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## CLINICAL STUDY PROTOCOL

### A PHASE 3, OPEN-LABEL, RANDOMIZED, MULTICENTER, 12 MONTHS, EFFICACY AND SAFETY STUDY OF WEEKLY MOD-4023 COMPARED TO DAILY GENOTROPIN<sup>®</sup> THERAPY IN PRE-PUBERTAL CHILDREN WITH GROWTH HORMONE DEFICIENCY

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**Protocol Number (No.):** CP-4-006 Amendment 2, 27-APR-2018

**IND No.:** **CCI** **EudraCT No.:** 2016-003874-42

**Safety Medical Officer:** PPD [REDACTED], MD

**Statistician:** PPD [REDACTED],  
PPD [REDACTED]

#### Confidentiality Statement

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**PROTOCOL SIGNATURE PAGE**

**Protocol Title** A phase 3, open-label, randomized, multicenter, 12 months, efficacy and safety study of weekly MOD-4023 compared to daily Genotropin® - therapy in pre-pubertal children with growth hormone deficiency

**Protocol Identification** CP-4-006 Amendment 2, 27-APR-2018

**Study Phase** 3

**Sponsor** OPKO Biologics Ltd.  
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**Sponsor Representatives**

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

PPD [Redacted] Signature \_\_\_\_\_ Date April 30, 2018  
PPD [Redacted] \_\_\_\_\_  
PPD [Redacted] PhD, \_\_\_\_\_  
PPD [Redacted] Transition Therapeutics Corp., ULC, a subsidiary of OPKO Health, LLC.

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PPD [Redacted] OPKO Pharmaceuticals, Inc. a subsidiary of OPKO Health, LLC.

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**Principal Investigator (PI)**

By signing below, I, the PI approve the protocol and agree to conduct the clinical study according to all stipulations of the protocol as specified in both the clinical and administrative sections. I agree to comply with the ICH-GCP, local regulatory authority's guidelines for the conduct of clinical trials, World Medical Association Declaration of Helsinki (and relevant updates) and applicable 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 OBL.

Investigator Signature

Date

Name

Institution

City, Country

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**PROTOCOL SYNOPSIS**

<b>STUDY TITLE</b>	A phase 3, open-label, randomized, multicenter, 12 months, efficacy and safety study of weekly MOD-4023 compared to daily Genotropin <sup>®</sup> therapy in pre-pubertal children with growth hormone deficiency.		
<b>PROTOCOL NO.</b>	CP-4-006, Amendment 2, 27-APR-2018		
<b>IND NO.</b>	CCI	<b>EUDRACT NO.</b>	2016-003874-42
<b>CLINICAL SITES</b>	The study will be conducted in approximately 30-40 countries at approximately 200 clinical sites.		
<b>STUDY PHASE</b>	3		
<b>THERAPEUTIC INDICATION</b>	Treatment of children with growth failure due to growth hormone deficiency (GHD).		
<b>STUDY PRIMARY OBJECTIVE</b>	To demonstrate that weekly MOD-4023 administration is non-inferior to daily Genotropin administration.		
<b>STUDY SECONDARY OBJECTIVES</b>	<ul style="list-style-type: none"> <li>• To evaluate the safety and tolerability of weekly MOD-4023 administration.</li> <li>• To demonstrate successful operation (single injection) of the MOD-4023 single patient use, multi-dose, disposable pre-filled pen (PEN).</li> <li>• Evaluation of participant and observer feedback on MOD-4023 device usability.</li> <li>• To confirm the correct operation of devices returned for evaluation.</li> </ul>		
<b>LT-OLE OBJECTIVE</b>	To demonstrate long term (LT) safety and efficacy of MOD-4023 in an open-label extension (OLE).		
<b>OTHER OBJECTIVES</b>	To evaluate the effect of weekly MOD-4023 and daily Genotropin <sup>®</sup> administration on quality of life (QoL), as measured by the QoLISSY (Quality of Life in Short Stature Youth) in a specific number of countries (determined by availability of validated translated tools) during the first 12 months of treatment.		
<b>STUDY DESIGN</b>	<p>The study will initially consist of a 12 month, open-label, randomized, active controlled, parallel group study comparing the efficacy and safety of weekly MOD-4023 to daily growth hormone (GH), Genotropin<sup>®</sup>. Patients will enter a long term open-label extension to demonstrate continued safety and efficacy of MOD-4023 treatment (all patients) after successful completion of the first 12 months of treatment.</p> <p><b>Initial Study Period (main study):</b> After a screening period lasting up to 8 weeks (wks), patients meeting the eligibility criteria, as approved by the Global Study Medical Monitor (MM), will be randomized in a 1:1 ratio to MOD-4023 or Genotropin<sup>®</sup> for 12 months.</p> <p>If the patient's screening process is delayed because of a benign illness or unforeseen benign condition (i.e. pharyngitis, viral gastrointestinal (GI) problems, minor accident or trauma, etc.) or a technical issue that is related to screening procedures (for example, delays with lab results), extra time will be added to the duration of the screening period, but not in excess of an additional 4 wks (total of 12 wks).</p> <p>An independent and external Data and Safety Monitoring Board (DSMB) will review the key safety data approximately every 4 months or on <i>ad hoc</i> basis.</p>		

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	<p><b>LT-OLE Period (LT-OLE):</b> Patients who received MOD-4023 during the main study will continue in the LT-OLE with the same dose (mg/kg/wk) of MOD-4023. Patients who received Genotropin® during the main study will be switched to MOD-4023 and will begin treatment with a dose of 0.66 mg/kg/wk beginning no less than one day after cessation of Genotropin® treatment. The key safety data will be reviewed by an independent DSMB approximately every 6 months. During the entire study, doses will be adjusted based on the patients' body weight every 3 months. The dose may be decreased or maintained for safety reasons according to the pre-defined dose-adjustment criteria (based on the severity of adverse events [AEs] or repeated, elevated levels of insulin-like growth factor -1 [IGF-1] Standard Deviation Score [SDS]).</p>
<p><b>STUDY PROCEDURES</b></p>	<p><b>Visit 1 - Screening Period (Day -56 to Day -1)</b></p> <p>The Screening period will last up to 8 wks<sup>a</sup> and can be conducted over several visits prior to eligibility approval and randomization. Screening visits are intended to collect current clinical data and to perform all required investigations needed to establish a patient's eligibility for the study. Prior to any study-specific investigations, written assent from pediatric patients (where applicable based on age and country) and consent from the parent(s) or legal guardian(s) will be obtained.</p> <p>The following assessments will be conducted at these screening visits:</p> <ul style="list-style-type: none"> <li>• Inclusion/exclusion verification.</li> <li>• Parental heights<sup>b</sup> (Ht), and patients' Ht, Ht SDS, Ht velocity (HV) and HV SDS.</li> <li>• Body weight and body mass index (BMI) SDS.</li> <li>• Medical history, including a description of pituitary deficiencies, concomitant and previous medications.</li> <li>• Overall health status assessment, including complete physical examination and vital signs.</li> <li>• Pubertal status (according to Tanner stages).</li> <li>• Bone age (BA) determination according to the method of Greulich-Pyle using a central BA reader<sup>c</sup>.</li> <li>• Assessment of biochemical markers and stimulation tests<sup>d</sup>:             <ul style="list-style-type: none"> <li>○ Two different GH stimulation (provocation) tests: insulin tolerance test (ITT) (with serum cortisol response to</li> </ul> </li> </ul>

<sup>a</sup> If the patient's screening process is delayed because of a benign illness or unforeseen benign condition (i.e. pharyngitis, viral GI problems, minor accident or trauma, etc.) or a technical issue that is related to screening procedures (for example, delays with laboratory results), extra time will be added to the duration of the screening period, but not in excess of an additional 4 wks (total of 12 wks screening period).

<sup>b</sup> It's recommended that parents' Ht be measured at the site. If measured parental Ht is not available an estimate should be provided by the parent.

<sup>c</sup> Historical BA assessment might be accepted if it was done according to the method of Greulich-Pyle no more than 6 months prior to the informed consent form (ICF) signature date. If the patient is eligible, the BA must be repeated at Visit 2 prior to dosing. The Visit 2 scan will be the baseline scan for these patients.

<sup>d</sup> Local, documented provocation tests that were performed prior to ICF signature, might be accepted by the global study MM according to his/her judgment.

<sup>e</sup> ITT with serum cortisol response to hypoglycemia is adequate for assessment of adrenal insufficiency and no ACTH stimulation test is required if such results are available. Historical ACTH test is acceptable.

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	<p>hypoglycemia if insulin stimulation test is chosen)/arginine test/clonidine test/glucagon test/L-dopa test.</p> <ul style="list-style-type: none"> <li>○ Analysis of serum GH levels (and glucose and serum cortisol if ITT is performed) may be performed by local laboratories and must be provided for global MM review and approval.</li> <li>○ Assessment of morning cortisol (at 8 am ± 1 hour)             <ul style="list-style-type: none"> <li>▪ If morning cortisol is below 190 nmol/L (7 µg/dL), test for adrenal insufficiency will be required – low dose adrenocorticotrophic hormone (ACTH)<sup>e</sup> or corticotropin releasing hormone (CRH) stimulation test (only if the patient was not previously assessed for the hypothalamus-pituitary-adrenal axis or has been diagnosed with adrenal insufficiency).</li> </ul> </li> <li>○ Assessment of IGF-1, IGF-1 SDS, IGF binding protein-3 (IGFBP-3) and IGFBP-3 SDS levels.</li> </ul> <ul style="list-style-type: none"> <li>• Assessment of anti-human GH (hGH) antibody (Ab) levels.</li> <li>• Assessments of routine safety: chemistry, hematology and urinalysis.</li> <li>• Assessment of thyroid function tests (thyroid stimulating hormone [TSH], free thyroxine [FT4]).</li> <li>• Assessment of glucose metabolism (overnight fasting insulin, overnight fasting glucose and glycated hemoglobin [HbA1C]).</li> <li>• Head magnetic resonance imaging<sup>a</sup> (MRI), if possible with contrast or computed tomography (CT) scan.</li> <li>• Assessment of karyotype in girls<sup>b</sup>.</li> <li>• SHOX (short stature homeobox) gene evaluation<sup>c</sup>. Patients with confirmed multiple pituitary hormone deficiencies or confirmed structurally abnormal pituitary gland or other anatomical reasons for GHD do not require SHOX gene evaluation. SHOX gene evaluation is mandatory for isolated GHD with normal brain MRI.</li> </ul> <p>All laboratory assessments are performed by a central laboratory unless stated otherwise.</p> <p>Key data and all test results obtained during screening will be reviewed by the Global Study MM and eligibility will be confirmed <u>prior to randomization</u> of each patient. It is recommended that the Investigator randomize the patient within 7 days of confirmed eligibility.</p> <p><b>Main Study Treatment Period (Day 1/Baseline to Month 12)</b></p> <p>Eligible patients will be randomized (centralized randomization within each region) in a 1:1 fashion to receive either weekly MOD-4023 or daily Genotropin<sup>®</sup> for 12 months.</p> <p>The following 3 stratification factors will be applied when randomizing patients to the treatment groups:</p>
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<sup>a</sup> Historical MRI or CT is permitted if within 12 months prior to ICF signature date. For GHD associated with a congenital central nervous system (CNS) defect, the global study MM could allow for use of the historic MRI or CT > 12 months old.

<sup>b</sup> Historical karyotype data and chromosomal microarray data are acceptable.

<sup>c</sup> Historical data is acceptable.

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	<ul style="list-style-type: none"> <li>• Region:             <ol style="list-style-type: none"> <li>1. Western Europe, Israel, Australia, New Zealand, Canada and USA;</li> <li>2. Central and Eastern Europe, Greece, Turkey, Latin America and Asia, except for India and Vietnam;</li> <li>3. India and Vietnam.</li> </ol> </li> <li>• Peak GH levels (<math>\leq 3</math> ng/mL; <math>&gt;3</math> to <math>\leq 7</math> ng/mL; and <math>&gt;7</math> to <math>\leq 10</math> ng/mL). The proportion of patients with peak GH levels <math>&gt;7</math> to <math>\leq 10</math> ng/mL, will be capped at 35-40% of total sample-size, in the randomization scheme.</li> <li>• Chronological age (CA) (<math>\geq 3</math> years to <math>\leq 7</math> years, 0 days; and <math>&gt;7</math> years, 0 days)</li> </ul> <p>During main study, patients will be scheduled for clinic visits at Visit 2 (Baseline/Day 1, first dose – no more than 2 wks post randomization), Visit 3 (Day 10<sup>ab</sup>; 10+4 days post first dose), and at Wk 4 (1 month), 3 months and every 3 months thereafter (up to 12 months).</p> <p>Visit 2 (Day 1/Baseline) will be conducted on day of first dosing– no more than 2 wks post randomization, Visit 4 (Month 1/Wk 4 [+1 wk]), Visit 5 Month 3/Wk 13 [<math>\pm 1</math> wk]), Visit 6 (Month 6/Wk 26 [<math>\pm 1</math> wk]), Visit 7 (Month 9/Wk 39 [<math>\pm 1</math> wk]), and Visit 8 (Month 12/Wk 52 [<math>\pm 1</math> wk]) will be conducted on day 4 (-1 day) post dose to obtain IGF-1 measurements expected to reflect average levels of IGF-1 throughout the wk.</p> <p>The following assessments will be obtained at these visits:</p> <ul style="list-style-type: none"> <li>• Auxology measurements (excluding Visit 3 and Visit 4): Actual Ht (average of three consecutive measurements) measured on a calibrated wall mounted stadiometer.</li> <li>• AEs, local tolerability, and concomitant medications (on site or by phone) (all visits).</li> <li>• Overall health status assessment, including complete physical examination and vital signs assessment (excluding Visit 3).</li> <li>• Safety laboratory tests (excluding Visit 3): chemistry, hematology and urinalysis.</li> <li>• Pubertal status (according to Tanner stages) (excluding Visits 3 and 4);</li> <li>• Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche) (excluding Visits 3 and 4).</li> <li>• Assessment of thyroid function (excluding Visits 3 and 4): TSH, FT4.</li> <li>• Assessment of biochemical markers (excluding Visit 3): IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.</li> <li>• Assessment of MOD-4023 serum levels (applicable for MOD-4023 arm only) (Visits 2, 3, 4, 5, 6a, 7 and 8a).</li> <li>• Parameters of glucose metabolism (excluding Visits 3 and 4): overnight fasting glucose, overnight fasting insulin, HbA1c.</li> <li>• Parameters of lipid metabolism (excluding Visits 3 and 4): overnight</li> </ul>
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<sup>a</sup> Applicable only for MOD-4023, Visit 3 assessments, if conducted on Day 14 (dosing day), should be performed **prior** to dosing.

<sup>b</sup> Blood samples for MOD-4023 treatment group can be collected at site OR at patient's home, based on local regulations and nurse availability. If home visit, a questionnaire, as described in [Appendix I](#), should be completed. If blood sample is collected on Day 14, it should be obtained **prior** to dosing.

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	<p>fasting cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), lipoprotein a (Lp(a)), Free Fatty Acids (FFA).</p> <ul style="list-style-type: none"> <li>• For males that are 13 years and older: Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH) and testosterone. For females that are 12 years and older: LH, FSH and estradiol (Visit 8 only).</li> <li>• Assessment of anti-MOD-4023 Ab (MOD-4023 arm) at Visits 2, 3, 4, 5, 6a, 7, 8a.</li> <li>• Assessment of anti-hGH Ab (Genotropin® arm) at Visits 2, 4, 5, 6, 7 and 8 only.</li> <li>• BA assessments at Visits 1, 2 (at Visit 2 only if historical data was provided for eligibility evaluation and not performed as part of Visit 1) and Visit 8 only.</li> <li>• Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).</li> <li>• ECG at Visit 2 for all patients, pre- dosing and ECG on Visit 6 for patients treated with daily Genotropin®. All MOD-4023 patients will undergo an ECG during Visit 6b, 7-12 hours post dosing.</li> <li>• <b>USA Only</b> - The Participant Assessment Tool (PAT) completed at Wks 1, 2, 3, 4, 5 and 6 for MOD-4023 treated patients. In any given wk a new PAT will be completed for each PEN used that wk (in some cases more than 1 PEN may be used for full dose administration, in which case a PAT will be completed for each PEN used that wk. In some cases, more than 1 injection from the same PEN may be needed, in which case only 1 PAT is completed for that PEN that wk).</li> <li>• <b>USA Only</b> - The Observer Assessment Tool (OAT) completed at Wk 1 for MOD-4023 treated patients. A new OAT will be completed for each PEN used (in some cases more than 1 PEN may be used for full dose administration, in which case an OAT will be completed for each PEN used. In some cases, more than 1 injection from the same PEN may be needed, in which case only 1 OAT is completed for that PEN). Wk 1 corresponds to study Visit 2, which will be at the site.</li> <li>• Individual dose adjustment every three months based on weight.</li> <li>• Drug dispensing Visits 2, 4, 5, 6, 7 and 8 (for patients entering the LT-OLE).</li> <li>• QoL questionnaire (Visits 2 and 8 only); patients below the age of 7 and 0 days will be completing the questionnaire with their parents/legal guardians using a parent questionnaire while patients above and including the age of 7 and 0 days will be encouraged to use the child questionnaire. The QoL questionnaire will be completed in specific countries (determined by availability of validated translated tools) as described in <a href="#">Appendix L</a>.</li> </ul> <p>For MOD-4023 patients arm only, Visit 3 (Day 10 [+4 days] post first dose), Visits 6a (Month 6/Wk 26 [<math>\pm</math>3 wks]) and Visit 8a (Month 12/Wk 52 [<math>\pm</math>1 wk]) will be conducted on dosing day, blood samples will be taken pre-dose for assessment of MOD-4023 serum levels. These blood samples can be collected at site OR at patient's home, based on local regulations and nurse availability. If home visit, a questionnaire as described in <a href="#">Appendix I</a> should be completed.</p> <p>For Genotropin® patients on Day 10 (+4 day) post first dose a phone interview will be conducted according to the questions as provided in <a href="#">Appendix I</a>.</p>
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For ECGs that will be conducted at Visit 6b, Month 6/Wk 26 ( $\pm$  3 wk) at Time 7-12 hours post-dose for MOD-4023 treated patients, patients will be requested to inject MOD-4023 during the day/night at their convenience and come to the study site at the requested time point for ECG.

Visit 6a and 6b may be combined on the same day (only if 6a is done prior to dosing).

Genotropin<sup>®</sup> patients will have an ECG assessment at Visit 6 (no time limitation, however date and time of the assessment will be recorded).

Both MOD-4023 and Genotropin<sup>®</sup> treated patients will be required to complete a patient diary card at home or at site (if injection done on site). MOD-4023 injected patients will complete the patient diary after every injection to collect data on AE, concomitant medications and local injection site reactions.

Genotropin<sup>®</sup> injected patients will complete a patient diary once a wk (preferably on the same day of the wk, each wk) to collect data on AE, concomitant medications and local injection site reactions.

**LT-OLE (Visit 10 to Visit 16):**

After successful completion of 12 months treatment in the main study and continuing to meet the LT-OLE inclusion/exclusion criteria of this protocol, patients will be eligible to rollover into a single arm LT-OLE treatment period with MOD-4023. An informed consent/assent will be obtained from patients and/or parent or legal/authorized guardian. Patients who received MOD-4023 during the main study will continue with the same dose (mg/kg/wk), adjusted for body weight, of MOD-4023 they received. For these patients, study visits will take place on Day 4 (-1) post-dose. These patients will consent to the LT-OLE preferably during Visit 7 of the main study to ensure availability of MOD-4023 at their next visit. If necessary, informed consent can be obtained at Visit 8 main study/10 LT-OLE. These Patients will continue treatment at visit 8/10, skip Visits 9 and 11 and have a telephone visit at Visit 12 (one month post LT-OLE entry (Month 13 [ $\pm$ 2wk])).

Patients who received Genotropin<sup>®</sup>, during the main study will be switched to MOD-4023 starting no less than one day [+2wk] after cessation of Genotropin<sup>®</sup> treatment. Recommended injection days are indicated in Appendix E. These patients will consent to the LT-OLE preferably during Visit 7 of the main study to ensure availability of MOD-4023 at their next visit. If necessary, informed consent can be obtained at Visit 8/10. Patients will begin treatment with MOD-4023 at Visit 8/10, skip Visit 9 and have additional onsite visits at Visit 11 (Month 12, Day 10 post first MOD-4023 dose [10+4 days]) and Visit 12 (one month post first MOD-4023 dose (Month 13 [ $\pm$ 2wk])). All patients will be provided with a diary card.

