insulin-like growth factor 1; IVRS/IWRS – Interactive voice/web response system; TSH = thyroid-stimulating hormone; Wk = week; WPAI = Work productivity questionnaire

Appendix E Schedule of Activities – [redacted] Study Extension and Follow-up Phases

Parameter		[redacted]	Study Extension Phase[2]		FU Phase[3]
Study Week/Month	Wk 0/RCT Week 62[4]		Wk 1 ☎[6]		
Visit window (days)				(±10)	(±3)
[redacted]	X				
Inclusion/exclusion criteria	X				
Signed informed consent	X				
ACRO-TSQ				Months 3, 6, 12 & every 12 M	Month 3 only[8]
EQ-5D-5L					
WPAI					
Weight				Months 3,6,9,12 and every 6 M	
Hematology[9] and chemistry[10]				Months 3,6,9,12 and every 6 M	
Hemoglobin A_{1c}				Months 6, 12, & every 12 M	
TSH, free T4					
Lipid profile[11]					

[1] Applicable for patients who completed the RCT phase on octreotide capsules with IGF-1< 1.3 × ULN at their last assessment (e.g. week 58 or an unscheduled visit) or are in the Extension Phase with IGF-1< 1.3 × ULN at their last assessment.

[2] During the first year of the Study Extension phase, clinic visits will be scheduled to occur every 12 weeks (±10 days). Thereafter, in-clinic visits will occur every 24 weeks (±10 days), with dispensing visits every 12 weeks (±10 days). .

[3] Follow-up - for patients who prematurely discontinued the study (any phase), or patient ineligible to enter RCT phase or Combination phase sub-study or patient ineligible or not opting into the [redacted] study Extension phase will be done at +4, +8 and +12 weeks post last dose of study medication; patients who premature discontinue from RCT phase or Study Extension phase will undergo a Follow-up visit 12 weeks after last dose of study medication.

[redacted]

[6] Patients who switched from SRLs during RCT phase to octreotide capsules will be contacted by phone a week after first dose.

[7] If continue to Study Extenstion

[8] Applicable only for patients discontinuing the study during the Run-in or do not continue into the RCT phase.

[9] Hematology: RBC, Hb, Htc, platelets and differential count.

[10] Chemistry glucose, total bilirubin (in case elevated direct and indirect bilirubin), albumin, Na, K, Ca, creatinine BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; for additional safety assessment in case of abnormal liver function, see Section 7.6. Blood sampling will be done under overnight fasting conditions at all visits.

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

Parameter		[redacted]	Study Extension Phase[2]		FU Phase[3]
Study Week/Month	Wk 0/RCT Week 62[4]		Wk 1 ☎[6]		
Visit window (days)				(±10)	(±3)
Urinalysis				Months 3,6,9,12 and every 6 M	
Serum pregnancy (if applicable)				every 6 M	
GH (mean integrated)[12]				every 12M & last visit	Month 3 only
IGF-1				Months 3, 6 and every 6 M	
Oral glucose tolerance test (OGTT)[13]					
Confirmation of disease activity					
Echocardiogram (ECHO)				Months 6,12 and every 12 M[14]	
Vital signs				Months 3,6,9,12 and every 6 M	X
Acromegaly directed physical examination				Months 3,6,9,12 and every 6 M	X
AIS				Months 3,6,9,12 and every 6 M	X
12-lead electrocardiogram (ECG)				Months 6 and 12	X
Concomitant medication			X	Months 3,6,9,12 and every 6 M	X
Adverse events			X	Months 3,6,9,12 and every 6 M	X
Dispense study medication (call IVRS/IWRS)				Every 3M	
Octreotide capsules at the site				Every 12 M	
Drug administration instruction				Months 3,6,9,12	

[12] GH: Five samples collected every 30 ± 5 minutes over two hours. 2 to 4 hours after octreotide capsules administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and during the 2 hours sampling).

[13] Blood sampling for OGTT will be done under fasting conditions (at least eight hours). Five samples every 30 minutes (0, 30, 60, 90 and 120 minutes) will be collected to assess glucose and GH levels, following 75 g glucose load. If OGTT is contraindicated, average GH of 7 samples will be taken within 3 hours ≥ 2.5ng/mL.

[14] Cardiac ECHO will be done at Month 6 and 12 and every 12 months only for patients on combination of octreotide capsules and cabergoline (Combination phase sub-study in selected sites).