For all patients switching from Genotropin<sup>®</sup> to MOD-4023, the following will also be done:

- MOD-4023 will be dispensed based on patient weight at a starting dose of 0.66 mg/kg/wk.
- Training on and administration of MOD-4023 using the device.
- Local tolerability after first dose administered at site.

Patients who experience a delay for any reason between completion of the main study and entry into the LT-OLE may have to temporarily stop treatment. If

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initiation/re-initiation of treatment occurs less than 90 days after Visit 8 only training on and administration of MOD-4023 and local tolerability after first dose administered at site is required.

Patients who are off treatment for more than 90 days due to technical reasons e.g. delay in approval of Protocol Amendment may be allowed to continue into the LT-OLE after confirmation of availability of all required baseline LT-OLE assessments (Visit 8/10). The following tests and assessments must be repeated:

- Safety laboratory tests: chemistry, hematology and urinalysis.
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Assessment of anti-MOD-4023 Ab for all patients (Genotropin® group – baseline for future tests).
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGF-BP-3 and IGF binding protein-3 (IGFBP-3) SDS serum levels.

Visit 11 (Month 12, Day 10 [+4 days] post first dose) will be performed for patients switching from Genotropin® to MOD-4023 only. The following assessments will be conducted at the study site or at the patient's home (if allowed according to local regulations):

- MOD-4023 serum levels.
- Anti-MOD-4023 Abs.
- AEs and local tolerability (aligned with Appendix H) assessment.
- Concomitant medication recording aligned with the questionnaire in [Appendix I](#).

Visit 12 (one month post first MOD-4023 dose (Month 13 [ $\pm 2$ wk])) will be performed on site for patients switching from Genotropin® to MOD-4023. The following assessments will be conducted:

- AEs, local tolerability, and concomitant medications.
- Overall health status assessment, including complete physical examination and vital signs.
- Urine pregnancy test once a female patient reports first menstrual cycle (menarche).
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- MOD-4023 serum levels.
- Anti-MOD-4023 Abs.
- Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension).
- Return of used and unused injection devices to the site and diary card.
- Drug dispensing and accountability.

Existing MOD-4023 patients will have a telephone visit at Visit 12 (one month post LT-OLE entry [Month 13  $\pm 2$ wk]) to ask about AEs, local tolerability and

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concomitant medications. This visit will be completed using the questionnaire in Appendix I.

All patients (existing MOD-4023 and Genotropin® to MOD-4023 switch): Visit 13 (Month 15/Wk 65 [ $\pm 2$ wk]), Visit 14 (Month 18/Wk 78 [ $\pm 2$ wk]), Visit 15 (Month 21/Wk 91 [ $\pm 2$ wk]), Visit 16 (Month 24/Wk 104 [ $\pm 4$ wk]): During the first year of LT-OLE, the following assessments will be conducted every three months (on day 4 (-1) post-dose for all patients:

- Auxology measurements: Actual height (average of three consecutive measurements) measured on a calibrated wall mounted stadiometer.
- Overall health status assessment, including complete physical examination and vital signs assessment.
- Individual dose adjustment based on weight.
- AEs, local tolerability, and concomitant medications.
- Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche).
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Assessment of MOD-4023 serum levels.
- Assessment of anti-MOD-4023 Ab.
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).
- Return of used and unused injection devices to the site and diary card.
- Drug dispensing and accountability.

The following assessments will also be conducted at Visit 13 (Months 15), Visit 14 (Month 18) and Visit 16 (Month 24) on day 4 (-1) post-dose visits:

- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of thyroid function: TSH, FT4.
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Parameters of lipid metabolism: overnight fasting cholesterol, triglycerides, HDL, LDL, Lp(a), FFA.

The following assessments will also be conducted at Visit 16 (Month 24) on day 4 (-1) post-dose:

- ECG.
- Bone age.
- Pubertal status.
- For males that are 13 years and older: LH, FSH and testosterone. For females that are 12 years and older: LH, FSH and estradiol.

Collection of samples for MOD-4023 serum levels and anti-MOD-4023 Ab levels must be performed on dosing day pre-dose. For the ECG that will be conducted at 7-12 hours post-dose patients will be requested to inject MOD-4023 during the day/night at their convenience and come to the study site at the requested timepoint for the ECG. Visits may be split to allow for pre-dose blood collection for serum levels and antibody tests and post-dose ECG or the patient

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will be asked to come to the study site for blood collection, administer the required dose, and return to the study site 7-12 hours post-dose.

**LT-OLE (Visits 17 to Study closure):**

Following completion of the first year of LT-OLE the following assessments will be conducted every three months on day 4 (-1) post-dose for all patients:

- Auxology measurements: Actual height (average of 3 consecutive measurements) measured on a calibrated wall mounted stadiometer.
- Overall health status assessment, including complete physical examination and vital signs assessment.
- Individual dose adjustment based on weight.
- AEs, local tolerability, and concomitant medications.
- Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche).
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).
- Return of used and unused injection devices to the site and diary card.
- Drug dispensing and accountability.

The following assessments will also be conducted every six months on day 4 (-1) post-dose visits:

- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of thyroid function: TSH, FT4.
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Parameters of lipid metabolism: overnight fasting cholesterol, triglycerides, HDL, LDL, Lp(a), FFA.
- Assessment of MOD-4023 serum levels.
- Assessment of anti-MOD-4023 Ab.

Additional assessments will be performed once a year, every 12 months on day 4 (-1) post-dose visits:

- ECG.
- Bone age.
- Pubertal status (according to Tanner stages).
- For males that are 13 years and older: LH, FSH and testosterone. For females that are 12 years and older: LH, FSH and estradiol.

After month 13 of LT-OLE, collection of samples for MOD-4023 serum levels, anti-MOD-4023 Ab levels and ECG can be conducted without a timeframe requirement i.e. at any time although the date and time that each is performed will be recorded. If the visit is performed on dosing day, samples should be obtained pre-dose.

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	Patients will be contacted by telephone 30 days [ $\pm$ 5 days] after EOS/ET visit in order to obtain safety related information.
<b>STUDY DURATION</b>	<p>Study duration for each participating patient in the main study will be up to 15 months in total as follows:</p> <p>Screening period: up to 8 wks.</p> <p>If the patient's screening process is delayed as described above, extra time will be added to the duration of the screening period, but not in excess of an additional 4 wks (total of 12 wks screening period).</p> <p>Treatment period: 12 months.</p> <p>The LT-OLE study will continue until marketing approval.</p> <p>Follow-up: during the main study one month post dosing for those withdrawn or not continuing on in the LT-OLE, and one month post EOS/ET in the LT-OLE.</p>
<b>NUMBER OF PATIENTS</b>	Approximately 220 pre-pubertal boys and girls not yet 12 and 11 years of age, respectively, will be included and randomized 1:1 to the weekly MOD-4023 arm or the daily Genotropin <sup>®</sup> comparator arm. Eligible patients that complete the main study will be allowed to continue in the LT-OLE.
<b>INCLUSION CRITERIA</b>	<p><u>Inclusion into the main study:</u></p> <ol style="list-style-type: none"> <li>Pre-pubertal children aged <math>\geq 3</math> years, and not yet 11 years for girls (10 years and 364 days) or not yet 12 years (11 years and 364 days) for boys, (on the date of ICF signature), with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency.</li> <li>Confirmed diagnosis of GHD by two different GH provocation tests defined as a peak plasma GH level of <math>\leq 10</math> ng/mL, determined by local or central laboratory using a validated assay<sup>a</sup>. Global study MM may accept prior local laboratory results; subject to pre-approval and if the tests were conducted as recommended in the protocol <a href="#">Appendix B<sup>b</sup></a>.</li> <li>BA is not older than CA and should be <math>&lt; 10</math> for girls and <math>&lt; 11</math> for boys.</li> <li>Without prior exposure to any recombinant hGH (r-hGH) therapy (naïve patients).</li> <li>Impaired Ht velocity defined as: <ul style="list-style-type: none"> <li>Annualized HV below the 25<sup>th</sup> percentile for CA (HV <math>&lt; -0.7</math> SDS) and gender according to the OPKO HV (Tanner, Prader and Hermanussen) calculator, provided.</li> <li>The interval between 2 Ht measurements should be at least 6 months, but should not exceed, 18 months prior to inclusion.</li> </ul> </li> <li>Baseline IGF-1 level of at least 1 standard deviation (SD) below the mean IGF-1 level standardized for age and sex (IGF-1 SDS <math>\leq -1</math>)<sup>c</sup> according to the central laboratory reference values. A single re-test will be allowed (subject to discussion with MM) if all other criteria are met.</li> <li>Normal calculated glomerular filtration rate (GFR) based on updated "bedside" Schwartz formula for pediatric patients (calculation is</li> </ol>

<sup>a</sup> ITT, with serum cortisol response to hypoglycemia if insulin stimulation test is chosen / Arginine test / Clonidine test / Glucagon test / L-dopa test

<sup>b</sup> Prior spontaneous nocturnal GH secretion should be  $\leq 10$  ng/mL.

<sup>c</sup> According to rounding policy IGF-1 results  $\leq -0.95$  **might** be acceptable as well

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	<p>recommended below):</p> <p style="padding-left: 40px;">Creatine Clearance Rate (CrCL) (mL/min/1.73 m<sup>2</sup>) = 0.413*Ht/serum creatine (Scr)</p> <p style="padding-left: 80px;">Ht: in cm;</p> <p style="padding-left: 80px;">Scr: in mg/dL.</p> <p>8. Children with multiple hormonal deficiencies must be on stable replacement therapies (no change in dose) for other hypothalamo-pituitary organ axes for at least 3 months prior to ICF signing.</p> <p>9. Normal 46XX karyotype for girls.</p> <p>10. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from pediatric patients (where applicable based on age and country regulation).</p> <p><u>Inclusion into the LT-OLE:</u></p> <p>11. Completion of the main study (12 months of treatment) with adequate compliance.</p> <p>12. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from pediatric patients (where applicable based on age and country regulation).</p> <p>13. Agreement to refrain from sexual activity during the LT-OLE i.e. observe complete sexual abstinence as the only acceptable contraceptive measure during the LT-OLE (for pubertal and post-pubertal patients).</p>
<p><b>EXCLUSION CRITERIA</b></p>	<p><u>Exclusion during the main study</u></p> <ol style="list-style-type: none"> <li>1. Children with prior history of leukemia, lymphoma, sarcoma or any other forms of cancer.</li> <li>2. History of radiation therapy or chemotherapy.</li> <li>3. Malnourished children defined as BMI &lt; -2 SDS for age and sex.</li> <li>4. Children with psychosocial dwarfism.</li> <li>5. Children born small for gestational age (SGA – birth weight and/or birth length &lt; -2 SDS for gestational age).</li> <li>6. Presence of anti-hGH Ab at screening.</li> <li>7. Any clinically significant (CS) abnormality likely to affect growth or the ability to evaluate growth, such as, but not limited to, chronic diseases like renal insufficiency, spinal cord irradiation, etc.</li> <li>8. Types 1 and 2 diabetic patients who, in the opinion of the investigator, are not receiving standard of care treatment, or are non-compliant with their prescribed treatment or who are in poor metabolic control (Criteria for controlled diabetes are defined in <a href="#">Appendix F</a>).</li> <li>9. Chromosomal abnormalities including Turner’s syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Russell-Silver syndrome, SHOX mutations/deletions and skeletal dysplasias.</li> <li>10. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids, or sex steroids, with the exception of Attention-Deficit/Hyperactivity Disorder (ADHD) drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin [DDAVP®]).</li> <li>11. Children requiring glucocorticoid therapy (e.g. for asthma) that are taking</li> </ol>

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	<p>chronically a dose greater than 400 µg/day of inhaled budesonide or equivalent as provided in <a href="#">Appendix J</a>.</p> <ol style="list-style-type: none"> <li>12. Major medical conditions and/or presence of contraindication to r-hGH treatment.</li> <li>13. More than 1 closed epiphyses.</li> <li>14. Known or suspected Human Immunodeficiency Virus (HIV)-positive patient, or patient with advanced diseases such as Acquired Immunodeficiency Syndrome (AIDS) or tuberculosis.</li> <li>15. Drug, substance, or alcohol abuse.</li> <li>16. Known hypersensitivity to the components of study medication.</li> <li>17. Other causes of short stature such as celiac disease, uncontrolled primary hypothyroidism and rickets.</li> <li>18. The patient and/or the parent/legal guardian are likely to be non-compliant in respect to study conduct.</li> <li>19. Participation in any other study of an investigational agent within 30 days prior to ICF signature (including administration of investigational agent).</li> <li>20. Study enrollment requirements have been met or the study has been closed by the Sponsor prior to the completion of screening process.</li> </ol> <p><u>Exclusion during the LT-OLE:</u></p> <ol style="list-style-type: none"> <li>21. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids, or sex steroids (other than for hormonal replacement), with the exception of ADHD drugs or hormone replacement therapies (thyroxin, hydrocortisone, testosterone, estrogen/progesterone, desmopressin [DDAVP®])</li> <li>22. Change in medical condition during the treatment period (such as, but not limited to, development of a serious inter-current critical illness, a severe adverse drug reaction, etc.)</li> <li>23. Positive pregnancy test.</li> <li>24. Unresolved drug related (MOD-4023 or Genotropin®) SAE from the treatment period as per MM judgement.</li> </ol>
<p><b>INVESTIGATIONAL PRODUCT (IP) ROUTE AND DOSAGE FORM</b></p>	<p>MOD-4023 is a long-acting modified r-hGH which utilizes C-terminal peptide (CTP) technology. It will be provided as a solution for injection containing 20 or 50 mg/mL MOD-4023 in a single patient use, multi-dose, disposable pre-filled pen (PEN).</p> <p>Somatrogon is the International Nonproprietary Name/United States Adopted Name (INN/USAN) of MOD-4023 and can be used interchangeably with MOD-4023.</p> <p>MOD-4023 will be administered as a subcutaneous (SC) injection, preferably (but not required) in the morning hours once weekly, using the PEN into the upper arms, buttocks, thighs, or abdomen (8 locations).</p> <p>Injection sites should be rotated, it is recommended that all 8 injection sites should be used successively, using a different injection site at each subsequent injection.</p> <p>The starting dose for the weekly administration will be 0.66 mg/kg/wk. All patients on Genotropin® that complete Visit 8/10 and continue into the LT-OLE will start treatment with MOD-4023 at 0.66 mg/kg/wk.</p> <p>IGF-1 SDS will be monitored throughout the study, and if a patient has an IGF-1 level above +2.0 SDS, they will be requested to return for an unscheduled visit</p>

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	<p>within 4-6 wks after the &gt; +2.0 SDS result, on <b>day 4(-1) post dose</b> (for MOD-4023 treated patients). If their IGF-1 level is still &gt; +2.0 SDS, the most recent dose will be reduced by 15%. They will continue to be monitored for any further dose reduction.</p>
<b>REFERENCE THERAPY</b>	<p>Genotropin<sup>®</sup> is a daily GH, and is used as the reference therapy in this study. A delivery device (Genotropin<sup>®</sup> Pen) will be used for daily (evening/bedtime) SC administration of Genotropin<sup>®</sup> into the region of the upper arms, buttocks, thighs or abdomen (8 locations). Injection sites should be rotated.</p> <p>Starting dose regimen for Genotropin<sup>®</sup>: 0.034 mg/kg/day (which is equivalent to 0.24 mg/kg/wk divided equally into 7 daily injections).</p> <p>IGF-1 SDS will be monitored throughout the study, and if a patient has an IGF-1 level above +2.0 SDS, they will be requested to return for an unscheduled visit within 4-6 wks after the &gt; +2.0 SDS result, on any day post dose (for Genotropin<sup>®</sup> treated patients). If their IGF-1 level is still above +2.0 SDS, the most recent dose will be reduced by 15%. They will continue to be monitored for any further dose reduction.</p>
<b>MAIN STUDY ENDPOINTS</b>	<p><b>Primary efficacy endpoint:</b></p> <ul style="list-style-type: none"> <li>• Annual HV in cm/year after 12 months of treatment.</li> </ul> <p><b>Secondary efficacy endpoints (Auxology/Clinical):</b></p> <ul style="list-style-type: none"> <li>• Annualized HV after 6 months of treatment.</li> <li>• Change in Ht SDS at 6 and 12 months, compared to baseline.</li> <li>• Change in bone maturation (BM) at the end of 12 months, compared to Baseline BA<sup>a</sup> (calculated as BA/CA).</li> </ul> <p><b>Secondary endpoints (Biochemical):</b></p> <ul style="list-style-type: none"> <li>• Absolute IGF-1 and IGF-1 SDS levels on Day 4 (-1) after MOD-4023 dosing across study visits.</li> <li>• IGFBP-3 levels and IGFBP-3 SDS on Day 4 (-1) after MOD-4023 dosing across study visits.</li> </ul>
<b>SAFETY ENDPOINTS</b>	<ul style="list-style-type: none"> <li>• Incidence of AEs and serious adverse events (SAEs).</li> <li>• Incidence of anti-MOD-4023 Ab formation (including characterization of the Ab and neutralizing properties).</li> <li>• Local injection site reaction assessment.</li> <li>• Parameters of glucose metabolism: blood fasting glucose, fasting insulin level, HbA1c.</li> <li>• Thyroid (endocrinology) status.</li> <li>• Lipid profile.</li> <li>• All other safety hematology, biochemical parameters and urinalysis.</li> <li>• Physical examination.</li> <li>• Vital signs.</li> <li>• Fundoscopy results- if performed (normal/abnormal).</li> <li>• ECG.</li> </ul>
<b>OTHER ENDPOINT(S)</b>	<ul style="list-style-type: none"> <li>• Proportion of successful single injections out of total number of single injections using the MOD-4023 PEN in USA patients at Wks 1, 2, 3, 4, 5, and</li> </ul>

<sup>a</sup> Baseline BA can be taken at either Screening or Visit 2.