Parameter		[redacted]	Study Extension Phase[2]		FU Phase[3]
Study Week/Month	Wk 0/RCT Week 62[4]		Wk 1 ☎[6]		
Visit window (days)				(±10)	(±3)
				and every 6 M	
Study medication accountability				Every 3M	
Compliance assessment			X	X	
Acromegaly symptoms by phone			X		
[redacted]					

Appendix F Labeling Information for Somatostatin Receptor Ligands and Cabergoline

Labels / package inserts for octreotide for injection (sc and LAR), lanreotide for injection (Autogel or Depot), and Cabergoline will be attached separately.

Octreotide for Injection
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019667s058,021008s023lbl.pdf

Lanreotide for Injection (Autogel or Depot)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022074s003lbl.pdf

Cabergoline
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020664s011lbl.pdf

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix H EuroQol – 5 Dimensions – 5 Levels Health Outcome questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort □ ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

We would like to know how good or bad your health is TODAY.

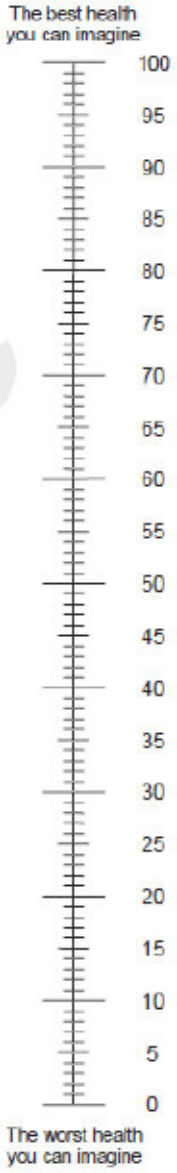
This scale is numbered from 0 to 100.

100 means the <u>best</u> health you can imagine.
0 means the <u>worst</u> health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix I Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

The Case Report Form will include the WPAI questionnaire, followed by two supplemental questions.

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)		
Please fill in the blanks or circle a number, as indicated.		
1.	Are you currently employed (working for pay)? *If NO, check "NO" and skip to question 6.*	_____ NO _____ YES
The next questions are about the **past seven days**, ***not including today***.		
2.	During the past seven days, how many hours did you miss from work because of problems associated with ACROMEGALY? *Include hours you missed on sick days, times you went in late, left early, etc., because of ACROMEGALY. Do not include time you missed to participate in this study.*	_____ HOURS
3.	During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?	_____HOURS
4.	During the past seven days, how many hours did you actually work?	_____HOURS *(If "0", skip to question 6.)*
5.	During the past seven days, how much did your ACROMEGALY affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If ACROMEGALY affected your work only a little, choose a low number. Choose a high number if ACROMEGALY affected your work a great deal.* Consider only how much ACROMEGALY affected productivity while you were working. ACROMEGALY had no effect on my work — 0 1 2 3 4 5 6 7 8 9 10 — ACROMEGALY completely prevented me from working CIRCLE A NUMBER	
6.	During the past seven days, how much did your ACROMEGALY affect your ability to do your regular daily activities, other than work at a job? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If ACROMEGALY affected your activities only a little, choose a low number. Choose a high number if ACROMEGALY affected your activities a great deal.* Consider only how much ACROMEGALY affected your ability to do your regular daily activities, other than work at a job. ACROMEGALY had no effect on my daily activities — 0 1 2 3 4 5 6 7 8 9 10 — ACROMEGALY completely prevented me from doing my daily activities	

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)	
	CIRCLE A NUMBER

Two supplemental questions focusing on the productivity loss and daily activity impairment TODAY due to the study visit can be added to the standard WPAI:

7.	If you are currently employed (working for pay), how many hours did you miss from work because of **today's clinic visit?** _____HOURS ☐ Not applicable as I am not currently employed
8.	How many hours does it take you for completing **today's clinic visit**? (including the time spent for traveling and with the visit) _____HOURS

WPAI:SHP V2.0 (US English)
Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993; 4(5):353-365.

Appendix J Acromegaly Symptoms - Index of Severity

Acromegaly symptom	Severity Index			
	0	1	2	3
	No Symptoms	Mild	Moderate	Severe
Headache				
Swelling of extremities				
Joint pain				
Sweating				
Fatigue				

Appendix K 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.