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	<p>6, based on the PAT.</p> <ul style="list-style-type: none"> <li>• Proportion of successful single injections out of total number of single injections using the MOD-4023 PEN in USA patients at Wk 1, based on the OAT.</li> <li>• Comments on the PAT related to successful or unsuccessful injection attempts.</li> <li>• Comments on the OAT related to successful or unsuccessful injection attempts.</li> <li>• Information gained by inspection of returned devices.</li> <li>• QoL core total score measured by the QoLISSY questionnaire at Baseline and month 12 in specific countries.</li> </ul>
<p><b>LT-OLE ENDPOINT(S)</b></p>	<p>Safety Endpoints</p> <ul style="list-style-type: none"> <li>• Incidence of AEs and SAEs;</li> <li>• Incidence of anti-MOD-4023 Ab formation (including characterization of the Ab and neutralizing properties);</li> <li>• Local injection site reaction assessment;</li> <li>• Parameters of glucose metabolism: blood fasting glucose, fasting insulin level, HbA1c;</li> <li>• Thyroid (endocrinology) status;</li> <li>• Lipid profile;</li> <li>• All other safety hematology, biochemical parameters and urinalysis;</li> <li>• Physical examination;</li> <li>• Fundoscopy results - if performed (normal/abnormal);</li> <li>• Vital signs;</li> <li>• ECG.</li> </ul> <p>Auxology/Clinical Endpoints</p> <ul style="list-style-type: none"> <li>• Annual HV in cm/year at each 12-month interval.</li> <li>• Change in height SDS every 12 months (compared to the previous values).</li> <li>• Change in bone maturation (BM) every 12 months, (compared to Week 52 BA (calculated as BA/CA) at completion of LT-OLE year 1 and to previous values from LT-OLE year 2 onwards).</li> </ul> <p>Biochemical Endpoints</p> <ul style="list-style-type: none"> <li>• IGF-1 and IGF-1 SDS levels on day 4 (-1) after MOD-4023 dosing across study visits.</li> <li>• IGFBP-3 levels and IGFBP-3 SDS on day 4 (-1) after MOD-4023 dosing across study visits.</li> </ul>
<p><b>SAMPLE SIZE CALCULATION</b></p>	<p>The aim of the study is to demonstrate that SC weekly MOD-4023 is non-inferior to SC daily Genotropin® administration with respect to the primary efficacy endpoint of annual HV in cm/year after 12 months of treatment.</p> <p>Non-inferiority will be concluded if the lower bound of the 2-sided 95% confidence interval (CI) for the mean treatment difference (MOD-4023 – Genotropin®) in the primary efficacy endpoint is <math>&gt;-1.8</math> cm/year.</p>

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	<p>The following assumptions were made in the sample size calculation:</p> <ul style="list-style-type: none"> <li>• 2-sided alpha of 0.05,</li> <li>• 80% power,</li> <li>• between-patient standard deviation of annual growth rate of 2.5 cm/year in all treatment groups,</li> <li>• non-inferiority margin of –1.8 cm/year,</li> <li>• true mean treatment difference (MOD-4023 – Genotropin<sup>®</sup>) in the primary efficacy endpoint of –0.8 cm/year.</li> </ul> <p>With these assumptions, 100 treated patients per group will provide 80% power for the non-inferiority test. To allow for an approximate 10% dropout rate, 110 patients will be randomized to each treatment group, for a total of 220 patients.</p>
<p><b>STATISTICAL ANALYSIS:</b></p>	<p>Details on the statistical methods will be provided in a Statistical Analysis Plan (SAP) prior to database lock.</p> <p>The aim of the present study is to demonstrate that in terms of annual HV at 12 months (primary efficacy endpoint), weekly MOD-4023 is non-inferior to daily Genotropin<sup>®</sup> administration by a non-inferiority margin of <b>1.8 cm/year</b>.</p> <p>With <math>\mu_M</math> and <math>\mu_C</math> representing the mean annual HV at 12 months for the MOD-4023 and the Genotropin<sup>®</sup> (Control) group, respectively, the following hypotheses will be tested:</p> <p>Null hypothesis <math>H_0</math>: <math>\mu_M &lt; \mu_C - 1.8</math> cm/year;</p> <p>Versus (vs.)</p> <p>Alternate hypothesis <math>H_1</math>: <math>\mu_M \geq \mu_C - 1.8</math> cm/year</p> <p>Non-inferiority will be concluded for the primary efficacy endpoint if the lower bound of the 2-sided 95% CI for the mean treatment difference (MOD-4023 – Genotropin<sup>®</sup>) is <math>\geq -1.8</math> cm/year.</p> <p><b>Primary Efficacy Analysis:</b> The CI for the difference of means between the 2 treatments will be derived from an analysis using Analysis of Covariance (ANCOVA). The ANCOVA model will include the stratification classes for treatment, age group, peak hGH value during stimulation test, region and gender, and Baseline Ht SDS as a covariate. The determination of non-inferiority will be based on least squares means for the 2 treatments from the ANCOVA and the 95% CI of the differences between the treatments.</p> <p>Summary statistics for HV at end of treatment and for absolute change in HV from Baseline to end of treatment, will be presented by treatment group (and further stratified by factors used in the ANCOVA model).</p> <p><b>Secondary Analyses:</b> Annualized HV after 6 months of treatment, and change (from Baseline) in Ht SDS at 6 and 12 months will be summarized with descriptive statistics. These 3 endpoints will each be analyzed using a similar ANCOVA model as used for the primary endpoint, with terms for treatment and the randomization strata (age, peak hGH value during stimulation test, region), gender and baseline value for each endpoint of interest. The model-derived least square means and standard error (SE) will be used to construct 95% CI for the difference between treatment groups. These analyses are considered as supportive efficacy analyses.</p> <p>Change in BM, calculated as BA/CA at the end of 12 months, compared to</p>

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Baseline will be characterized with descriptive statistics (mean, SD, and 95% CI) for each treatment group.

**Primary Efficacy Sensitivity Analysis:** The ANCOVA-based primary efficacy analysis will be repeated using the modified intent-to-treat (mITT) set and the per protocol (PP) set.

The ANCOVA-based primary efficacy analysis will be repeated on the full analysis set using last observation carried forward (LOCF) in place of multiple imputation for the handling of missing data.

OAT and PAT (USA Only)

OAT and PAT results will be summarized by using descriptive statistics.

Proportion and counts of successful single injections out of total number of single injections using the MOD-4023 PEN in USA patients at Wks 1, 2, 3, 4, 5, and 6, based on the PAT will be reported. Similarly, counts and proportion of successful single injections out of total number of single injections using the MOD-4023 PEN in USA patients at Wk 1, based on the OAT will be reported. Details on the criteria constituting a successful single injection based on OAT and PAT, along with statistical methods to be used for descriptive summaries will be included in the SAP.

Comments on the PAT and OAT related to successful or unsuccessful injection attempts

The written comments provided on the PAT and OAT for successful or unsuccessful injection attempts will be listed. Any other written comments will also be listed.

Information gained by inspection of returned devices

Summary of the information gathered by inspecting the returned devices will be reported.

The QoLISSY core total score at Baseline, 12 months and change from Baseline to month 12, for each group will be summarized using descriptive statistics. This will be done for specific countries as listed in the [Appendix L](#).

**Biochemical Endpoints**

IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS will be summarized descriptively by visit. Statistical comparisons between treatment groups are not planned. Incidence of IGF-1 SDS >2.0 will be summarized at each visit and in total as percentage of total samples.

Safety data will be reported mainly using descriptive summaries for treatment emergent AEs and laboratory values that fall outside of pre-determined ranges. Both listings and tabular summaries will be reported for all safety endpoints.

LT-OLE:

The assessment of safety and efficacy (auxology/clinical and biochemical endpoints) during the LT-OLE will be based on descriptive statistics and summarized by patient's treatment in the treatment period and overall. No hypothesis testing will be performed. The descriptive statistics will include means, standard deviations, quartiles/ranges for continuous variables, and counts with percentages for categorical data. 95% CI will be used to further describe the clinical endpoints. A separate SAP for the LT-OLE will be provided.

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## GLOSSARY

<b>Abbreviation</b>	<b>Definition</b>
µg	Microgram
Ab	Antibody
ACTH	Adrenocorticotrophic Hormone
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransaminase (SGPT)
ANCOVA	Analysis of Covariance
AST	Asparate Transaminase (SGOT)
BA	Bone Age
BM	Bone Maturation
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CA	Chronological Age
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
cm	Centimeter
CNS	Central Nervous System
CPK	Creatinine Phosphokinase
CrCL	Creatinine Clearance
CRH	Corticotropin Releasing Hormone
CRO	Contract Research Organization
CS	Clinically Significant
CT	Computed Tomography
CTP	C-terminal Peptide
day 4(-1)	Day 3 or 4 Post-injection
DBPC	Double-Blind Placebo-Controlled
DDAVP	Desmopressin
dL	Deciliter
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EMA	European Medicinal Agency



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<b>Abbreviation</b>	<b>Definition</b>
EOS	End of Study
ET	Early Termination
EU	European Union
FAS	Full Analysis Subset
FDA	Food and Drug Administration
FFA	Free Fatty Acids
FSH	Follicle-Stimulating Hormone
FT4	Free Thyroxine
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GHR	Growth Hormone Receptor
GI	Gastrointestinal
GLP	Good Laboratory Practices
GRS	Growth Hormone Research Society
H <sub>0</sub>	Null Hypothesis
H <sub>1</sub>	Alternative Hypothesis
HbA1C	Glycated Hemoglobin (Hemoglobin A1c)
hCG	Human Chorionic Gonadotropin
HCT	Hematocrit
HDL	High Density Lipoproteins
HGB	Hemoglobin
hGH	Human Growth Hormone
HIV	Human Immunodeficiency Virus
HV	Height Velocity
HV SDS	Height Velocity Standard Deviation Score
Ht	Height
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGFBP-3	IGF-1 Binding Protein 3
IGF-1	Insulin-like Growth Factor-1
IM	Intramuscular
IND	Investigational New Drug
INN	International Nonproprietary Name
INR	International Normalized Ratio (for blood clotting time)
IP	Investigational Product

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<b>Abbreviation</b>	<b>Definition</b>
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator's Site File
ITT	Insulin Tolerance Test
IV	Intravenous
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LDL	Low Density Cholesterol
LFT	Liver Function Test
LH	Luteinizing Hormone
LOCF	Last Observation Carried Forward
LP(a)	Lipoprotein (a)
LT	Long term
m	Meter
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min.	Minute
mITT	Modified Intent-to-Treat
mL	Milliliter
MM	Medical Monitor
MoH	Ministry of Health
mmol	Millimole
MRI	Magnetic Resonance Imaging
mSV	Millisievert
N	Number
ng	Nanogram
nmol	Nanomole
No.	Number
NOAEL	No Observed Adverse Effect Level
OAT	Observer Assessment Tool
OBL	OPKO Biologics Ltd.
OLE	Open Label Extension
PA	Posterior to Anterior
PAT	Participant Assessment Tool
PD	Pharmacodynamics

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<b>Abbreviation</b>	<b>Definition</b>
PEN	Single patient use, multi-dose, disposable pre-filled pen containing 20 or 50 mg/mL MOD-4023
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PT	Prothrombin Time
PT	Preferred Term
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QoL	Quality of Life
QoLISSY	Quality of Life in Short Stature Youth
RA	Regulatory Authority
RBC	Red Blood Cells
r-hGH	Recombinant Human Growth Hormone
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
Scr	Serum Creatinine
SD	Standard Deviation
SDS	Standard Deviation Score
SE	Standard Error
SGA	Small for Gestational Age
SHOX	Short stature homeobox
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
t	Time
t <sub>1/2</sub>	Half-life
Tmax	Time Of Maximum Concentration
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
USA	United States of America
USAN	United States Adopted Name
vs	Versus
WBC	White Blood Cells
WHO	World Health Organization
wk	Week

## 1. INTRODUCTION

### 1.1 GROWTH HORMONE DEFICIENCY

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates hepatic production and release of IGF-1 into the systemic circulation. IGF-1 is an important mediator in the promotion of linear growth in children and may play a role in the regulation of metabolism and body composition in adults. These factors are regulated through complex feedback mechanisms involving hGH, IGF-1 and their complexes (Shalet, Toogood et al. 1998; Bach 2004).

A GHD results in inadequate circulating IGF-1 levels and is manifested as abnormal linear growth in children (Krysiak, Gdula-Dymek et al. 2007; Thomas and Monson 2009).

Childhood GHD can be congenital, acquired, or idiopathic. Underlying causes for congenital malformation include pituitary dysfunction due to abnormal neurodevelopment *in utero* of certain brain regions and genetic abnormalities. Etiology for acquired GHD includes brain tumors in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation and surgical intervention. The idiopathic origin of GHD is poorly understood but it appears to be multifactorial (Rona and Tanner 1977).

Data on incidence and prevalence rates of GHD are scarce. A nationwide study in Denmark reported average incidence rate of 2.58 males, and 1.7 females per 100,000 population for childhood onset of GHD (Stochholm, Gravholt et al. 2006). The prevalence and demographics of childhood GHD in Belgium during the period 1986-2001 was estimated to be 1/5600. The origin of GHD was idiopathic in 41% of the patients, congenital in 20% and acquired in 7%; there was male predominance in all 3 categories (Thomas, Massa et al. 2004). The number of new cases has remained fairly constant over the last 2 decades. The Belgian data are comparable to other countries; the prevalence of GHD in the USA in the 1990's was at least 1:3480, with male predominance (Lindsay, Feldkamp et al. 1994).

Most morbidity in children with GHD relates to short stature. The inability to achieve normal Ht can lead to early onset of severe psychosocial problems directly related to short stature. This is confounded by delayed puberty and deficits in facial, dental and (in males) genital development. Approximately 5% of children with GHD have episodes of hypoglycemia, particularly in infancy (Krysiak, Gdula-Dymek et al. 2007). Persistency of GHD into adulthood is associated with increased risk of cardiovascular morbidity and mortality.

### 1.2 CURRENT THERAPY

Recombinant hGH (r-hGH) replacement therapy has been used for over 30 years in tens of thousands of patients (primarily children) and has proved to be safe and effective (Ho 2007; Cohen, Rogol et al. 2008). The main therapeutic goal of GH treatment in children with GHD is to enable short children to achieve normal Ht, with early improvement of the psychosocial problems related to short stature. Treatment is by daily SC injection of r-hGH. The Growth Hormone Research Society (GRS) consensus guideline recommends a dose range of 0.025-0.05 mg/kg/day, although in Europe generally a dose of 0.025-0.035 mg/kg/day or 0.7-1.0 mg/m<sup>2</sup> body surface area/day is recommended (according to the Summary of Product Characteristics (SmPC) of Somatropin products). Treatment response is assessed by measurement of Ht and growth velocity and is usually continued until final Ht, epiphyseal closure, or both have been recorded.

The majority of currently available hGH products require daily or every other day SC or intramuscular (IM) injections to maintain hGH blood levels within the effective therapeutic window. The burden of daily administration and its concomitant side effects (e.g., injection site discomfort, transient edema and arthralgia) cause a reduction in compliance (Rosenfeld and Bakker 2008) and can limit the therapeutic utility of existing formulations.

Developments in drug delivery technology have allowed the use of slow-release preparations of GH in humans (Cook, Biller et al. 2002; Kemp, Fielder et al. 2004; Bidlingmaier, Kim et al. 2006). The most successful technology so far has been the encapsulation of GH molecules in poly (D,L-lactic-co-glycolic acid) biodegradable microspheres (Makadia and Siegel 2011). A more recent formulation of GH called LB03002 is an injectable, sustained-release GH suspension of microparticles, consisting of GH incorporated into sodium hyaluronate, which are dispersed in an oil base of medium-chain triglycerides before injection. Hyaluronate is a natural biomaterial found in connective tissues including skin and cartilage and is naturally degraded by hyaluronidase as part of the physiological turnover process. This formulation has been demonstrated to have long acting properties with suitable pharmacokinetic (PK) and pharmacodynamic (PD) profiles (Bidlingmaier, Kim et al. 2006) and efficacy indistinguishable from daily GH treatment in childhood GHD when administered weekly (Peter, Bidlingmaier et al. 2012).

### 1.3 INVESTIGATIONAL THERAPY

MOD-4023 is a long-acting r-hGH for SC administration. It consists of hGH fused to three copies of the CTP of the beta chain of human chorionic gonadotropin (hCG); one copy at the N-terminus and two copies (in tandem) at the C-terminus.

The CTP provides hCG with the required longevity to maintain pregnancy (initial half-life ( $t_{1/2}$ ) ~ 10 hours, terminal  $t_{1/2}$  ~ 37 hours). The beta chain of luteinizing hormone (LH), a gonadotropin that triggers ovulation, is almost identical to hCG, but does not include the CTP. As a result, LH has a significantly shorter half-life in blood (initial  $t_{1/2}$  ~ 1 hour, terminal  $t_{1/2}$  ~ 10 hours). It is, therefore, suggested that the addition of CTP to a protein other than hCG may enable to increase the corresponding protein longevity (Hershkovitz et al. 2015).

Somatrogon is the INN/USAN of MOD-4023 and can be used interchangeably with MOD-4023.

#### 1.3.1 Clinical Studies

MOD-4023 clinical development program includes, apart from the current study, five studies which have been completed. Two (2) Phase 1 studies (CP-4-001, CP-4-007) in healthy adult male volunteers, and Phase 2 studies in GHD adults (CP-4-003) and pre-pubertal GHD children (CP-4-004) were completed. A Phase 3 pivotal study (CP-4-005) in adult patients with GHD is completed and pending final clinical study report. Currently, both CP-4-004 and CP-4-005 are continuing as an OLE until marketing approval.

The Phase 1 study (CP-4-001) was conducted in 24 healthy adult male volunteers CCI

CCI

Another Phase 1 study (CP-4-007) was conducted in healthy male Caucasian and Japanese volunteers. A total of 42 subjects were enrolled and randomized, CCI

The Phase 2, randomized, open-label, multicenter study (CP-4-003) in adults with GHD was designed to assess the safety, tolerability and PK/PD profile of three doses of MOD-4023 administered on a weekly regimen and one exploratory dose on an every other wk regimen. MOD-4023 was administered for a period of four wks in adult GHD patients who were previously on a stable, standard r-hGH treatment for at least six months. Fifty-four (54) patients (48 men and 6 women) were enrolled and completed the study. The clinical adverse effects (such as headache) were consistent with those expected in a GHD population and were mostly of a mild nature.

The completed Phase 2 study (CP-4-004) in a pediatric population was designed to assess the safety, efficacy and tolerability of three MOD-4023 doses as compared to that of a commercially available standard daily r-hGH formulation in up to 56 pre-pubertal children with growth failure due to insufficient secretion of endogenous GH. Fifty-three (53) patients were enrolled and treated with 52 of them finishing the 12-month portion of the study. All three MOD-4023 dose groups demonstrated a growth response comparable to daily r-hGH after 12 months of treatment, as described in detail in the Investigator Brochure (IB), with a safety profile consistent with commercially available r-hGH products.

A Phase 3 pivotal study (CP-4-005) in adult patients with GHD was recently completed. The study is a randomized, parallel-group, multi-center study consisting of a 26-wk double-blind, placebo-controlled (DBPC) period, a 26-wk long-term OLE, in which all patients receive MOD-4023, and a two-wk washout period<sup>a</sup>. The starting dose of study drug differed by gender, age and estrogen therapy. Individual dose titration was conducted according to a dose modification plan. The main study, first 12 months, has been completed and is currently being analyzed and reported.

For additional information on clinical studies, please refer to the current version of the IB.

### 1.3.2 Study Rationale

OBL's proprietary CTP technology has enabled the production of a long-acting hGH (MOD-4023), which may obviate the need for the numerous injections currently required in marketed hGH products. As demonstrated in animal models and clinical studies, MOD-4023 may be injected once per wk resulting in similar clinical efficacy as compared to daily injections of r-hGH.

<sup>a</sup> To obtain blood samples for MOD-4023 Ab assessment and MOD-4023 serum levels.

The purpose of the current Phase 3 study is to demonstrate that weekly MOD-4023 administration in pre-pubertal children with GHD is clinically comparable (non-inferior) to daily Genotropin<sup>®</sup> administration in terms of safety and efficacy after 12 months treatment duration. The study will be conducted in a randomized, open-label, active-controlled, parallel-group design. After completion of an initial 12 months treatment patients will be eligible to continue treatment with weekly MOD-4023 in a single arm, long term open-label extension (LT-OLE) study for the purpose of collecting additional long term safety and efficacy information.

### 1.3.3 Rationale for Dose Selection

MOD-4023 is a new molecular entity with GH mechanism of action demonstrating reduced receptor affinity, lower specific activity, but with an extended, optimized  $t_{1/2}$ .

The *in vitro* activity and receptor binding affinity of MOD-4023 were established based on comprehensive characterization studies as part of the non-clinical program. MOD-4023, which is comprised of 72.3% net hGH on a molar basis, demonstrated 10 to 20-fold reduction in affinity to GH receptors (GHR) as compared to r-hGH (Biacore analysis). This was further strengthened by two independent cell-based assays analysis indicating that MOD-4023 had a significantly lower biological activity as compared to daily hGH.

Based on the *in vitro* non-clinical pharmacological findings and Phase 2 data it was concluded that any dose comparisons between MOD-4023 and hGH that were initially done on molar basis were not reflective of the biological effect of the molecule. Therefore, the selection of MOD-4023 dose for the Phase 3 studies was determined by safety parameters and in particular by the clinical effect, i.e. HV.

This assumption was confirmed during the Phase 2 pediatric study, when monitoring the IGF-1 response. Two (2) of the doses of MOD-4023 administered in the Phase 2 study, 0.48 and 0.66 mg/kg/wk, resulted in comparable IGF-1 and IGFBP-3 profiles to that of Genotropin<sup>®</sup> administered daily at a dose of 34 µg/kg/day. These two doses of MOD-4023 were shown to maintain IGF-1 serum levels, with values that were in the middle part of the gender and age-adjusted normal range (~0 SDS). MOD-4023 dose of 0.25 mg/kg/wk failed to maintain normal IGF-1 serum levels mainly during the second part of the wk, indicating that IGF-1 levels will be at the lower part of the normal range or even below it with the use of this dose on weekly basis. These observations were further confirmed by the population-based model. Mean IGF-1 SDS values for Cohort 3 and Cohort 2 (MOD-4023 dose of 0.66 and 0.48 mg/kg/wk, respectively) were around 0 SDS IGF-1, and consistently much lower than 0 for Cohort 1 (0.25 mg/kg/wk). Therefore, it is proposed that MOD-4023 doses of 0.48 and 0.66 mg/kg/wk are more likely to result in IGF-1 and IGFBP-3 levels that are comparable to daily Genotropin<sup>®</sup> injections within the well-established suitable safety range with no direct correlation to GH molar content.