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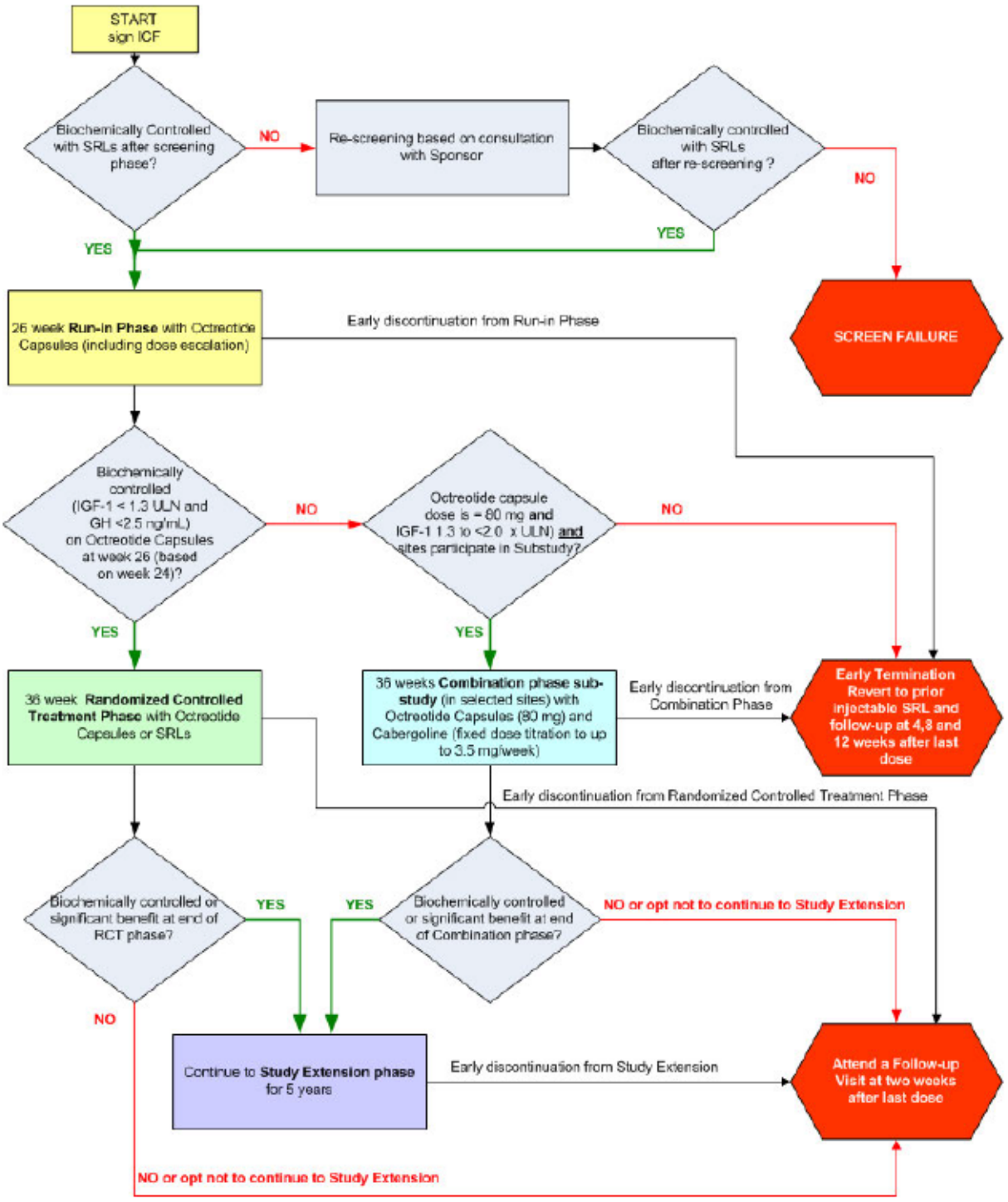
Appendix A Study Decision Tree



Appendix B Schedule of Activities - Core Study – Screening and Run-in Phase

Parameter	Screening	Run-in Phase with octreotide capsules										
Study Week/Month	≥-28 days	Baseline[1]	Wk 1 ☎	Wk 2 ☎	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24[2]	Wk 25	Wk 26/End of Run-In
Visit Window (days)			±3	±3	±3	±3	±3	±3	±3	±3		-3 to +10
Signed informed consent	X											
Inclusion/exclusion criteria	X	X										X
Magnetic Resonance Imaging (MRI) [3]	X											
Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ)	X	X										X
EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L)	X	X										X
Work productivity questionnaire (WPAI)	X	X										X
Medical history/demographics and height	X											
Weight	X	X			X	X	X	X	X	X		X
Hematology[4] and chemistry[5]	X	X			X	X	X	X	X	X		X
Fasting Plasma Glucose (FPG)[6]	X											
Hemoglobin A_{1c} (HbA_{1c})	X											X
Thyroid-stimulating hormone (TSH), free T4		X										X
Lipid profile[7]		X										X
Urinalysis	X	X										X
Serum pregnancy for women with childbearing potential	X	X[8]										X
Urine pregnancy test for women with childbearing potential		X										
Growth Hormone (GH, mean integrated)[9]	X	X								X		X
Insulin-like growth factor 1 (IGF-1)	X	X			X	X	X	X	X	X		X
Abdominal (Gall bladder) ultrasound	X											X
Complete physical examination	X											
Acromegaly directed physical examination	X	X			X	X	X	X	X	X		X
Acromegaly symptoms - Index of Severity (AIS)	X	X	X	X	X	X	X	X	X	X		X

[1] Time from last dose should not exceed injection interval +3 days

[2] Week 24 biochemical response (IGF-1 and GH), will be used to determine response and inclusion into Randomized Controlled Treatment

[3] 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.

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

[5] Chemistry: glucose, total bilirubin (in case elevated direct and indirect bilirubin), albumin, Na, K, Ca, creatinine, BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; for additional safety assessment in case of abnormal liver function, see Section 7.6. Blood sampling will be done under overnight fasting conditions at all visits except week 24/26, where only a four-hour fast is required.

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

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

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

[9] GH: Five samples collected every 30 ± 5 minutes over two hours. At screening from time 0-2 hours (prior to SOC SRL administration, if planned), at Baseline before octreotide capsules administration from 0-2 hours, at all other visits 2-4 hours after octreotide capsules administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and the 2 hours after GH sampling)

Parameter	Screening	Run-in Phase with octreotide capsules										
Study Week/Month	≥-28 days	Baseline[1]	Wk 1 ☎	Wk 2 ☎	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24[2]	Wk 25	Wk 26/End of Run-In
Visit Window (days)			±3	±3	±3	±3	±3	±3	±3	±3		-3 to +10
Vital signs	X	X			X	X	X	X	X	X		X
12-lead electrocardiogram (ECG)	X	X										X
Echocardiogram (ECHO) - Verify availability within the last 6 months		X[10]										X[11]
Concomitant medication	X	X			X	X	X	X	X	X		X
Adverse events		X	X	X	X	X	X	X	X	X		X
Pre-randomization (not a site visit by patient)											X	
Randomization (call IVRS/IWRS)												X
Dispense study medication (call IVRS/IWRS)		X			X	X	X	X	X	X		X[12]
Study medication administration at the site		X								X		X
Dose titration[13]					X	X	X	X	X	X		
Drug administration instructions		X			X		X					X
Compliance assessment			X	X	X		X					X
Study medication accountability					X	X	X	X	X	X		X
Treatment Phase Completion form												X (Run-in)

[10] Only at selected sites participating in the Combination phase sub-study, an ECHO should be performed for all patients enrolling into the Combination sub-study. For those sites who cannot perform an ECHO from the time frame between week 25 (availability of week 24 IGF-1 and GH results) and week 26 (enrollment into the Combination sub-study phase), the ECHO may be performed, within the initial 12 weeks of the Run-in phase, so that results are available prior to study entry into the Combination phase sub-study

[11] Verify availability of Echocardiogram within the last six months for patients continuing to Combination phase sub-study (in selected sites).

[12] If patients are eligible to enter RCT phase, depending on randomization scheme, they can either receive octreotide capsules or SRL injections; if patients eligible to enter Combination phase sub-study (in selected sites), they will receive octreotide capsules + cabergoline

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

Appendix D Schedule of Activities – Combination Phase sub-study (in selected sites)

Parameter		Combination Phase sub-study (in selected sites)[1]										
Study Week/Month	Day 0[2]	Wk 2 ☎	Wk 4	Wk 6 ☎	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36/EOT[3]
Site visit window (days)			±3		±3	±3	±3	±3	±3	±3	±3	
Inclusion/exclusion criteria	X											X
Signed informed consent for Study Extension												X
ACRO-TSQ	X											X
EQ-5D-5L	X											X
WPAI	X											X
Weight	X		X		X	X	X	X	X	X	X	X
Hematology[4] and chemistry[5]	X		X		X	X	X	X	X	X	X	X
Hemoglobin A_{1c}	X											X
TSH, free T4	X											X
Lipid profile[6]	X											X
Urinalysis	X											X
Serum pregnancy (if applicable)	X											X
GH (mean integrated)[7]	X											X
IGF-1	X		X		X	X	X	X	X	X	X	X
Echocardiogram (ECHO)	X					X			X			X
Abdominal (Gall bladder) ultrasound	X											X
Vital signs	X		X		X	X	X	X	X	X	X	X
Acromegaly directed physical examination	X		X		X	X	X	X	X	X	X	X
AIS	X		X		X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X											X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication (call IVRS/IWRS)	X		X		X	X	X	X	X	X	X	
Cabergoline dose titration instructions[8]	X	X	X	X	X	X	X	X	X	X	X	