As the dose selection is driven by evaluating the annual increment in HV, the annual HV data obtained for MOD-4023 was compared to Genotropin<sup>®</sup> results in the Phase 2 study for 52 patients (one patient was mis-diagnosed). Based on 12-month auxology data, it is most likely that a minimum MOD-4023 dose of 0.66 mg/kg/wk will provide an annualized HV comparable to daily hGH at a dose of 34 µg/kg/day.

## 2. STUDY OBJECTIVES

### Primary Objective:

To demonstrate that weekly MOD-4023 administration is non-inferior to daily Genotropin<sup>®</sup> administration.

**Secondary Objective:**

- To evaluate the safety and tolerability of weekly MOD-4023 administration.
- To demonstrate successful operation (single injection) of the MOD-4023 single patient use, multi-dose, disposable pre-filled pen (PEN).
- Evaluation of participant and observer feedback on MOD-4023 device usability.
- To confirm the correct operation of devices returned for evaluation.

**LT-OLE Objective:**

- To demonstrate LT safety and efficacy of MOD-4023 in an OLE.

**Other Objectives:**

To evaluate the effect of weekly MOD-4023 and daily Genotropin<sup>®</sup> administration on QoL, as measured by the QoLISSY in a specific number of countries (determined by availability of validated translated tools) during the first 12 months of treatment.

**3. STUDY DESIGN**

The study will consist of 12 months, open-label, multi-center, randomized, active controlled, parallel group study comparing efficacy and safety of weekly MOD-4023 to daily GH, Genotropin<sup>®</sup>.

Both drugs will be injected using a PEN device.

The study will be divided into two parts:

**Main Study Period (main study):** After an 8 wk screening period<sup>a</sup>, patients meeting the eligibility criteria, as approved by global study MM, will be randomized in a 1:1 ratio to weekly SC doses of MOD-4023 (investigational treatment) or daily SC administration of Genotropin<sup>®</sup> (reference therapy) for 12 months. The key safety data will be reviewed by an independent DSMB every 4 months or on an *ad hoc* basis.

**LT-OLE Period (LT-OLE):** Patients who received MOD-4023 during the main study will continue in the LT-OLE with the same dose (mg/kg/wk) of MOD-4023. Patients who received Genotropin<sup>®</sup> during the main study will be switched to MOD-4023 and will begin treatment with a dose of 0.66 mg/kg/wk beginning no less than one day after cessation of Genotropin<sup>®</sup> treatment. The key safety data will be reviewed by an independent DSMB approximately every 6 months.

During the entire study (main study and LT-OLE), the dose of MOD-4023 and Genotropin<sup>®</sup> will be adjusted every 3 months based on the patient's body weight. Doses may be decreased for safety reasons according to the pre-defined dose-adjustment criteria (which will be based on the severity

<sup>a</sup> If the patient's screening process is delayed because of a benign illness or unforeseen benign condition (i.e. pharyngitis, viral GI problems, minor accident or trauma, etc.) or other technical issue that is related screening procedures (for example, delays with laboratory results) extra time will be added to the duration of the screening period, but not in excess of an additional four wks (total of 12 wks screening period).



of AEs or repeated, elevated levels of IGF-1). The dose will be decreased based on two, repeated day 4(-1) post-dose levels of IGF-1 SDS  $\geq +2.0$  (Section 6.4). During the LT-OLE, dose reduction for IGF-1 level  $>+2.0$  SDS will be made following consultation with the Global Study MM on an individual patient basis

The total duration of patient participation in the main study will be up to 15 months (12 months of treatment, up to eight<sup>a</sup> (+4) wks of screening and one month post dosing EOS follow up for patients not continuing in the LT-OLE, discontinued early or following study closure).

The LT-OLE will continue until marketing approval.

The study will be conducted at approximately 200 sites in 30-40 countries worldwide.

## 4. STUDY POPULATION

Pre-pubertal children (boys 3-11 years, girls 3-10 years), diagnosed with GHD.

### 4.1 INCLUSION CRITERIA

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

1. Pre-pubertal children aged  $\geq 3$  yrs old and not yet 11 years for girls (10 years and 364 days) or not yet 12 years (11 years and 364 days) for boys (on the date of ICF signature) with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiencies.
2. Confirmed diagnosis of GHD by 2 different GH provocation tests defined as a peak plasma GH level of  $\leq 10$  ng/ml, determined by local (if done prior to signing the ICF) or central laboratory using a validated assay<sup>a</sup>. Prior local laboratory results will be accepted subject to pre-approval by global study MM and if the tests were conducted according to one of the protocols in [Appendix B<sup>b</sup>](#).
3. BA is not older than CA and should be  $< 10$  for females and  $< 11$  for males.
4. No prior exposure to any r-hGH therapy.
5. Impaired Ht and HV defined as:
  - Annualized HV below the 25<sup>th</sup> percentile for CA (HV  $< -0.7$  SDS) and gender according to the OPKO HV (Tanner, Prader and Hermanussen) calculator, provided.
  - The interval between 2 Ht measurements should be at least 6 months, but should not exceed 18 months prior to inclusion.
6. Baseline IGF-1 level of at least 1 SD below the mean IGF-1 level standardized for age and sex (IGF-1 SDS  $\leq -1$ )<sup>c</sup> according to the central laboratory reference values. A single re-test will be allowed (subject to discussion with MM) if all other criteria are met.
7. Normal calculated GFR based on updated “bedside” Schwartz formula for pediatric patients (recommended calculation is provided below):
 
$$\text{CrCL (mL/min/1.73 m}^2\text{)} = 0.413 * \text{Ht} / \text{Scr};$$

Ht: in cm;  
Scr: mg/dL;

<sup>a</sup> ITT, with serum cortisol response to hypoglycemia if insulin stimulation test is chosen / Arginine test / Clonidine test / Glucagon test / L-dopa test.

<sup>b</sup> Prior spontaneous nocturnal GH secretion should be  $\leq 10$  ng/mL.

<sup>c</sup> According to rounding policy IGF-1 results  $\leq -0.95$  **might** be acceptable as well.

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8. Children with multiple hormonal deficiencies must be on stable replacement therapies (no change in dose) for other hypothalamo-pituitary-organ axes for at least 3 months prior ICF signing.
9. Normal 46XX karyotype for girls.
10. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from pediatric patients (where applicable based on age and country regulation).

#### Inclusion into the LT-OLE:

11. Completion of the main study (12 months of treatment) with adequate compliance.
12. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from pediatric patients (where applicable based on age and country regulation).
13. Agreement to refrain from sexual activity during the LT-OLE i.e. observe complete sexual abstinence as the only acceptable contraceptive measure during the LT-OLE (for pubertal and post-pubertal patients).

#### **4.2 EXCLUSION CRITERIA**

1. Children with prior history of leukemia, lymphoma, sarcoma or any other form of cancer.
2. History of radiation therapy or chemotherapy.
3. Malnourished children defined as BMI <-2 SDS for age and sex.
4. Children with psychosocial dwarfism.
5. Children born small for gestational age (SGA – birth weight and/or birth length <-2 SDS for gestational age).
6. Presence of anti-hGH Ab at screening.
7. Any CS abnormality likely to affect growth or the ability to evaluate growth, such as, but not limited to, chronic diseases like renal insufficiency, spinal cord irradiation, etc.
8. T2 and T1 diabetic patients, who in the opinion of the investigator are not receiving standard of care treatment or are non-compliant with their prescribed treatment or who are in poor metabolic control. Criteria for controlled diabetes are defined in [Appendix F](#).
9. Chromosomal abnormalities including Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Russell-Silver syndrome, SHOX mutations/deletions and skeletal dysplasias.
10. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids, or sex steroids, with the exception of ADHD drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin [DDAVP<sup>®</sup>]).
11. Children requiring glucocorticoid therapy (e.g. for asthma) that are taking chronically a dose greater than 400 µg/day of inhaled budesonide or equivalent as described in [Appendix J](#).
12. Major medical conditions and/or presence of contraindication to r-hGH treatment.
13. More than 1 closed epiphyses.
14. Known or suspected HIV-positive patient, or patient with advanced diseases such as AIDS or tuberculosis.
15. Drug, substance, or alcohol abuse.

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16. Known hypersensitivity to the components of study medication.
17. Other causes of short stature such as celiac disease, uncontrolled primary hypothyroidism and rickets.
18. The patient and/or the parent/legal guardian are likely to be non-compliant in respect to study conduct.
19. Participation in any other study of an investigational agent within 30 days prior to ICF signature (including administration of investigational agent).
20. Study enrollment requirements have been met or the study has been closed by the Sponsor prior to the completion of screening process.

Exclusion during the LT-OLE:

21. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids, or sex steroids (other than for hormonal replacement), with the exception of ADHD drugs or hormone replacement therapies (thyroxin, hydrocortisone, testosterone, estrogen/progesterone, desmopressin [DDAVP®])
22. Change in medical condition during the treatment period (such as, but not limited to, development of a serious inter-current critical illness, a severe adverse drug reaction, etc.)
23. Positive pregnancy test.
24. Unresolved drug related (MOD-4023 or Genotropin®) SAE from the treatment period as per MM judgement.

**4.3 PATIENT IDENTIFICATION**

A unique identification number will be assigned by the Electronic Data Capture (EDC) system when an individual patient or their legal guardian or parent signs the ICF and starts the screening process. Following eligibility confirmation by global study MM, the patient will be randomized through the Interactive Web Response Technology system (IRT). The randomization will be stratified based on:

1. Geographical region (1. Western Europe, Israel, Australia, New Zealand, Canada and USA; 2. Central and Eastern Europe, Greece, Turkey, Latin America, Asia except for India and Vietnam; 3. India and Vietnam);
2. GH peak levels at Screening  $\leq 3$  ng/mL;  $>3$  to  $\leq 7$  ng/mL; and  $>7$  to  $\leq 10$  ng/mL; and
3. CA (3-7 and 0 days, above 7).

The unique identification number assigned during the main study will continue to be used in the LT-OLE.

**4.4 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 or parent/legal guardian requests to be withdrawn. Patients withdrawn from the study during the 12 months of treatment post first dose will not be replaced. Those patients withdrawn who have successfully completed screening, but prior to first dose, will be replaced.

The patient's participation in this study may be discontinued due to the following reasons:

- Request from regulatory agency, sponsor, primary care physician, or Investigator.
- Withdrawal of the patient's/parent's/legal guardian's consent for any additional study participation or procedure, including lost to follow up (with specific withdrawal reason collected, as possible).
- AE:
  - Occurrence of a malignancy during the course of the study.
  - Development of serious intercurrent critical illness.
  - Development of benign intracranial hypertension, if the symptoms return following resumption of drug (after a temporary stop).
  - Occurrence of AEs following which the Investigator, or the patient wishes to discontinue treatment (such as, but not limited to, slipped capital femoral epiphysis, scoliosis, avascular necrosis and development of lipoatrophy, etc.).
- Intake of prohibited concomitant medication (in consultation with the MM).
- Investigator decides that withdrawal from the study is in the best interest of the patient e.g. patient non-compliance, occurrence of neutralizing Ab, protocol deviation(s) (including protocol deviation(s) that affect patient safety and accuracy, and/or validity of data) etc.
- Any clinically significant change in the patient's medical condition.

During the LT-OLE:

- Girls with a BA of  $\geq 13.5$  years and boys with a BA of  $\geq 16$  years.
- Positive urine pregnancy test or confirmed pregnancy. In case of pregnancy, the study drug should be discontinued, and the Global Study MM be alerted immediately. All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. Pregnancy tests will also be done whenever one menstrual cycle is missed during treatment (main study and LT-OLE) and when potential pregnancy is otherwise suspected and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study for follow up.
- When the patient's annualized growth rate is  $\leq 2$  cm/12 months (the interval between two height measurements should be at least six months).

Patients can be re-screened for inclusion in the main study **one** time. Any data collected during the original screening period will be acceptable as historical data, EXCEPT safety laboratory data and IGF-1 and IGFBP-3 levels, which must be repeated and evaluated for eligibility. In this case, the patient will be assigned a new screening number.

**4.5 HANDLING OF WITHDRAWALS**

If a patient is withdrawn from the study or fails to return either at his or her request or at the investigator's discretion after randomization, every effort should be made to determine the reason. This information will be recorded on the patient's electronic case report form (eCRF). All patients who withdraw from the study prematurely, regardless of cause, should undergo all early termination assessments (see Section 5.5). It is vital to obtain follow-up data for any patient withdrawn due to an AE or abnormal laboratory test finding. In any case, every effort must be

made to undertake safety follow-up procedures. If a patient wishes to withdraw, the difference between treatment discontinuation and study withdrawal will be explained. Patients should be encouraged to continue the follow up visits and at minimum provide a Ht measurement at 12 months of the initial treatment period even if they discontinue the study treatment early.

#### 4.6 SPONSOR'S TERMINATION OF STUDY

The Sponsor reserves the right to discontinue the study at any time for any reason.

Regulatory Authorities also have the right to terminate the study.

### 5. INVESTIGATIONAL PLAN AND STUDY PROCEDURES

A schedule of events for this study is shown in [Appendix A](#). No protocol related procedures, including the cessation of prohibited concomitant medications should be performed before patients provide written<sup>a</sup> assent (where applicable) and consent from the parent(s) or legal guardian(s) is obtained. Study related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drugs and descriptions of AEs should be recorded in the appropriate source documents and/or eCRF.

#### 5.1 VISIT 1 - SCREENING PERIOD (DAY – 56 TO DAY -1)

The screening period will last up to 8 wks<sup>b</sup> and can be conducted over several visits prior to randomization, to minimize blood volume withdrawals per visit. Screening visits are intended to collect current clinical data and to perform all required investigations needed to establish a patient's eligibility for the study. Prior to any study specific assessments, written assent from pediatric patients (where applicable based on age and country) and consent from the parent(s) or legal guardian(s) will be obtained. Upon completion of the Informed Consent process and obtaining written consent from the parent(s) or legal guardians(s) a patient is deemed to be 'enrolled into the study'.

The following assessments will be conducted at these screening visits:

- Inclusion/exclusion verification.
- Parental Ht<sup>c</sup>, and patients' Ht, Ht SDS, HV and HV SDS.
- Body weight and BMI SDS.
- Medical history, including a description of pituitary deficiencies, concomitant and previous medications.
- Overall health status assessment, including complete physical examination and vital signs.
- Pubertal status (according to Tanner stages).

<sup>a</sup> Illiterate patients should provide their consent in a method that is accepted according to local regulations.

<sup>b</sup> If the patient's screening process is delayed because of a benign illness or unforeseen benign condition (i.e. pharyngitis, viral GI problems, minor accident or trauma, etc.) or other technical issue that is related screening procedures (for example, delays with laboratory results) extra time will be added to the duration of the screening period, but not in excess of an additional four wks (total of 12 wks screening period).

<sup>c</sup> It's recommended that parents will be measured at the site. If measured parental Ht is not available an estimate should be provided by the parent. It should also be noted that the patient's birth date is required for accurately reporting of Ht SDS.

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- BA<sup>a</sup> determination with the method of Greulich-Pyle using a central BA reader.
- Assessment of biochemical markers and stimulation tests:
  - Two (2) different GH stimulation (provocation) tests from the following list: ITT (with serum cortisol response to hypoglycemia if insulin stimulation test is chosen); arginine test; clonidine test; glucagon test; L-dopa test. The minimal duration and number of samples must conform to the specifications in [Appendix B](#) for each test.

The use of a local laboratory for assessment of GH serum levels (and glucose and serum cortisol if the insulin tolerance test is performed) might be acceptable, if done prior to ICF signature, and if the results are reviewed and approved by the global study MM **prior to study entry**.

- Assessment of morning cortisol (at 8 am ± 1 hour).  
If morning cortisol is below 190 nmol/L (7 µg/dL), test for adrenal insufficiency will be required – Low dose ACTH or CRH stimulation test (only if the patient was not previously assessed for the hypothalamus-pituitary-adrenal axis<sup>b</sup> or has been diagnosed with adrenal insufficiency).
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Assessment of anti-hGH Ab.
- Safety laboratory tests: chemistry, hematology, urinalysis.
- Assessment of thyroid function: TSH, FT4.
- Parameters of glucose metabolism: overnight fasting insulin, overnight fasting glucose and HbA1C.
- Head MRI<sup>c</sup>, if possible with contrast or CT scan – recommended to be performed only after the two GH stimulation tests.
- Assessment of karyotype in girls<sup>d</sup>.
- SHOX gene evaluation<sup>e</sup>.

The Global Study MM will review key data and all test results obtained during Screening; the eligibility will be confirmed by the Global Study MM **prior to randomization** of each patient.

It is recommended that the Investigator randomize the patient within 7 days of Global Study MM confirmation of eligibility and to bring the patient back in for the Baseline visit (Visit 2) within 2 wks of randomization.

<sup>a</sup> Historical BA assessment might be accepted if they were done with the method of Greulich-Pyle no more than 6 months prior to the ICF signature date. If the patient is eligible, the BA should be repeated at Visit 2 prior to dosing. The Visit 2 scan will be the Baseline scan for these patients.

<sup>b</sup> ITT with serum cortisol response to hypoglycemia is adequate for assessment of adrenal insufficiency and no ACTH stimulation test is required if such results are available.

<sup>c</sup> Historical MRI or CT is permitted if within 12 months; MRI or CT which was conducted no more than 12 months prior to ICF signature data will be acceptable. For GHD associated with a congenital CNS defect, the medical monitor could allow for use of the historic MRI or CT > 12 months old.

<sup>d</sup> Historical karyotype data and chromosomal microarray data are acceptable.

<sup>e</sup> Historical data is acceptable. SHOX gene evaluation is only necessary for isolated GHD with a normal brain MRI. Patients with clear multiple pituitary hormone deficiencies or structurally abnormal pituitary gland do not require SHOX gene evaluation.

## 5.2 MAIN STUDY TREATMENT PERIOD (DAY 1/BASELINE TO MONTH 12)

Eligible patients will be randomized (central randomization within each region<sup>a</sup>) in a 1:1 fashion within each stratum to receive either weekly MOD-4023 (0.66 mg/kg/wk) or daily Genotropin<sup>®</sup> (0.034 mg/kg/day or 0.24 mg/kg/wk) for 12 months.

Visit 2 (Day 1/Baseline) will be conducted on day of first dosing. Subsequent visits, Visit 4 (Month 1/Wk 4 [+1 wk]), Visit 5 (Month 3/Wk 13 [ $\pm 1$  wk]), Visit 6 (Month 6/Wk 26 [ $\pm 1$  wk]), Visit 7 (Month 9/Wk 39 [ $\pm 1$  wk]), and Visit 8 (Month 12/Wk 52 [ $\pm 1$  wk]) will be conducted on day 4 (-1 day) post dose<sup>b</sup> to obtain IGF-1 measurements expected to reflect average levels throughout the wk.

Visit 3 (Day 10 [+4 days]<sup>c</sup> post first dose) for the collection of immunogenicity and PK sample will be conducted for MOD-4023 arm only. This visit can be done at the patient's home or at the study site, based on local regulations and nurse availability. If home visit is conducted, a questionnaire, as described in [Appendix I](#) should be completed, collecting information on AE, local tolerability and concomitant medications.

Visits 6a (Month 6/Wk 26 [ $\pm 3$  wk]) and Visit 8a (Month 12/Wk 52 [ $\pm 1$  wk]) will be conducted on dosing day for the MOD-4023 arm only for the collection of immunogenicity and PK sample. This visit can be done at the patient's home or at the study site, based on local regulations and nurse availability. If home visit is conducted, a questionnaire as described in [Appendix I](#) should be completed as well. Samples must be collected prior to dosing of MOD-4023.

In parallel to MOD-4023 patients Visit 3 (Day 10 [+4 days]), a phone interview will be conducted to Genotropin<sup>®</sup> arm patients and/or parents/guardians according to the questionnaire provided in [Appendix I](#) in which AE, local tolerability and concomitant medication information will be collected.

For the ECG that will be conducted at Visit 6b (Month 6/Wk 26 [ $\pm 3$  wks]) at 7-12 hours post-dose for MOD-4023 treated patients, patients will be requested to inject MOD-4023 during the day/night at their convenience and come to the study site at the requested time point for ECG.

Visits 6a and 6b might be combined on the same day (only if 6a is done prior to dosing).

The patient will come to the study site in the morning, perform the blood tests, afterwards will inject on site and will come back 7-12 hours post dosing for ECG assessment.