[1] In selected sites where the Combination phase sub-study is conducted, patients who fail to respond to octreotide capsules 80 mg for at least two weeks therapy during the course of the Run-in phase, or patients ineligible to enter the RCT phase on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 ≥ 1.3 × ULN) will be eligible to enter the Combination phase sub-study. These patients will receive co-administration of octreotide capsules 80 mg with cabergoline [redacted] for 36 weeks. The 36 weeks will parallel RCT duration.

[2] This visit is either week 26 for subjects not eligible to enter the RCT and eligible for Combination phase sub-study (based on week 24 biochemical response) or any earlier visit for subjects who discontinued treatment in the Run-in phase due to treatment failure as defined in the protocol. Visit window will be -3 to +10 days.

[3] EOT procedures will also be performed for patients who early discontinue treatment.

[4] Hematology: RBC, Hb, Htc, platelets and differential count.

[5] Chemistry glucose, total bilirubin (in case elevated direct and indirect bilirubin), albumin, Na, K, Ca, creatinine BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; for additional safety assessment in case of abnormal liver function, see Section 7.6. Blood sampling will be done under overnight fasting conditions at all visits except week 36.

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

[7] GH: Five samples collected every 30 ± 5 minutes over two hours. 2 to 4 hours after octreotide capsules administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and during the 2 hours sampling)

[8] Cabergoline should be taken at dinner; dose escalation every two weeks per protocol.

Parameter		Combination Phase sub-study (in selected sites)[1]									
Study Week/Month	Day 0[2]	Wk 2 ☎	Wk 4	Wk 6 ☎	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36/EOT[3]
Site visit window (days)			±3		±3	±3	±3	±3	±3	±3	±3	
Octreotide capsules at the site	X											X
Study medication accountability	X		X		X	X	X	X	X	X	X	X
Compliance assessment		X		X								
Acromegaly symptoms by phone												
Treatment Phase Completion form												X (Combination)

ACRO-TSQ= Acromegaly Treatment Satisfaction Questionnaire; AIS = acromegaly symptoms - index of severity; EQ-5D-5L = EuroQol – 5 Dimensions – 5 Levels; EOT = end of treatment; GH = growth hormone; IGF-1 = insulin-like growth factor 1; IVRS/IWRS – Interactive voice/web response system; TSH = thyroid-stimulating hormone; Wk = week; WPAI = Work productivity questionnaire

Appendix E Schedule of Activities – [redacted] Study Extension and Follow-up Phases

Parameter		[redacted]	Study Extension Phase[2]		FU Phase[3]
Study Week/Month	Wk 0/RCT Week 62[4]		Wk 1 ☎[6]		
Visit window (days)				(±10)	(±3)
[redacted]	X				
Inclusion/exclusion criteria	X				
Signed informed consent	X				
ACRO-TSQ				Months 3, 6, 12 & every 12 M	Month 3 only[8]
EQ-5D-5L					
WPAI					
Weight				Months 3,6,9,12 and every 6 M	
Hematology[9] and chemistry[10]				Months 3,6,9,12 and every 6 M	
Hemoglobin A_{1c}				Months 6, 12, & every 12 M	
TSH, free T4					
Lipid profile[11]					

[1] Applicable for patients who completed the RCT phase on octreotide capsules with IGF-1< 1.3 × ULN at their last assessment (e.g. week 58 or an unscheduled visit) or are in the Extension Phase with IGF-1< 1.3 × ULN at their last assessment.

[2] During the first year of the Study Extension phase, clinic visits will be scheduled to occur every 12 weeks (±10 days). Thereafter, in-clinic visits will occur every 24 weeks (±10 days), with dispensing visits every 12 weeks (±10 days). .

[3] Follow-up - for patients who prematurely discontinued the study (any phase), or patient ineligible to enter RCT phase or Combination phase sub-study or patient ineligible or not opting into the [redacted] study Extension phase will be done at +4, +8 and +12 weeks post last dose of study medication; patients who premature discontinue from RCT phase or Study Extension phase will undergo a Follow-up visit 12 weeks after last dose of study medication.