Genotropin<sup>®</sup> patients will have an ECG assessment at Visit 6 (no time limitation).

### 5.2.1 Visit 2 (Day 1/Baseline) – recommended injection days as indicated in [Appendix E](#)

Visit 2 must be conducted within 2 wks of randomization.

The following assessments will be conducted on Day 1/Baseline:

<sup>a</sup> 1. Western Europe, Israel, Australia, New Zealand, Canada and USA; 2. Central and Eastern Europe, Greece, Turkey, Latin America and Asia except for India and Vietnam 3. India and Vietnam.

<sup>b</sup> All visits, except Visit 3, can be conducted within the specified window to accommodate patient availability, but must be conducted on day 4 (-1) post dose.

<sup>c</sup> Applicable only for MOD-4023, Visit 3 assessments, if conducted on Day 14 (dosing day), should be done prior to dosing.

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- Auxology measurements: Actual Ht (mean of three consecutive measurements) measured on a calibrated wall mounted stadiometer.
- AEs, local tolerability (aligned with Appendix H), and concomitant medications.
- Overall health status assessment, including complete physical examination and vital signs.
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Pubertal status (according to Tanner stages).
- Assessment of thyroid function and biochemical markers: TSH, FT4, IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Assessment of MOD-4023 serum levels (applicable for MOD-4023 arm only).
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Parameters of lipid metabolism: overnight fasting cholesterol, triglycerides, HDL, LDL, Lp(a), FFA.
- Assessment of anti-MOD 4023 and anti-hGH Ab (depending on arm of study).
- BA<sup>a</sup>.
- ECG pre-dosing.
- Training for patients, parents or legal guardians on drug administration.
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).
- Training for patients, parents or caregiver for completing the PAT assessment.
- Administration of study drug at the study site by patient or parent/caregiver.
- MOD-4023 on-site OAT assessment (USA only).
- MOD-4023 on-site PAT assessment (USA only).
- QoL Questionnaire completion (in specific countries as indicated in [Appendix L](#)).
- Drug dispensing and accountability.

### 5.2.2 Visit 3<sup>b,c</sup> (Day 10 [+4days] post first dose) for MOD-4023 arm only

The following assessments will be conducted at the study site or at the patient's home (if allowed according to local regulations):

- MOD-4023 serum levels.
- Anti-MOD-4023 Abs.
- AEs and local tolerability (aligned with Appendix H) assessment.
- Concomitant medication recording aligned with the questionnaire in [Appendix I](#).

<sup>a</sup> BA will be done at Visit 2 only in cases where historical bone scans (<6 months prior to Screening) were used to fulfill entry criteria. When performed, BA scans will be completed prior to dosing.

<sup>b</sup> Applicable only for MOD-4023, Visit 3 assessments, if conducted on Day 14 (dosing day), should be done prior to dosing.

<sup>c</sup> Blood samples for MOD 4023 treatment group can be collected at site OR at patient's home, based on local regulations and nurse availability. If home visit, a questionnaire, as described in [Appendix I](#), should be completed. If blood sample is collected on Day 14, it should be done prior to dosing.



### 5.2.3 Visit 3 (Day 10 [+4 days] post first dose) for Genotropin arm only<sup>a</sup>

- Phone interview and questionnaire completion as provided in [Appendix I](#).
- AEs and local tolerability (aligned with Appendix H) assessment.
- Concomitant medication recording aligned with the questionnaire in [Appendix I](#).

### 5.2.4 Visit 4 (Month 1/Wk 4 [+1wk])

The following assessments will be conducted at Visit 4 on Day 4 (-1) post dose:

- AEs, local tolerability, and concomitant medications.
- Overall health status assessment, including complete physical examination and vital signs.
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- MOD-4023 serum levels (applicable for MOD-4023 arm only).
- Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension).
- Anti-MOD-4023 Abs (MOD-4023 arm only).
- Anti-hGH Abs (Genotropin<sup>®</sup> arm).
- Return of used and unused injection devices to the site, diary card and PAT forms (USA patients only).
- Drug dispensing and accountability.

### 5.2.5 Visit 5 (Month 3/Wk 13 [ $\pm 1$ wk]), Visit 6 (Month 6/Wk 26 [ $\pm 1$ wk]), Visit 7 (Month 9/Wk 39 [ $\pm 1$ wk]), Visit 8 (Month 12/Wk 52 [ $\pm 1$ wk])

The following assessments will be conducted at Visits 5, 6, 7 and 8 on Day 4 (-1) post dose:

- Auxology measurements: Actual Ht (mean of three consecutive measurements) measured on a calibrated wall mounted stadiometer.
- AEs, local tolerability, and concomitant medications.
- Overall health status assessment, including complete physical examination and vital signs.
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Pubertal status (according to Tanner stages);
- Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche).
- Assessment of thyroid function and biochemical markers: TSH, FT4, IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Parameters of lipid metabolism: overnight fasting cholesterol, triglycerides, HDL, LDL, Lp(a), FFA.

<sup>a</sup> For the Genotropin<sup>®</sup> arm a visit by phone interview will be conducted as described in [Appendix I](#).

- Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension).
- BA at Visit 8 only.
- Individual dose adjustment every three months.
- Drug dispensing and accountability.
- MOD-4023 serum levels (MOD 4023 patients only).
- Anti-hGH Ab (Genotropin® patients only).
- ECG (Visit 6 only for Genotropin® patients). Patients in the Genotropin® arm will be requested to inject the study drug preferably at night and come to the clinic the following day for ECG assessment.
- Return of used and unused injection devices and diary cards.
- Return of completed PAT forms (USA only) (Visit 5 only) (applicable for MOD-4023 arm only).
- Anti-MOD-4023 Ab (Visits 5 and 7, MOD-4023 arm only, Visit 8 both arms).
- Informed consent for the LT-OLE (Visit 7 (preferred) or 8).
- QoL questionnaire (QoLISSY) at Visit 8 only.
- For males that are 13 years and older: LH, FSH and testosterone. For females that are 12 years and older: LH, FSH and estradiol (Visit 8 only).

#### 5.2.6 Visit 6a (Month 6/Wk 26 [ $\pm 3$ wk]) and Visit 8a (Month 12/Wk 52 [ $\pm 1$ wk]) – MOD-4023 Arm Only

Visit 6a and 8a will be conducted on dosing day before dosing<sup>a</sup>, for MOD-4023 arm patients only. The following assessments will be conducted at the study site or at the patient home (if allowed according to local regulations):

- MOD-4023 serum levels.
- Anti-MOD-4023 Ab.
- AEs and local tolerability (aligned with Appendix H) assessment.
- Concomitant medication recording aligned with the questionnaire in [Appendix I](#).

#### 5.2.7 Visit 6b (Month 6/Wk 26 [ $\pm 3$ wk]) – MOD-4023 Arm Only

Patients in the MOD-4023 arm will be requested to inject the study drug during the day/night at their convenience and come to the study site at 7-12 hours post-dose for ECG assessment.

Visit 6a and 6b may be combined and conducted on the same date; in such case, the patient will inject the study drug at the study site following blood samples collection and will come back for ECG measurements (Visit 6b) 7-12 hours post dosing.

#### 5.2.8 Visit 9 (Month 13/Wk 56 ( $\pm 5$ days)) – Only for patients not continuing on into the OLE study

Patients not continuing in the OLE study will be contacted 30 days ( $\pm 5$  days) after Visit 8 (inclusive of 8a) in order to obtain safety related information (see questionnaire in Appendix I).

<sup>a</sup> These visits can be done on any dosing day within the visit window.

### 5.3 LT-OLE PERIOD (VISITS 10 TO 16)

After completion of 12 months treatment in the main study and continuing to meet the LT-OLE inclusion/exclusion criteria of this protocol, patients will be eligible to rollover into a single arm LT-OLE treatment period with MOD-4023. An informed consent/assent will be obtained from patients and/or parent/s or legal/authorized guardian as required per local regulation.

Patients who received MOD-4023 during the main study will continue with the same dose of MOD-4023 (mg/kg/wk), adjusted for body weight. For these patients, study visits will take place every three months on Day 4 (-1) post-dose. These patients will consent to the LT-OLE preferably during Visit 7 of the main study to ensure availability of MOD-4023 at their next visit. If necessary, informed consent can be obtained at Visit 8 main study/10 LT-OLE. These Patients will continue treatment at Visit 8/10, skip Visits 9 and 11 and have a telephone visit at Visit 12 (one month post LT-OLE entry (Month 13 [ $\pm 2$ wk])).

Patients who received Genotropin<sup>®</sup>, during the main study will be switched to MOD-4023 starting no less than one day [ $+2$ wk] after cessation of Genotropin<sup>®</sup> treatment. Recommended injection days are indicated in Appendix E. These patients will consent to the LT-OLE preferably during Visit 7 of the main study to ensure availability of MOD-4023 at their next visit. If necessary, informed consent can be obtained at Visit 8/10. Patients will begin treatment with MOD-4023 at Visit 8/10, skip Visit 9 and have additional onsite visits at Visit 11 (Month 12, Day 10 post first MOD-4023 dose [ $10+4$  days]) and Visit 12 (one month (Month 13 post first MOD-4023 dose [ $\pm 2$ wk])). All Patients will be provided with a diary card.

For all patients switching from Genotropin<sup>®</sup> to MOD-4023, the following will also be done:

- MOD-4023 will be dispensed based on patient weight at a starting dose of 0.66 mg/kg/wk.
- Training on and administration of MOD-4023 using the device.
- Local tolerability after first dose administered at site.

Patients who experience a delay for any reason between completion of the main study and entry into the LT-OLE may have to temporarily stop treatment. If initiation/re-initiation of treatment occurs less than 90 days after Visit 8 only training on and administration of MOD-4023 and local tolerability after first dose administered at site is required.

Patients who are off treatment for more than 90 days due to technical reasons e.g. delay in approval of Protocol Amendment may be allowed to continue into the LT-OLE after confirmation of availability of all required baseline LT-OLE assessments (Visit 8/10). The following tests and assessments must be repeated:

- Safety laboratory tests: chemistry, hematology and urinalysis.
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Assessment of anti-MOD-4023 Ab for all patients (Genotropin<sup>®</sup> group – baseline for future tests).
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGF-BP-3 and IGF binding protein-3 (IGFBP-3) SDS serum levels.

5.3.1 Visit 11 (Month 12, Day 10 [+4days] post first MOD-4023 dose) for patients switching from Genotropin® to MOD-4023 only

The following assessments will be conducted at the study site or at the patient's home (if allowed according to local regulations):

- MOD-4023 serum levels.
- Anti-MOD-4023 Abs.
- AEs and local tolerability (aligned with Appendix H) assessment.
- Concomitant medication recording aligned with the questionnaire in [Appendix I](#).

5.3.2 Visit 12 (one month post first MOD-4023 dose(Month 13 [ $\pm 2$ wk])) will be performed on site for patients switching from Genotropin® to MOD-4023

The following assessments will be conducted at Visit 12 on Day 4 (-1) post dose:

- AEs, local tolerability, and concomitant medications.
- Overall health status assessment, including complete physical examination and vital signs.
- Urine pregnancy test once a female patient reports first menstrual cycle (menarche).
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension).
- MOD-4023 serum levels.
- Anti-MOD-4023 Abs.
- Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension).
- Return of used and unused injection devices to the site and diary card.
- Drug dispensing and accountability.

Existing MOD-4023 patients will have a telephone visit at Visit 12 (one month post LT-OLE entry [Month 13  $\pm 2$ wk]) to ask about AEs, local tolerability and concomitant medications. This visit will be completed using the questionnaire in Appendix I.

5.3.3 Visit 13 (Month 15/Wk 65 [ $\pm 2$ wk]), Visit 14 (Month 18/Wk 78 [ $\pm 2$ wk]), Visit 15 (Month 21/Wk 91 [ $\pm 2$ wk]), Visit 16 (Month 24/Wk 104 [ $\pm 4$ wk])

During the first year of LT-OLE, the following assessments will be conducted every three months on day 4 (-1) post-dose for all patients:

- Auxology measurements: Actual height (average of three consecutive measurements) measured on a calibrated wall mounted stadiometer.
- Overall health status assessment, including complete physical examination and vital signs assessment.
- Individual dose adjustment based on weight.
- AEs, local tolerability, and concomitant medications.

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- Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche).
- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Assessment of MOD-4023 serum levels.
- Assessment of anti-MOD-4023 Ab.
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).
- Return of used and unused injection devices to the site and diary card.
- Drug dispensing and accountability.

The following assessments will also be conducted at Visit 13 (Month 15), Visit 14 (Month 18) and Visit 16 (Month 24) on day 4 (-1) post-dose visits:

- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of thyroid function: TSH, FT4.
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Parameters of lipid metabolism: overnight fasting cholesterol, triglycerides, HDL, LDL, Lp(a), FFA.

The following assessments will also be conducted at Visit 16 (Month 24) on day 4(-1) post-dose:

- ECG.
- Bone age.
- Pubertal status.
- For males that are 13 years and older: LH, FSH and testosterone. For females that are 12 years and older: LH, FSH and estradiol.

Collection of samples for MOD-4023 serum levels and anti-MOD-4023 Ab levels must be obtained on dosing day pre- dose. For the ECG that will be conducted at 7-12 hours post-dose patients will be requested to inject MOD-4023 during the day/night at their convenience and come to the study site at the requested timepoint for the ECG. Visits may be split to allow for pre-dose blood collection for serum levels and antibody tests and post-dose ECG or the patient will be asked to come to the study site for blood collection, administer the required dose, and return to the study site 7-12 hours post-dose.

#### **5.4 LT-OLE (VISITS 17 TO STUDY CLOSURE)**

Following completion of the first year of LT-OLE the following assessments will be conducted every three months on day 4 (-1) post-dose for all patients:

- Auxology measurements: Actual height (average of 3 consecutive measurements) measured on a calibrated wall mounted stadiometer.
- Overall health status assessment, including complete physical examination and vital signs assessment.
- Individual dose adjustment based on weight.

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- AEs, local tolerability, and concomitant medications.
- Urine pregnancy test at every visit once a female reports first menstrual cycle (menarche).
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).
- Return of used and unused injection devices to the site and diary card.
- Drug dispensing and accountability.

The following assessments will also be conducted every six months on day 4 (-1) post-dose visits:

- Assessment of biochemical markers: IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of thyroid function: TSH, FT4.
- Parameters of glucose metabolism: overnight fasting glucose, overnight fasting insulin, HbA1c.
- Parameters of lipid metabolism: overnight fasting cholesterol, triglycerides, HDL, LDL, Lp(a), FFA.
- Assessment of MOD-4023 serum levels.
- Assessment of anti-MOD-4023 Ab.

Additional assessments will be performed once a year, every 12 months on dosing day or Day 4(-1):

- ECG.
- Bone age.
- Pubertal status (according to Tanner stages).
- For males that are 13 years and older: LH, FSH and testosterone. For females that are 12 years and older: LH, FSH and estradiol.

The following assessments will be conducted during the EOS/ET visit:

- Auxology measurements- Actual Ht (mean of 3 consecutive measurements) measured on a calibrated wall mounted stadiometer.
- AEs, local tolerability, and concomitant medications.
- Overall health status assessment, including complete physical examination and vital sign assessments.
- Safety laboratory (chemistry, hematology and urinalysis).
- Pubertal status.
- Urine pregnancy test for female patients who have reported menarche.
- Thyroid function and biochemical markers: TSH, FT4, IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS serum levels.
- Parameters of glucose metabolism (overnight fasting glucose, overnight fasting insulin, HbA1c).

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- Parameters of lipid metabolism (overnight fasting cholesterol, triglycerides, HDL, LDL, Lp(a), FFA).
- For males that are 13 years and older: LH, FSH and testosterone. For females that are 12 years and older: LH, FSH and estradiol.
- Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension).
- Bone age.
- MOD-4023 serum levels.
- ECG.
- Return of used and unused injection devices and diary cards.
- Anti-MOD-4023 Abs.

Patients will be required to visit the study site for assessment of biochemical markers on day 4 (-1) post-dose. If a visit is performed on a dosing day, collection of MOD-4023 serum levels and anti-Mod-4023 Ab levels must be obtained pre-dose. For End of Treatment during LT-OLE Year 1, the ECG will be conducted at 7-12 hours post-dose and patients will be requested to inject MOD-4023 during the day/night at their convenience and come to the study site at the requested timepoint for the ECG. An ECG must still be obtained even if patients do not take the final dose. Visits may be split to allow for pre-dose blood collection for serum levels and antibody tests and post-dose ECG or the patient will be asked to come to the study site for blood collection, administer the required dose, and return to the study site 7-12 hours post-dose. For ET from LT-OLE Year 2 onwards ECG can be conducted without a timeframe requirement i.e. at any time, although the date and time that each is performed will be recorded.

Patients will be contacted by telephone 30 days [ $\pm$  5 days] after EOS/ET visit in order to obtain safety related information.

### 5.5 EARLY DISCONTINUATION STUDY VISIT

If, during the main study, a patient discontinues prematurely from the study for the reasons specified in Section 4.4, the same procedures planned for Visit 8 (12 months/Wk 52 [ $\pm$ 1 wk]) will be conducted. Other procedures and evaluations will be completed as deemed necessary by the Investigator.

If, during the LT-OLE, a patient discontinues prematurely from the study for the reasons specified in Section 4.4, the same procedures for LT-OLE EOS/ET will be conducted.

### 5.6 UNSCHEDULED VISIT

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the Investigator or requested by the Global Study MM. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not limited to) laboratory tests, ECG, vital signs and physical examination.

## 5.7 EFFICACY ASSESSMENTS AND ENDPOINTS

### 5.7.1 Ht and Annual HV

Ht measurements must be performed according to [Appendix C](#) with a calibrated wall-mounted (e.g. Harpenden or similar) stadiometer and should ideally be conducted at the same time of the day for each visit, preferably in the morning. To ensure consistency of results, ideally the same auxologist will perform these measurements for each patient at each visit to minimize the variability of measurements. The time of measurement and the observer's initials is to be recorded in the eCRF. Three (3) independent readings will be recorded for each visit in the eCRF.

The Ht Standard Deviation Score (Ht SDS) will be derived from the age and gender standards from 2000 Center for Disease Control Growth Charts ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts)) by the Sponsor during the study.

Annualized HV will be calculated in cm as the change in Ht from Visit 2 to Visit 8 (after 12 months of treatment) during the main study and again every 12 months thereafter compared to the measurement taken 12 months prior during the LT-OLE.

### 5.7.2 BA

BA will be determined by X-ray according to Greulich-Pyle method ([Greulich 1959](#)) using central BA reader during the main study at Screening (Visit 1), Visit 2<sup>a</sup>, and Visit 8 (Month 12). X-ray films of the left hand and wrist will be taken as outlined in [Appendix D](#) and will be sent to a qualified central reader. The central reader will be blinded to the CA, drug allocation, and name of the patients. X-ray films will hold only an identification number and gender. Details of the central BA reader and the procedure for blinding and shipping of X-rays will be provided to the investigator.

During the LT-OLE, BA will be determined by X-ray every 12 months. The central reader will be blinded to the CA and name of the patient.

### 5.7.3 Biochemical Markers: IGF-1 and IGFBP-3

hGH stimulates hepatic production and release of IGF-1 into the systemic circulation. IGF actions are modulated by a family of 6 structurally-related binding proteins (IGFBPs 1-6), which bind IGFs, but not insulin with high affinity. More than 99% of IGFs bind to IGFBPs. In particular, IGFBP-3 is the predominant circulating IGFBP.

Clinical evaluations of IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS will be performed at every study visit during the main study except Visits 3, 6a, 6b, 8a, and 9. During the LT-OLE, these evaluations will be performed as per the schedule of events in [Appendix A](#).

## 5.8 SAFETY ASSESSMENTS AND ENDPOINTS

Safety assessments will be based on changes from baseline of clinical AEs (including local tolerability, i.e. injection site reaction) reported by the patient or observed by the investigator, concomitant medication use, treatment compliance, vital signs, ECG, physical examination, fundoscopy and laboratory assessments (hematology, blood chemistry, glucose metabolism, lipid

<sup>a</sup> If not done with the central reader during the Screening visit.



metabolism, thyroid function, IGF-1 levels, immunogenicity and urinalysis). AEs and concomitant medication use will be assessed at every visit. Physical examination and safety laboratory assessments will be performed according to the schedule of events in Appendix A.

#### 5.8.1 AEs

AEs, including local tolerability (i.e. injection site reactions), will be assessed at all study visits (excluding Visits 1 and 6b) throughout the study. In addition, patients will be requested to complete a patient diary at home to collect data on AE, concomitant medications and local tolerability.

Any AEs that occur throughout the study will be recorded. Any new AE that occurs between scheduled visits should be brought to the attention of the investigator and recorded in the patient's medical file and on the appropriate eCRF page. AEs should be followed until resolution or stabilization.

#### 5.8.2 Local Tolerability (Injection Site Reactions)

Assessment of local tolerability will be performed by examining the injection sites (by the investigator if a reaction is present at the time of every visit, excluding Visit 1) and on the basis of anamnestic data and records in the patient diary. Observations of local injection site reactions will be recorded on the appropriate eCRF pages.

The patients and parents/legal guardians will be trained to record, at least once weekly, any injection site reaction in their diaries.

An abnormal injection site reaction is defined as:

- Injection site reaction which is reported or observed at the time of visit or during a phone call and is of moderate to severe in intensity.
- Injection site reaction between the last and present visit or remaining at the time of visit which require medical attention, or injection site reaction resulting from a previous injection, other than the last injection.
- Any other injection site reaction deemed abnormal to the investigator's judgment, other than those ordinarily observed in subcutaneous injections.
- Pain score  $\geq 4$  (as reported in the patient diary).

If an injection site reaction meets the criteria for "abnormal" defined above, it will be considered and assessed as an AE.

- Pain: For patients, injection site pain will be evaluated by the investigator or designated personnel if the injection is given at the medical center, and by the parent/legal guardian if the injection is given at home. The pain will be evaluated at least once weekly using a Pain Rating Scale and recorded in the patient diary. In addition, each patient and parent/guardian will be queried during study visits regarding possible injection site pain.
- Pain score  $\geq 4$  should be reported as an AE.

#### **Photographs of Injection Site Reactions**

An optional photograph of an abnormal local injection site reaction may be taken. Photographs may be taken by site staff during a visit or by a patient or parent/caregiver between study visits in which case a copy should be given to study staff at the next study visit. The photograph, if available will be kept signed and dated in the patient medical record.

### 5.8.3 Concomitant Medication Use

Use of concomitant medication will be recorded at all study visits (excluding visit 6b).

### 5.8.4 Treatment Compliance

Diary cards will be reviewed at each visit for treatment compliance from previous visits.

### 5.8.5 Vital Signs

Vital signs measurements will be recorded at all study visits during the main study except Visits 3, 6a, 6b, 8a and 9 and as per the schedule of events in Appendix A during the LT-OLE. Vital Signs will include body temperature, respiration, blood pressure (BP) and heart rate after the patient has sat quietly for at least 5 minutes.

### 5.8.6 Physical Examination

A complete physical examination will be performed at all study visits during the main study except Visits 3, 6a, 6b, 8a and 9 and as per the schedule of events in Appendix A during the LT-OLE. The physical examination will include appearance, eyes, ears, nose, head, throat, neck, chest, lungs, heart, abdomen, extremities, skin and musculoskeletal system. Weight will be measured as part of the physical examination at relevant visits, ideally fasted in the morning, without shoes and having removed all outwear such as jackets, sweaters or sweatshirts and heavy pocket items. CS findings at screening will be reported as medical history and as AEs after the Screening visit.

### 5.8.7 ECG

During the main study, ECG (preferably 12-lead) will be performed at Visit 2 (pre-dose), Visit 6b at 7-12 hours post dosing (MOD-4023 arm) and at Visit 6 for Genotropin<sup>®</sup> arm (no time limitation). During the LT-OLE, ECG (preferably 12-lead) will be performed annually every 12 months until study closure.

Initially ECG output will be evaluated by the Investigator at time of performance (signed and dated) and the printout (including photocopy) should be kept in the patient's medical file. When potentially CS findings are detected by the investigator, a cardiologist should be consulted for a definitive interpretation. All communications and diagnoses should be filed in the patient's medical file.

The final determination of whether the ECG findings are of CS to the patient rests with the PI and reported as normal /abnormal in the eCRF.

### 5.8.8 Fundoscopy

Fundoscopy evaluations will be conducted only if there are symptoms of increased intracranial pressure (persisting headache different from typical headache patterns or headache accompanied by nausea/vomiting that is not self-limited and/or associated with other symptoms suggestive of infectious illness such as fever or myalgias).

Fundoscopy will be performed according to standard of care and confirmed by an ophthalmology evaluation if necessary.

### 5.8.9 Laboratory Assessments

All routine clinical laboratory assessments will be performed by central laboratory as provided in [Appendix K](#) according to the schedule in [Appendix A](#), other than urine pregnancy testing, when required, which will be conducted at the local laboratory. The laboratory evaluations will include:

1. Hematology: Red Blood Cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), Mean Cell Hemoglobin (MCH), Mean Cell Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), White Blood Cell (WBC) count and differential, platelet count, prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT) (if indicated only).
2. Serum chemistry: total protein, albumin, total bilirubin, alanine aminotransaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), alkaline phosphatase, sodium, potassium, calcium, phosphate, blood urea nitrogen (BUN), liver function test (LFT), creatinine.
3. Lipid metabolism: overnight fasting cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), lipoprotein a (Lp(a)), Free Fatty Acids (FFA).
4. Glucose metabolism: overnight fasting glucose and insulin, HbA1C.
5. Thyroid function: TSH, FT4.
6. Immunogenicity: anti-MOD-4023 Ab (MOD-4023 arm only during the main study and all patients during the LT-OLE) and Abs to r-hGH (all patients). It is recommended that if the Genotropin patients normally administer their drug in the morning, that they wait on those visit days to administer the Genotropin<sup>®</sup> until after the blood sampling.
7. IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS levels.
8. MOD-4023 serum levels (MOD-4023 arm only during the main study and all patients during the LT-OLE).
9. Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.
10. Urine pregnancy test.
11. Luteinizing hormone (LH), Follicle-stimulating hormone (FSH) and testosterone (for males that are 13 years and older).
12. LH, FSH and estradiol (for females that are 12 years and older).

For further details on blood sample collection and shipment to the central laboratory, please refer to the Central Laboratory Manual.

## 5.9 MOD-4023 DEVICE USABILITY

### 5.9.1 PAT as provided in [Appendix M](#) (USA Only).

The PAT will be used to record all the patient's or caregiver's injections using MOD-4023 PEN at Wks 1, 2, 3, 4, 5 and 6. It will be completed on site at Wk 1 and at home at Wks 2, 3, 4, 5, and 6 by the actual user of the PEN or parent/legal guardian. The PAT will be completed for all injection attempts at Wks 1, 2, 3, 4, 5, and 6 whether the patient was able to complete the injection or not.

At Visit 2, prior to MOD-4023 on site injection, patients and caregivers will be trained to use the device as outlined in the Patient Dosing Instructions Booklet. In addition, patients and caregivers will be trained on the completion of the PAT and instructed the following:

- In any given wk a new PAT will be completed for each PEN used that wk (in some cases more than 1 PEN may be used for full dose administration; in some cases, more than 1 injection from the same PEN may be needed, in which case only 1 PAT is completed for that PEN that wk).
- On Visit 4 (Month 1/Wk 4 [+1 wk]), to bring the completed PATs and confirming proper recording by the study staff.
- To complete the PAT forms (including the first injection) post MOD-4023 weekly injections. The PAT forms completed after Visit 4 will be collected on Visit 5 (3 months).
- To return all used injection devices and PAT forms as defined in the schedule of activities. If the PAT forms are not completely and correctly filled in as determined by the PI, up to 4 additional wks will be added to the PAT assessment time, not to exceed a total of 6 dose administrations.

#### 5.9.2 OAT as provided in [Appendix N](#) (USA Only).

The OAT will be used to record the observer's assessment of an administration with the device on site during Visit 2 after patient or caregiver injected MOD-4023.

- A new OAT will be completed for each PEN used (in some cases more than 1 PEN may be used for full dose administration, in which case an OAT will be completed for each PEN used; in some cases, more than 1 injection from the same PEN may be needed, in which case only 1 OAT is completed for that PEN).

#### 5.9.3 Assessment of Successful Operation of the MOD-4023 PEN

All USA MOD-4023 injection devices used during the main study will be collected and returned to the study site. A subset of returned devices will be examined to provide evidence of appropriate device function and robustness. In addition, any devices which are perceived to malfunction (either before or during use) will be returned through a formal complaint system and evaluated to understand the root cause of the failure.

### 5.10 PUBERTAL ASSESSMENT

Patients may enter puberty during the course of the study and contraception might become relevant. The puberty state is evaluated on routine basis as described above. Once a female patient reports first menstrual cycle (menarche) study sites should perform urine pregnancy test at every visit.

For a female child, even though she is pre-pubertal at enrollment, it is possible that she may enter puberty during the course of the study and could theoretically become pregnant. As she cannot continue in the study if she were to become pregnant, the investigator or delegated study staff is obligated to discuss this issue ahead of time with the patient and her parents/legal guardian. Patients must refrain from sexual activity during the study i.e. observe complete sexual abstinence as the only acceptable contraceptive measure in this study.

If a patient were to become pregnant or thinks she may have become pregnant during the study, the Investigator should be informed immediately, such information will be recorded in study documentation and the patient will be asked to stop taking the study medication as it may cause unforeseen risks to the unborn baby. Serum pregnancy test will be scheduled immediately in such

cases, and in the case of the negative result the test should be repeated in two wks to confirm or exclude the pregnancy.

In case of negative test results confirmed by the second negative test result, based on the Investigator's recommendation, the Sponsor may allow the patient to return to the full study schedule with guidance from Sponsor, if applicable. or the patient will be offered to remain in the study without study medication, but to complete the remaining study procedures as scheduled (missed visits are recommended to be realized).

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. Pregnancy tests will also be done whenever one menstrual cycle is missed during treatment (main study and LT-OLE) and when potential pregnancy is otherwise suspected and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study for follow up.

The pregnancy must be reported to the Global Study MM, pharmacovigilance (see section 7.6) and Sponsor. A follow-up period on mother and child will be defined based on individual basis and per discussion with DSMB.

#### Male patients

The effect of MOD-4023 on sperm is not known.

The Investigator is obligated to discuss this issue of possible conception ahead of time with male patients and his parents/legal guardian. Patients are requested to refrain from sexual activity during the study i.e. observe complete sexual abstinence as the only acceptable contraceptive measure in this study.

If partner of the male patient becomes pregnant, the Investigator should be informed immediately. The patient doesn't need stop taking the study medication. The pregnancy will be reported to the Global Study MM, pharmacovigilance and Sponsor and follow-up period on mother and child will be defined based on individual basis and per discussion with DSMB.

### **5.11 QoL QUESTIONNAIRE**

QoL will be measured using the QoLISSY questionnaire which was developed to provide clinicians and researchers a validated tool to assess the impact of short stature on children. The QoLISSY core questionnaire consists of 22 like-scaled items assigned to the core dimensions: Physical, Social, and Emotional.

For patients below the age of 7 and 0 days a parental QoLISSY core questionnaire will be completed guided by the parent or caregiver. Patients above and including the age of 7 and 0 days will be encouraged to complete the child QoLISSY core questionnaire on its own. Both questionnaires are provided in [Appendix L](#) as well as a designated list of countries in which it will be completed.

The QoLISSY core total score is calculated by the sum of the means of these 3 dimensions and divided by 3. All scores will be transformed from raw scores to 0 to 100 scores, consistent with the QoLISSY scoring manual. Higher values represent a higher QoL.

The QoLISSY will be administered at Visit 2 and at the end of the study Visit 8, i.e., after 12 months of treatment at designated countries (determined by availability of translated tools) per the list in [Appendix L](#).

## 6. IP

### 6.1 IDENTITY OF IP

MOD-4023 is a long-acting modified r-hGH which utilizes CTP technology.

MOD-4023 will be provided as a solution for injection containing 20 or 50 mg/mL MOD-4023 in a multi-dose disposable pre-filled PEN.

The formulation will include citrate, histidine, sodium chloride, m-cresol, Poloxamer 188, pH = 6.6.

### 6.2 REFERENCE THERAPY

Genotropin<sup>®</sup> is a daily GH, which will be used as the reference therapy during the main study.

A delivery device (Genotropin<sup>®</sup> Pen) will be used for daily (evening/bedtime) SC administration of Genotropin<sup>®</sup> into the region of the upper arms, buttocks, thighs or abdomen (8 locations). Injection sites should be rotated.

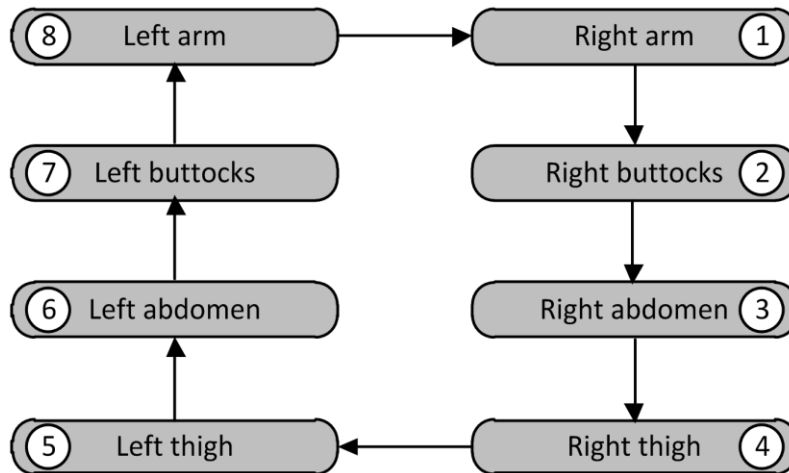
The device is intended to assist self-injecting adult and paediatric patients, healthcare professionals and caregivers with the daily SC injection of the r-hGH, primarily self-administered at home or in a healthcare environment

Starting dose regimen for Genotropin<sup>®</sup>: 0.034 mg/kg/day (or 0.24 mg/kg/wk divided equally to 7 injections over a wk). Genotropin<sup>®</sup> will be used and monitored according to the approved product labeling and dose adjusted based on weight every 3 months during the main study.

### 6.3 STUDY DRUG ADMINISTRATION

MOD-4023 will be administered as a SC injection preferably (but not required) in the morning hours once weekly, using the PEN into the upper arms, buttocks, thighs, or abdomen (8 locations). It is recommended that all 8 injection sites are used successively, using a different injection site at each subsequent injection. The same injection site should be used only after all other injection sites have been rotated (see recommended rotation scheme below).

The starting dose for the administration will be 0.66 mg/kg/wk. All patients on Genotropin<sup>®</sup> that complete Visit 8/10 and continue into the LT-OLE will start treatment with MOD-4023 at 0.66 mg/kg/wk.



**Figure 1: Recommended rotation of injection sites for Genotropin® and MOD-4023**

If a patient on MOD-4023 treatment misses a dose for not more than 72 hours (i.e. the dose is  $\leq 72$  hours late), then he/she will take a full dose as soon as he/she remembers that an injection was missed. Then the patient will go back to taking the study medication on the regular day of the wk. If the dose is more than 72 hours late, the patient will not take a dose for the whole wk and will continue taking the study medication on the regular day the following wk.

The patient should notify site staff about the delayed injection or the missed dose and be instructed by the site as for the next visit schedule.

In case the delayed injection is in the wk when an on-site visit is planned, the site should confirm that the visit date follows the proper post injection interval (for example: three to four days post dosing, in case IGF-1 samples should be collected). If not, the visit date should be rescheduled to meet protocol visit dates requirements. In case the injection was missed, the on-site visit in that wk should be rescheduled, to meet the required post dosing interval.

If a patient on Genotropin® misses a dose he/she should resume the medication with the next scheduled dose and should not double any doses.

In case the prescribed dose cannot be fully set for a single injection on a PEN, the patient should be instructed how to split the dose into 2 injections. The partial dosing can occur in 2 cases:

1. Two (2) injections using 1 PEN. In case the prescribed dose is higher than the maximum dose which can be selected according to the PEN amount, the patient should be instructed to subtract the dose already received from the prescribed dose and set the PEN accordingly.

For example, if the full prescribed dose is 33.5 mg and the PEN only allows the dose selector to be set to 30.0 mg, the patient should inject another 3.5 mg using the same PEN.

2. Split dose between 2 PENS, the current PEN and a new PEN. This may happen when the complete dose cannot be fully administered from the PEN in use, the patient should be instructed to subtract the dose already delivered from the prescribed dose and set the new PEN accordingly.

For example, if the full prescribed dose is 25.0 mg and the volume left on the current PEN only allows the dose selector to be set to 20.5 mg, the patient should inject another 4.5 mg from the new PEN.

It is recommended to encourage the patients to use a calculator to plan the doses and to calculate the dose that should be adjusted for the second injection.

It is very important that for the second injection, whether from the same PEN or from a new PEN the patient replaces the needle and rotates the injection site and complete the patient diary for each of the 2 injections administered.

Further details are provided in the Patient Dosing Instructions Booklet.

Missing/Delayed dose should be reported in the patient diary and eCRF.

#### 6.4 DOSE MODIFICATION PLAN

The dose of MOD-4023 and Genotropin<sup>®</sup> (main study) will be assessed every 3 months based on patient's body weight. Doses will be determined by the IRT system and will include an automatic rounding – either up or down – to the closest PEN increment (0.2 increments in 20 mg/ml pens and 0.5 increments in 50 mg/ml pens).

Doses may be decreased for safety reasons according to the pre-defined dose-adjustment criteria (which will be based on the severity of AEs or repeated, elevated levels of IGF-1 SDS).

##### 6.4.1 Dose Decrease

For patients on MOD-4023, the dose will be decreased based on two, repeated day 4 (-1) levels of IGF-1 > +2.0 SDS. For patients on Genotropin<sup>®</sup>, the dose may be decreased based on repeated IGF-1 levels > +2.0 SDS.

If a patient has an IGF-1 level > +2.0 SDS, they will be requested to return for an unscheduled visit within 4-6 wks after the > +2.0 SDS result, on **day 4(-1) post dose (for MOD-4023 treated patients or any day for Genotropin<sup>®</sup>)**. If their IGF-1 level is still > +2.0 SDS, the most recent dose will be reduced by 15% (i.e. to 0.56 mg/kg/wk for MOD-4023; 29 µg/kg/day for Genotropin<sup>®</sup>). The patient will be treated with the new dose for at least 4 wks before a subsequent IGF-1 determination can result in a further dose modification. If the next scheduled visit is less than 4 wks after the dose reduction was effectuated, the IGF-1 result at that visit must NOT be used for additional dose recalculation). At the time of the next visit (or at an extra, unscheduled visit which complies with the 4 wk minimum time period), IGF-1 will be retested. If the IGF-1 is still > +2.0 SDS, the dose will be reduced an additional 15% to 0.48 mg/kg/wk for MOD-4023 and to 24.7 µg/kg/day for Genotropin<sup>®</sup> arm. If the IGF-1 is still > +2.0 SDS following 2 dose reductions (at least 4 wks after second dose reduction), the Global Study MM (with the assistance of the DSMB if necessary) will decide on course of treatment on an individual basis. During the LT-OLE dose reduction for IGF-1 level >+2.0 SDS will be made following consultation with the Global Study MM on an individual patient basis.

If AEs are defined as “severe” AND drug-related, dose reduction will be introduced upon discussion with the Global Study MM and DSMB - dose should be reduced at a similar manner as above in a 2-step approach.