[redacted]

[6] Patients who switched from SRLs during RCT phase to octreotide capsules will be contacted by phone a week after first dose.

[7] If continue to Study Extenstion

[8] Applicable only for patients discontinuing the study during the Run-in or do not continue into the RCT phase.

[9] Hematology: RBC, Hb, Htc, platelets and differential count.

[10] Chemistry glucose, total bilirubin (in case elevated direct and indirect bilirubin), albumin, Na, K, Ca, creatinine BUN, phosphorus, uric acid, GOT, GPT, ALP, GGT, LDH, CPK, total protein; for additional safety assessment in case of abnormal liver function, see Section 7.6. Blood sampling will be done under overnight fasting conditions at all visits.

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

Parameter		[redacted]	Study Extension Phase[2]		FU Phase[3]
Study Week/Month	Wk 0/RCT Week 62[4]		Wk 1 ☎[6]		
Visit window (days)				(±10)	(±3)
Urinalysis				Months 3,6,9,12 and every 6 M	
Serum pregnancy (if applicable)				every 6 M	
GH (mean integrated)[12]				every 12M & last visit	Month 3 only
IGF-1				Months 3, 6 and every 6 M	
Oral glucose tolerance test (OGTT)[13]					
Confirmation of disease activity					
Echocardiogram (ECHO)				Months 6,12 and every 12 M[14]	
Vital signs				Months 3,6,9,12 and every 6 M	X
Acromegaly directed physical examination				Months 3,6,9,12 and every 6 M	X
AIS				Months 3,6,9,12 and every 6 M	X
12-lead electrocardiogram (ECG)				Months 6 and 12	X
Concomitant medication			X	Months 3,6,9,12 and every 6 M	X
Adverse events			X	Months 3,6,9,12 and every 6 M	X
Dispense study medication (call IVRS/IWRS)				Every 3M	
Octreotide capsules at the site				Every 12 M	
Drug administration instruction				Months 3,6,9,12	

[12] GH: Five samples collected every 30 ± 5 minutes over two hours. 2 to 4 hours after octreotide capsules administration. GH assessment should be done under fasting conditions (patients to fast 4 hours prior to and during the 2 hours sampling).

[13] Blood sampling for OGTT will be done under fasting conditions (at least eight hours). Five samples every 30 minutes (0, 30, 60, 90 and 120 minutes) will be collected to assess glucose and GH levels, following 75 g glucose load. If OGTT is contraindicated, average GH of 7 samples will be taken within 3 hours ≥ 2.5ng/mL.

[14] Cardiac ECHO will be done at Month 6 and 12 and every 12 months only for patients on combination of octreotide capsules and cabergoline (Combination phase sub-study in selected sites).

Appendix F Labeling Information for Somatostatin Receptor Ligands and Cabergoline

Labels / package inserts for octreotide for injection (sc and LAR), lanreotide for injection (Autogel or Depot), and Cabergoline will be attached separately.

Octreotide for Injection
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019667s058,021008s023lbl.pdf

Lanreotide for Injection (Autogel or Depot)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022074s003lbl.pdf

Cabergoline
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020664s011lbl.pdf

Appendix H EuroQol – 5 Dimensions – 5 Levels Health Outcome questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort □ ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

We would like to know how good or bad your health is TODAY.

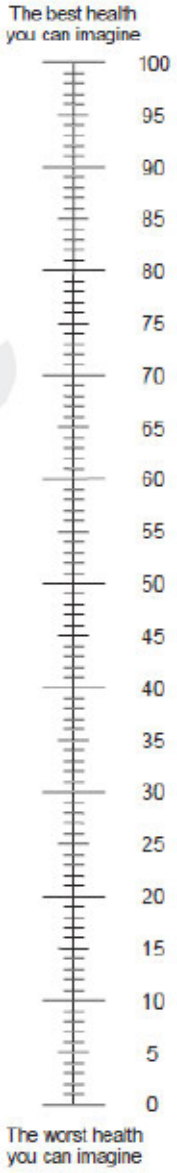
This scale is numbered from 0 to 100.

100 means the <u>best</u> health you can imagine.
0 means the <u>worst</u> health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix J Acromegaly Symptoms - Index of Severity

Acromegaly symptom	Severity Index			
	0	1	2	3
	No Symptoms	Mild	Moderate	Severe
Headache				
Swelling of extremities				
Joint pain				
Sweating				
Fatigue				

Appendix K 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.