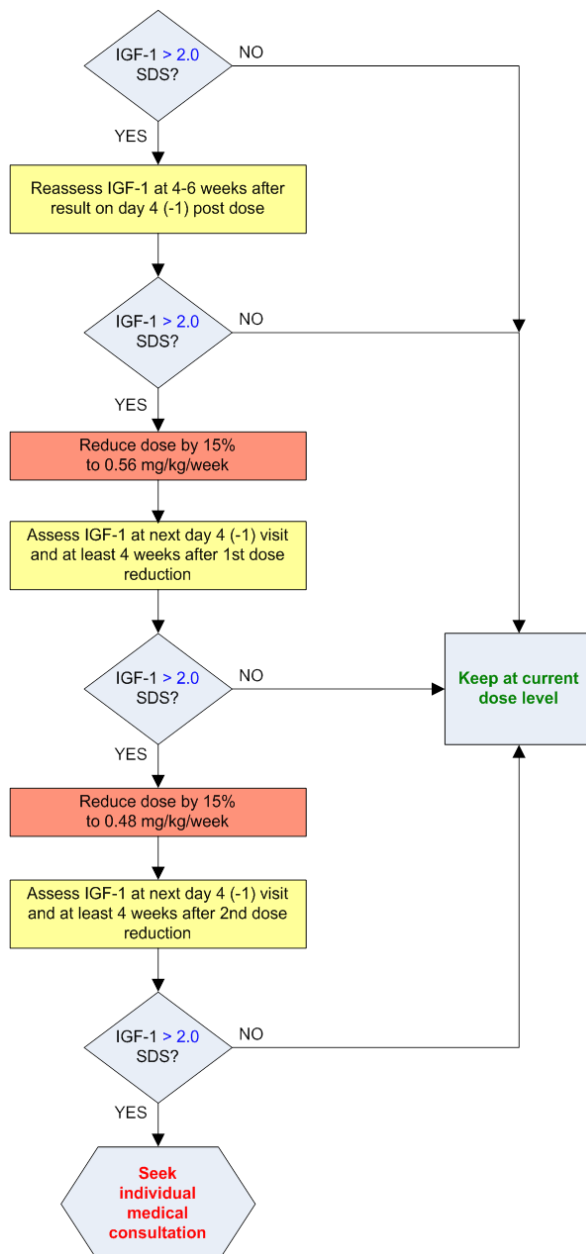


Every attempt should be made to maintain the patient on the originally allocated dose if possible. In case that the investigator does not plan to decrease the dose as described in the protocol, the Global Study MM should be notified.

The key safety data will be reviewed by an independent and external DSMB at least once every 4 months during the main study and approximately every 6 months during the LT-OLE. The DSMB will also include review of number or percentage of patients requiring dose reductions due to IGF-1 > +2.0 SDS and number or percentage of patients whose IGF-1 remains > +2.0 SDS, despite dose reductions (in both MOD-4023 and Genotropin<sup>®</sup> cohorts). DSMB review will also include review of number or percentage of patients requiring dose reductions due to AEs.

**Figure 2: Dose Decrease Adjustment Scheme**

The scheme and percent reduction is applicable for the Genotropin<sup>®</sup> arm as well, and in case that AEs are defined as “severe” AND drug-related.



## 6.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

During the main study, eligible patients will be randomly assigned in a 1:1 ratio (centralized randomization for each region as defined in the stratification factors) to one of two treatment groups, MOD-4023 or Genotropin<sup>®</sup> (reference therapy) for 12 months.

The following stratification factors will be considered when adding patients to one of the treatment groups:

1. Peak GH levels<sup>a</sup> ( $\leq 3$  ng/mL;  $>3$  to  $\leq 7$  ng/mL; and  $>7$  to  $\leq 10^a$  ng/mL).
2. CA ( $\geq 3$  years to  $\leq 7$  years, 0 days; and  $> 7$  years, 0 days.).
3. Region (1. Western Europe, Israel, Australia, New Zealand, Canada and USA; 2. Central and Eastern Europe, Greece, Turkey, Latin America and Asia except for India and Vietnam; 3. India and Vietnam).

Randomization will be performed through an IRT. The treatment codes for each patient will be held according to EDC. Shipment, Storage, Dispensing and Return of the IP will be managed through the IRT.

## 6.6 BLINDING

In order to minimize any potential sources of bias in this open-label study, certain identified roles will remain blinded to the treatment assignments (and to any other treatment-identifying information), during the main study. Details on the blinding procedures used will be provided in the Data Management Plan (DMP).

## 6.7 ACCOUNTABILITY AND COMPLIANCE OF IP

The IP will be packed and shipped at 2-8°C in appropriate boxes with temperature loggers. If, upon arrival at the study site, study drug supplies appear to be damaged or temperature control does not appear to have been maintained, the study monitor and drug supplier should be contacted immediately.

The investigator or study pharmacist should refer to the Pharmacy Manual for instructions on how to acknowledge receipt of all shipments of study drug and ancillary supplies, how to keep record of how much study drug was returned used and unused by each patient.

All IP must be kept refrigerated (2-8°C) in a locked area with access to the study drug limited to designated study personnel. Only personnel under the supervision of either the investigator or investigator trained and certified team member or the local pharmacist are authorized to dispense and administer study drug.

The investigator must maintain complete and adequate records documenting the receipt, use, loss, or other disposition of the IP supplies. All IP will be accounted for using a drug accountability form/record either on paper or electronically. The investigator is responsible that all IP accountability records are accurate and available for review by the study monitor, Sponsor or designee or the relevant regulatory authority.

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<sup>a</sup> Proportion of patients with peak GH levels  $>7$  to  $\leq 10$  ng/mL, will be capped at 35-40% of total sample-size, in the randomization scheme.

All used and unused study drugs (PENs) will be assessed for accountability by the study monitor as detailed in the study monitoring plan. Interim accountability and destruction may also be performed during the study, following Sponsor's written approval.

## 6.8 DESTRUCTION OF IP AND OTHER SUPPLIES

The Sponsor or designee will provide guidance on the destruction of used and unused IP, used and unused ancillaries and expired laboratory kits. If destruction is authorized to take place at the Investigator's site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. All destruction must be approved in advance in writing by the Sponsor and adequately documented.

## 6.9 PRIOR AND CONCOMITANT THERAPY

### 6.9.1 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 and food supplements and health store products) to be taken during the study must be approved by the Investigator.

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

### 6.9.2 Disallowed Previous Medications/Therapies

The following medications are not permitted prior to the Screening visit:

- Any r-hGH therapy.
- Systemic corticosteroids other than in replacement doses within the 3 months before ICF signing (temporary adjustment of glucocorticoids, as appropriate, is acceptable).
- Anabolic steroids other than gonadal steroid replacement therapy within 2 months before study entry.
- Use of IP (within 30 days of ICF signing).

### 6.9.3 Allowed Medications

The only concomitant medications allowed to be used in this study are those used at Baseline to control existing medical condition and/or those taken during the study to treat AEs. All concomitant medications used to treat AEs will be recorded in the patient's medical file and on the appropriate eCRF page.

Careful monitoring is advisable when MOD-4023 is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted. In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when MOD-4023 treatment is initiated.

#### 6.9.4 Prohibited Concomitant Medication

The following medications are not permitted during the study and may lead to withdrawal of the patient from the study:

- Any hormonally active medication other than replacement therapy for pituitary failure. Glucocorticoid replacement dosing should be carefully adjusted in children receiving MOD-4023 and Genotropin<sup>®</sup> and glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth.
- Any new long-term glucocorticoid treatment should be noted on the concomitant medication form and the patient should be retained in the safety population, but not the per-protocol population. Short term glucocorticoid treatment is allowed.
- Anabolic steroids (including testosterone replacement therapy) should not be taken.
- Weight loss drugs.
- Psychiatric medications typically associated with weight changes and/or diabetes excluding medications used to treat ADHD.

## 7. SAFETY AND PHARMACOVIGILANCE

### 7.1 ADVERSE EVENT

An AE is any adverse change from the patient baseline condition, whether or not considered IP related. This includes any subjective signs, symptoms or diagnosis, clinical significant deviation from baseline laboratory values or vital signs, or worsening (more severe, more frequent or increased in duration during the IP treatment) of the concomitant disease present at baseline visit (after initiation of IP treatment). Stable chronic conditions that are present prior to study entry and do not worsen during the study will not be considered AEs. Disease-related AEs will be considered AEs only if they worsen beyond what would be expected in the normal progression of the disease. In all cases, the etiology should, as much as possible, be identified and the Sponsor notified.

An abnormal result of diagnostic procedures including abnormal laboratory or vital sign findings will be considered an AE if it:

- Results in patient's withdrawal by the investigator,
- Is associated with clinical signs or symptoms,
- Is considered by the physician to be of CS.

AEs reported by the patient or observed by the Investigator will be individually listed on an AE form in the eCRF as follows: the specific event or condition, whether the event was present pre-study, the dates and times of occurrence, duration, severity, relationship to study medication, specific counter measures and outcome.

The intensity or severity of the AE will be characterized as:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible.

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The investigator will document in his/her opinion the relationship of the AE to study treatment using the criteria outlined in Table 1.

**Table 1: AE Relationship Criteria**

Relationship	Criteria
Not related	<ul style="list-style-type: none"> <li>The temporal sequence of the AE onset relative to administration of the IP is not reasonable.</li> <li>Disease or other drugs provide plausible explanations.</li> <li>Dechallenge (if performed) is negative or ambiguous.</li> </ul>
Unlikely related	<ul style="list-style-type: none"> <li>The temporal sequence of the AE onset relative to the administration of the IP is reasonable.</li> <li>Could also be explained by disease or other drugs.</li> <li>Dechallenge (if performed) is positive or uncertain.</li> <li>Rechallenge is negative.</li> </ul>
Possibly related	<ul style="list-style-type: none"> <li>The temporal sequence of the AE onset relative to administration of the investigational is reasonable.</li> <li>Unlikely to be attributed to disease or other drugs.</li> <li>Dechallenge (if performed) is positive.</li> </ul>
Related	<ul style="list-style-type: none"> <li>The temporal sequence of the AE onset relative to administration of the IP is reasonable.</li> <li>Cannot be explained by disease or other drugs.</li> <li>Dechallenge (if performed) is positive and pharmacologically/ pathologically plausible.</li> <li>Rechallenge (if feasible) is positive.</li> <li>The AE shows a pattern consistent with previous knowledge of the IP or product class, i.e., pharmacologically or phenomenologically recognized/plausible or an objective and specific medical disorder.</li> </ul>

## 7.2 SERIOUS ADVERSE EVENT

A SAE is any AE occurring at any dose that suggests a significant hazard or side effect, regardless of the investigator or Sponsor's opinion on the relationship to the IP and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause),
- a life-threatening adverse drug experience,
- 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,
- 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.

Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and hospitalizations for treatment of non-AEs (e.g. cosmetic surgery or diagnostic procedure) are not considered SAEs.

**Significant 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.

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.

Any new SAE that occurs after the study period and is considered to be related (possibly/probably) to the IP or study participation should be recorded and reported immediately.

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 drug experience (event) is any AE, the specificity or severity of which is not consistent with information in the current IB for an unapproved IP or package insert/summary of product characteristics for an approved product (package inserts are available separately at the participating center).

### 7.4 DEFINITION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

A SUSAR is a Suspected Unexpected Serious Adverse Reaction. An Adverse Reaction is defined as any AE caused by a drug. A suspected adverse reaction is defined as an AE for which there is reasonable possibility that the drug caused the AE. The "reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. Any unexpected SAE that may be related to study drug is a SUSAR; however, unexpected SAEs that occur following treatment with a placebo solution usually does not qualify as a SUSAR. Because knowledge of treatment assignment during the main study is needed to complete the determination, the Sponsor's designee will provide the final determination as to whether an SAE is a SUSAR. During the LT-OLE the Sponsor will provide the final determination as to whether an SAE is a SUSAR.

### 7.5 NOTIFICATION ABOUT SERIOUS OR UNEXPECTED ADVERSE EVENTS

#### 7.5.1 Initial Notification

Each SAE must be reported by the Investigator to the Safety group immediately (within 24 hours) upon learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported SAE must also be reported within 24 hours of the investigator receiving it. If the SAE is unexpected and is thought to be possibly related to the study drug, a Clinical Safety Associate shall urgently request further information from the investigator. This is essential for collecting information to report to the competent regulatory authority (RA).

#### 7.5.2 Contact Persons and Numbers:

All SAE forms should be electronically sent via EDC both to the Global Study MM and to the global pharmacovigilance group. An appropriate distribution list is maintained within the EDC for reporting purposes.

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PPD [REDACTED]

PPD [REDACTED], MD

PPD [REDACTED]

Phone: PPD [REDACTED]

Fax: PPD [REDACTED]

Email: PPD [REDACTED]

Pharmacovigilance Unit:

inVentiv Health Clinical / Syneos Health  
"Commerzone", Bldg # 4, 6<sup>th</sup> Floor, Yerwada Jail Road,  
Yerwada, Pune 411006, India

These preliminary reports will be followed within 24 hours by detailed descriptions that will include a completed SAE form, copies of hospital case reports, autopsy reports and other documents, when requested and applicable and available.

The Investigator must complete the SAE Report Form (in the EDC system) in English, assess the relationship to study treatment and submit it electronically via eCRF within 24 hours to the global pharmacovigilance group.

Follow-up information is to be submitted on a new SAE Form (in the EDC system). The new form should clearly state that it is a follow-up to the previously reported SAE and give the date of the original report. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or discontinued study participation.

The following information should be provided in the SAE form to accurately and completely record the event (some of the data is automatically populated by the EDC which still maintains data privacy requirements):

1. Investigator name and site address.
2. Patient study identification number.
3. Patient demographics (gender, date of birth or age (in accordance with local regulations), weight, Ht).
4. Clinical Event:
  - Description - Description of event, referral to experts, additional tests done and results of these tests.
  - Date and time of onset, stop date, or duration.
  - Severity.
  - Treatment (including hospitalization).
  - Relationship to study drug (causality).
  - Action taken regarding study drug.
  - Information on recovery and any sequelae.

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- If the SAE resulted in death:
  - Cause of death (whether or not the death was related to study drug).
  - Autopsy findings (if available).
- Medical History CRF (copy).
- Concomitant Medication CRF (copy).
- Any relevant reports (laboratory, discharge, etc.).

Accompanying documentation, such as copies of hospital case reports, autopsy reports and other documents when applicable, should be summarized on the SAE form and a copy of the source document may be sent if required. The patient's personal details will be removed and replaced with study identifiers i.e. study number and initials, if applicable.

In addition, all AEs / SAEs / SUSARs will be reported to the local Ethics Committees (EC) and RAs as required by local regulations and ICH-GCP guidelines.

Minimal information should include:

- An identifiable patient (e.g. patient study code number).
- An identifiable reporting source.
- All related AEs.
- The suspect medicinal product.

#### **Follow-Up of SAEs / SUSARs**

Follow-up of SAEs / SUSARs that occur during the study will continue until their satisfactory resolution or stabilization.

If supplementary information becomes available, a follow-up SAE Report Form must be completed by the site based on EDC system and emailed within 24 hours to Safety group.

The contact information for follow up SAE reporting is the same as for initial SAE reports (see above section).

The SAE form and accompanying documentation should be placed in the SAE section of the Investigator's file and/or patient medical file. If supplementary information on a SAE has to be sent, the SAE form to be used must be marked as "follow-up report".

#### **Follow-Up Reports on Non-Serious AE**

All AEs must be followed until resolution or stabilization. In exceptional cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

### **7.6 REPORTING OF PREGNANCIES OCCURRING DURING THE STUDY**

Following administration of IP, pregnancy cases in any female patient (as well as in female partners of male patients) will be reported, if known, until the patient completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time, but not more than, 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. Dosing in the study should be stopped upon immediate notification of the pregnancy.



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If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing/emailing a completed SAE Form to the Sponsor (or designee) within 24 hours of knowledge of the event, as outlined above.

### **7.7 INDEPENDENT DATA AND SAFETY MONITORING BOARD (DSMB)**

An independent and external DSMB will be established for the study, to periodically review the safety information generated during the conduct of the study and is allowed to request efficacy data if considered necessary for benefit/risk assessment. The primary responsibility of the DSMB is to provide guidance to the Sponsor regarding the safe conduct of the study based on their periodic review of safety data. The DSMB will review study safety summaries reported.

The DSMB's membership, full scope of responsibilities, operating procedures, data availability and reporting and record keeping requirements will be established by Sponsor and/or its representative. DSMB working procedures will be described in a DSMB Charter prior to enrolling the first patient.

The key safety data will be reviewed by an independent DSMB in approximately once every 4 months during the main study and approximately every 6 months during the LT-OLE. DSMB will also include review of number or percentage of patients requiring dose reductions due to IGF-1 > +2.0 SDS and number or percentage of patients whose IGF-1 remains above +2.0 SDS, despite dose reductions (in both MOD-4023 and Genotropin<sup>®</sup> cohorts). DSMB will also include review of number or percentage of patients requiring dose reductions due to AEs.

### **7.8 MEDICATION ERRORS**

Medication errors may result from the administration or consumption of the IP by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the IP;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a patient is to be captured in the EDC system.

### **7.9 MEDICAL DEVICE COMPLAINT REPORTING REQUIREMENTS**

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be reported to the Sponsor on a designated form through a formal complaint system. Complaints may include incidents, potential incidents, and/or queries by clinical study patients and or clinical study site personnel on the function or use of the PEN or the drug product within the PEN. An incident or malfunction of the PEN is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Sponsor is to be notified of all medical device complaints within 24 hours of the Investigator's awareness of the event.

## 8. STATISTICAL ANALYSIS METHOD

### 8.1 SAMPLE SIZE CONSIDERATION

The aim of the main study is to demonstrate that weekly MOD-4023 is not inferior to daily r-hGH administration. Non-inferiority will be claimed if the 2-sided 95% CI for mean treatment difference (MOD-4023 – Genotropin<sup>®</sup>) in the primary efficacy endpoint will lie entirely above “non-inferiority margin” of -1.8 cm/year.

The following assumptions were made in the sample size calculation:

- 2-sided alpha of 0.05.
- 80 % power.
- Between-patient SD of annual growth rate is 2.5 cm/year in all treatment groups.
- Non-inferiority margin is -1.8 cm/year.
- The true mean treatment difference (MOD-4023 – Genotropin<sup>®</sup>) is -0.8 cm/year.

With these assumptions, 100 patients per group will provide 80 % power for the non-inferiority test. To allow for an approximate 10 % dropout rate, 110 patients will be randomized to each treatment group (Total N=220 patients).

### 8.2 ANALYZED POPULATION SETS

Five (5) analysis sets will be used for this study: Safety Analysis Set, Full Analysis Set, Full Analysis Subset (FAS), modified intent-to-treat (mITT) Set, and the per Protocol (PP) Set.

#### 8.2.1 Safety Analysis Set

The safety analysis set will include all patients who have received at least one dose of study treatment. Patients will be analyzed according to actual treatment received.

#### 8.2.2 Full Analysis Set

The full analysis set will include all patients randomized and will be the primary efficacy analysis set. Patients will be analyzed according to randomized treatment group.

If study enrollment is closed prior to subject full qualification and/or study closure for any other reason by the Sponsor and/or patients lost to follow up between Visit 1 and Visit 2, the patient will be excluded from the study.

#### 8.2.3 Modified Intent-to-Treat Set

The mITT set will include all patients who received at least one dose of study drug and had at least one post-baseline assessment of Ht. Patients will be analyzed according to randomized treatment group.

#### 8.2.4 Per Protocol Set

The PP set will consist of all randomized patients who did not have any major protocol deviations.

The patients who have any major protocol deviations will be identified before database lock by the clinical team in a blinded review.

### LT-OLE:

### 8.2.5 Full Analysis Subset

The term “full analysis subset” is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat (ITT) ideal of including all enrolled patients.

The full analysis set will comprise all treated patients who have received at least one dose of active treatment and who provide any follow-up data. The patients will be grouped by their original treatment in the treatment period.

### 8.3 HANDLING OF MISSING DATA

The method for handling missing data will be described in the SAP. The primary method of imputation will be with multiple imputation assuming missing at random, using SAS PROC MI. Details on all sensitivity analyses related to the handling of missing data will also be provided in the SAP.

#### LT-OLE:

No imputation will be made for missing measurements. Patients who discontinued early will have their last available data summarized.

### 8.4 ENDPOINTS

#### 8.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint during the main study is the Annual HV in cm/year after 12 months of treatment.

*HV (cm/year) at Visit 8 (12 months)*

$$= (Ht \text{ at Visit } 8 - Ht \text{ at Visit } 2) / ((Date \text{ of Visit } 8 - Date \text{ of Visit } 2) / 365.25);$$

where Visit 2 is the Baseline visit.

(Note: HV at any other post-baseline *Visit xx* is also computed using formula above by replacing *Visit 8* with *Visit xx*).

#### 8.4.2 Secondary Efficacy Endpoints (Auxology/Clinical)

- Annualized HV after 6 months of treatment;
- Change in Ht SDS at 6 and 12 months, compared to Baseline;
- Change in bone maturation (BM) at the end of 12 months, compared to Screening bone age (BM calculated as BA/CA).

#### 8.4.3 Biochemical Endpoints

- Absolute IGF-1 and IGF-1 SDS levels on day 4(-1) after MOD-4023 dosing across study visits;
- IGFBP-3 and IGFBP-3 SDS levels at on day 4(-1) after MOD-4023 dosing across study visits.

#### 8.4.4 Safety Endpoints

- Incidence of AEs and SAEs;

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- Incidence of anti-MOD-4023 Ab formation (including characterization of the Ab and neutralizing properties);
- Local injection site reaction assessment;
- Parameters of glucose metabolism: blood fasting glucose, fasting insulin level, HbA1c;
- Thyroid (endocrinology) status;
- Lipid profile;
- All other safety hematology, biochemical parameters and urinalysis;
- Physical examination;
- Fundoscopy results - if performed (normal/abnormal);
- Vital signs;
- ECG.

#### 8.4.5 Additional Endpoints

- Proportion of successful single injections out of total number of single injections using the MOD-4023 PEN in US patients at Wks 1, 2, 3, 4, 5, and 6, based on the PAT.
- Proportion of successful single injections out of total number of single injections using the MOD-4023 PEN in US patients at Wk 1, based on the OAT.
- Comments on the PAT related to successful or unsuccessful injection attempts.
- Comments on the OAT related to successful or unsuccessful injection attempts.
- Information gained by inspection of returned devices.
- QoL endpoint measured by the QoLISSY core questionnaire at Baseline and month 12 at specific countries per [Appendix L](#).

#### LT-OLE:

#### 8.4.6 Safety Endpoints

- Incidence of AEs and SAEs;
- Incidence of anti-MOD-4023 Ab formation (including characterization of the Ab and neutralizing properties);
- Local injection site reaction assessment;
- Parameters of glucose metabolism: blood fasting glucose, fasting insulin level, HbA1c;
- Thyroid (endocrinology) status;
- Lipid profile;
- All other safety hematology, biochemical parameters and urinalysis;
- Physical examination;
- Fundoscopy results - if performed (normal/abnormal);
- Vital signs;
- ECG.

#### 8.4.7 Auxology/Clinical Endpoints

- Annual HV in cm/year at each 12-month interval.

- Change in height SDS every 12 months (compared to the previous values).
- Change in bone maturation (BM) every 12 months, (compared to Week 52 BA (calculated as BA/CA) at completion of LT-OLE year 1 and to previous values from LT-OLE year 2 onwards).

#### 8.4.8 Biochemical Endpoints

- IGF-1 and IGF-1 SDS levels on day 4 (-1) after MOD-4023 dosing across study visits.
- IGFBP-3 levels and IGFBP-3 SDS on day 4 (-1) after MOD-4023 dosing across study visits.

### 8.5 STATISTICAL ANALYSIS

The main study database will be cleaned and locked for analysis after the last patient completes 12 months treatment.

The assessment of safety during the LT-OLE will be based on descriptive statistics and summarized by patient's treatment in the treatment period, and overall. No hypothesis testing will be performed. The descriptive statistics will include means, standard deviations, quartiles/ranges for continuous variables, and counts with percentages for categorical data. 95% CI will be used to further describe the clinical/auxological and biochemical endpoints.

The Sponsor reserves the right to stop enrollment when the targeted number of randomized patients is reached. If this situation arises, non-randomized patients that are undergoing Screening will be considered a Screen Failure.

Details of applicable statistical methods for the main study and LT-OLE will be provided in two separate SAPs prior to database lock of the main study and final study closure of the LT-OLE.

### 8.6 EFFICACY ANALYSIS

The aim of the present study is to demonstrate that in terms of the primary efficacy endpoint, Annualized HV at 12 months, weekly MOD-4023 is non-inferior to daily Genotropin<sup>®</sup> by a non-inferiority margin of 1.8 cm/year.

With  $\mu_M$  and  $\mu_C$  representing the mean annual HV for the MOD-4023 and the Genotropin<sup>®</sup> (Control) group, respectively, the following hypotheses will be tested:

Null hypothesis  $H_0$ :  $\mu_M < \mu_C - 1.8$  cm/year;

vs.

Alternate hypothesis  $H_1$ :  $\mu_M \geq \mu_C - 1.8$  cm/year

Non-inferiority will be concluded if the lower bound of the 2-sided 95 % CI for the mean treatment difference "MOD-4023 – Genotropin<sup>®</sup>", in the primary efficacy endpoint is  $\geq -1.8$  cm/year.

The CI for the difference of means between the 2 treatments will be derived from an analysis using ANCOVA. The ANCOVA model will include classification terms for treatment, age group, gender, peak hGH levels, and region. The model will also include Baseline Ht SDS as a covariate. The determination of non-inferiority will be based on least squares means for the 2 treatments from the ANOCVA and the 95 % CI of the differences between the treatments.

Descriptive statistics will be reported for observed and change from Baseline to annual HV values at 12 months during the main study and every 12 months thereafter.

ANCOVA-based statistics will be reported by the categorical terms used in the ANCOVA model: age group, gender, peak GH levels, and region.

#### 8.6.1 Secondary Endpoint Analyses

A similar ANCOVA model as used for the primary endpoint will be used to analyze:

- annualized HV at 6 months;
- change in Ht SDS at 6 months;
- change in Ht SDS at 12 months.

Least square mean estimates for the 2 treatments and the 95 % CI of the difference between the treatments will be presented.

Descriptive statistics will also be reported for each of these endpoints.

Descriptive statistics (including univariate 95 % CI) will be reported for BM observed and change from Baseline to 12 months.

Descriptive statistics will be reported for HV and Ht SDS at each visit.

Series plots of mean values +/- SE will be reported for HV and Ht SDS by visit and treatment.

ANCOVA-based statistics will be reported by the categorical terms used in the ANCOVA model: age group, gender, peak GH levels, and region.

#### 8.6.2 Primary Efficacy Sensitivity Analysis

The ANCOVA-based primary efficacy analysis will be repeated using the mITT set and the PP set.

The ANCOVA-based primary efficacy analysis will be repeated on the full analysis set using last observation carried forward (LOCF) in place of multiple imputations for the handling of missing data.

#### 8.6.3 Biochemical Markers Analysis

Descriptive statistics will be reported for observed and change from Baseline for all biochemical endpoints at each visit.

The number and percent of patients who achieved IGF-1 normalization (defined as IGF-1 SDS between -0.5 and 1.5, inclusive) will be summarized. The number and percent of patients who had IGF-1 SDS > 2.0 will be summarized at each visit.

#### 8.6.4 Additional Endpoints Analysis

##### OAT and PAT (USA Patients Only)

OAT and PAT results will be summarized by using descriptive statistics.

The number and percentage of successful single injections for PAT will be summarized overall. A successful single injection for PAT will be based on the questions “Did the dose window show ‘0’ when you finished your injection?” and “Do you believe that a full dose was injected?” The single

injection is considered successful if the subject answers “Yes” to both questions for all attempts on the form. A subject can have multiple successful single injections at one visit.

Intermittent missing observations for the PAT will be imputed as a failure if both the prior and subsequent observations are a failure. Otherwise, intermittent missing observations will be imputed as a success.

The number and percentage of successful single injections for OAT will be summarized overall. A successful single injection for OAT will be based on the question “...did the user successfully inject into an acceptable injection site without physical assistance?” The single injection is considered successful if the observer answers “Yes” to the question for all attempts on the form. A subject can have multiple successful single injections at 1 visit.

The number and percentage of successful single injections for PAT and OAT will also be summarized by age group, sex, and race.

The number and percentage of the number of attempts required to achieve a success will be summarized for PAT and OAT.

Comments on the PAT and OAT related to successful or unsuccessful injection attempts will be listed.

Information gained by inspection of returned devices will be listed.

#### Quality of Life Questionnaire

The 3 dimensions (physical, social, and emotional) of the QoLISSY questionnaire will be calculated individually and as a combined core total score based on the QoLISSY scoring manual. This core score is calculated as the sum of the means of these 3 dimensions and divided by 3. All scores will be transformed from raw scores to 0 to 100 scores.

#### 8.6.5 LT-OLE Analysis

During the LT-OLE the primary goal of this safety and efficacy analysis is to report on the effect of long-term treatment on Annual HV and other auxological/clinical and biochemical measures.

- Annual HV will be summarized with descriptive statistics each year of LT-OLE treatment. For patients who discontinue without annual measurement, their HV will be calculated based on their last available measure.
- Change in Ht SDS every 12 months (the last value within each year compare to the value 12 months earlier) will be summarized with descriptive statistics.
- Change in bone maturation (BM) every 12 months, (compared to Week 52 BA (calculated as BA/CA) at completion of LT-OLE year 1 and to previous values from LT-OLE year 2 onwards).
- IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS will be summarized with descriptive statistics at each visit. A summary of the incidence of IGF-1 SDS >2.0 at each visit will be provided.

### 8.6.6 Safety Analysis

The assessment of safety will be based mainly on the frequency of treatment emergent AEs and on the number of laboratory values that fall outside of pre-determined ranges. Data of all safety endpoints will be listed and tabulated.

#### **LT-OLE:**

The assessment of safety will be based mainly on the frequency of treatment emergent AEs and on the number of laboratory values that fall outside of pre-determined ranges. Each of the listed safety endpoints will be summarized with descriptive statistics for each year and overall. Data of all safety endpoints will be listed.

### 8.6.7 Adverse Events

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

For analysis purposes, all AEs will be classified to the appropriate MedDRA preferred term (PT) and system organ class (SOC). For each patient, multiple events that map to the same PT will only be counted once for the PT, and multiple PTs within an SOC will only be counted as 1 occurrence for that SOC to assess patient incidence of events by PT and SOC. The count and percentage of patients with each PT and SOC will be summarized for each treatment group.

Relationship and severity of AEs will be summarized (patient count, % of patients) for each treatment group. For these summaries, multiple occurrences of an event within a patient will be classified as a single observation with the strongest relationship and maximum severity ratings. In addition, frequency tables of all reported events with each associated relationship and severity will be presented.

SAEs will be classified as SAEs by the investigator and will be summarized by treatment group, PT and SOC, as well as total patients exposed.

### 8.6.8 Clinical Laboratory Findings

Any CS laboratory data will be reported as an AE. Laboratory data will be reported by analyte for each treatment group. There will not be any hypothesis testing. The laboratory results will be presented at each visit along with the raw change from Baseline for quantitative data. Presence/absence or normal/abnormal results will be summarized as count and percentage. In addition, shift tables summarizing changes from normal to out-of-normal range will be provided.

Descriptive statistics (the number and percentage of patients) of patients with the presence of anti-r-hGH and anti-MOD-4023 Abs will be summarized.

### 8.6.9 Vital Signs, Fundoscopy and ECG

Any CS findings will be reported as an AE. The summary of abnormal findings at each visit will be displayed by treatment group. Descriptive statistics of vital signs will be calculated at each scheduled visit and will include the raw change from Baseline.



## 9. ETHICS

### 9.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

Prior to initiation of the study, the PI 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, 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 Sponsor's standards operating procedures (SOPs) and the following guidelines:

- GCP: International Council for Harmonization (ICH): Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), 09 November 2016.
- Declaration of Helsinki: Brazil, 2013 ([Appendix G](#)).
- Local country guidelines for conducting clinical studies.

### 9.3 PROTOCOL REVISIONS AND/OR DEVIATIONS

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 IRB/IEC in accordance with local requirements and, if required, to RAs, 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 study. No approval will be required for notifications.

### 9.4 PATIENT INFORMATION AND CONSENT

Prior to screening for the study each patient and parent(s)/legal guardian will be informed in detail about the study drugs 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.<sup>a</sup> Written consent will be obtained from each patient to be involved in the clinical study 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. 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. Each patient's chart will include the signed ICF for study

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<sup>a</sup> Illiterate patients should provide their consent in a method that is accepted according to local regulations.

participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the Investigator's Site File for the required period of time. RAs may check the existence of the signed ICF in this central study folder if not having done so during the study.

Children and adolescents are legally unable to provide informed consent to participate in clinical studies. Informed consent must be obtained instead from the legally acceptable representative of the child or adolescent, usually their parent(s) or legal guardian. However, children and adolescents should be involved in health-care decisions affecting them. To that end, ICH guidelines, EMA Guideline on the Ethics of Clinical Trials in Children and FDA regulations require that the assent from the child or adolescent be obtained when this is appropriate and when the potential patient is capable of providing assent. The determination of appropriateness and capacity of children in the study to provide assent is made by the relevant IRB/EC, though it may be left to the investigator to assess whether assent is actually obtainable from children of a young age, such as preschool-aged children.

Assent may not be required if, consistent with local law and regulatory requirements, the IRB/EC determines that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the potential patients and is available only in the context of the research. Even where the IRB/EC determines that patients are capable of assenting, the IRB/EC may still waive the assent requirement under special circumstances. Where parental permission is to be obtained, the IRB/EC may find that permission of 1 parent is sufficient if consistent with local law and regulatory requirements. For clinical investigations involving greater than minimal risk, permission is generally required from both parents unless only 1 parent has legal custody, or one parent is deceased, unknown, incompetent, or not reasonably available.

## **9.5 PATIENT INSURANCE**

The Sponsor has an insurance policy for the total duration of the study covering the patients and Investigators in respect to the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's Site File and can be made available to the Investigator and to the IRB/IEC upon request.

## **9.6 INFORMING THE GENERAL PRACTITIONER**

The Investigator will inform the patient's primary care physician of his/her participation in the study annually, by sending a letter or email to the physician if required by the local authorities.

## **9.7 PERSONAL DATA PROTECTION**

The Sponsor complies with a patient's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number, date of birth and patient initials (where/if applicable).

The personal data will be blinded in all data analyses. The patient must be informed and consent is required that authorized personnel of the Sponsor and/or designee (Study Monitor, Auditor, strategic partners etc.) and relevant health RA will have direct access to personal medical data to assure a high-quality standard of the study.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

The Sponsor and designated clinical research organizations (CRO) maintain a quality assurance system with written SOPs to ensure that clinical studies 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 Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Sponsor Quality Assurance or its designees or to RA 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. Prior to Screening, the study monitor will evaluate the site's source documents to ensure thorough, accurate and compliant source worksheets/systems are available for study reporting. 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, remote monitoring via the EDC 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 may periodically request review of the Investigator's Site File to ensure completeness of documentation in all respects of clinical study conduct.

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. 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.

#### 10.2.1 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, x-rays and laboratory results, printouts, pharmacy records, care records, completed scales for each study participant. Source documents should be kept in a secure and limited access area. All source documents must 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 informed consent/assent was signed, participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

### 10.2.2 Electronic Case Report Form (eCRF)

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by treating personnel or the study coordinator. The eCRF must be completed as soon as possible after any patient evaluation or communication. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to Study Monitors and other regulatory auditors.

## 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 central laboratories.

## 10.4 DATA MANAGEMENT

An eCRF will be used for the current study and a data management plan will be prepared by the Sponsor and/or designated representative.

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

AEs will be coded using the MedDRA, version 18.1 or higher. Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

## 11. STUDY ADMINISTRATION

### 11.1 PARTICIPATING CENTERS

Approximately 200 sites in 30-40 countries worldwide will participate in this study. A list of all participating sites will kept in the electronic study master file.

### 11.2 REQUIRED DOCUMENTS PRIOR TO STUDY INITIATION

Prior to the start of the study, Investigator's and study site compliance with all pre-investigational requirements will be evaluated and confirmed based on the site essential documents. The list may include:

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- Appropriate local health authority documentation properly signed and dated by the required Investigators (i.e., the submission package);
- Signed copy (original) of the approved protocol and Investigator's Brochure;
- Completed and signed statement of Investigator;
- Signed Clinical Trial Agreement;
- Curriculum vitae for the Investigator and sub-Investigators<sup>a</sup>;
- IRB/IEC name and address; and membership list;
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number), informed consent form (identified by protocol title and number) and other study related patient materials;
- Provisions for direct access to source/data documents if necessary for study-related monitoring, audits, IRB/IEC review and regulatory inspection.

Upon satisfactory receipt of all required regulatory documents, Sponsor will arrange that IP be delivered to the study site. Supply of all other study materials will be the responsibility of OBL and/or designee. Patient entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting 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 or CRO/study monitor will prepare an investigator's study file (ISF). This file should be used for all study related documents. The investigator will be responsible for keeping the ISF updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

### 11.3 CLINICAL STUDY SUPPLIES

The Sponsor and/or designated representative will be responsible for supplying clinical study supplies. The Investigator will be responsible for inventory and accountability of all clinical study supplies at his/her study site, exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. 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 drugs to be used other than as directed by this protocol.**

### 11.4 INVESTIGATOR SITE FILE (ISF)

The ISF partitions may be provided by the designated CRO at the initiation visit. 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 in the ISF and made available for monitoring and/or auditing by the Sponsor or designee, strategic partners and/or RAs.

<sup>a</sup> Can be collected at the Site Initiation Visit.

## 11.5 STUDY COMPLETION

This study is expected to end at drug approval. An annual extension request will be submitted to local EC/IRB, where applicable. 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 properly completed by appropriate study personnel and 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).

## 11.6 FINAL REPORT

A study report will be developed at completion of data analysis following completion of the main study. A final study report will be developed at study closure. These reports will comprise clinical and statistical integrated reports, according to the ICH E3 guidelines.

## 11.7 RETENTION OF STUDY RECORDS

The Investigator will retain copies of the approved protocol, completed eCRF, informed consent documents, relevant source documents and all other supporting documentation related to the project for 15 years. If the Investigator is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed in writing of the individual who will be assuming this responsibility.

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

## 11.8 CONFIDENTIALITY AND PUBLICATION

Patient medical information obtained by the study is confidential and disclosure to third parties other than those noted below is prohibited. Throughout the study, all data will be identified only by the patient identification number and where applicable, the patient's initials (where applicable/available) and birth dates.

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. The personal physician will be notified by site personnel of patient participation in the study if required by the local authorities.

All information supplied by OBL in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the IB, 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 OBL, shall not be disclosed to others without the written consent of OBL and shall not be used except in the performance of this study.

The information developed during the conduct of this study is also considered confidential and will be used by OBL. This information may be disclosed as deemed necessary by OBL. To allow the use

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of this information derived from this study, the investigator is obliged to provide OBL with complete test results and all data developed in this study.

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## APPENDIX A: STUDY FLOW CHART / SCHEDULE OF EVENTS

### Main Study

Study Procedure	Screening		Baseline	Treatment								Follow-up <sup>b</sup>	
Study Day ( $\pm$ in dy/s)	<sup>a</sup> -56 to -1		1/	10 (+4)							EOS <sup>b</sup>		
Study Wk ( $\pm$ in wk/s)	-8 to -1 (+4) <sup>a</sup>		0 (+4 from Eligibility)		4 (+1)	13 ( $\pm$ 1)	26 ( $\pm$ 1)	26 ( $\pm$ 3)	26 ( $\pm$ 3)	39 ( $\pm$ 1)	52 ( $\pm$ 1)	52 ( $\pm$ 1)	56 ( $\pm$ 5 days)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12	13
Study Visit	1		2	3	4	5	6	6a <sup>c</sup>	6b	7	8/10 <sup>d</sup>	8a <sup>c</sup> /10 <sup>d</sup>	9
Informed consent	X									X <sup>e</sup>	X <sup>f</sup>		
Inclusion/exclusion criteria	X										X <sup>e</sup>		
Demographic & medical history including parent Ht	X												
Auxology measurements <sup>g</sup>	X		X			X	X			X	X		
Physical examination and vital signs <sup>h</sup>	X		X		X	X	X			X	X		
ECG			X pre-dose				X <sup>i</sup>		X <sup>j</sup>				
Pubertal status (Tanner stages)	X		X			X	X			X	X		

<sup>a</sup> For the screening period, additional 4 wks might be added due to technicalities or patient's benign illness.

<sup>b</sup> If ET during the main study or **not** continuing to LT-OLE.

<sup>c</sup> Dosing day (assessments will be conducted pre-dose). This visit is applicable only for patients in MOD-4023 arm.

<sup>d</sup> Visit 8 if EOS at completion of the main study, Visit 10 if continuing to LT-OLE.

<sup>e</sup> If continuing to LT-OLE.

<sup>f</sup> Informed consent for the LT-OLE may be obtained at Visit 7 or Visit 8.

<sup>g</sup> Actual Ht (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall mounted stadiometer.

<sup>h</sup> Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

<sup>i</sup> Genotropin<sup>®</sup> patients.

<sup>j</sup> ECG will be conducted at 7-12 hours post-dose (MOD-4023 arm only). Patients will be requested to inject MOD-4023 during the day/night at their convenience and come to the clinic at the requested time point for ECG.

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Study Procedure	Screening		Baseline	Treatment								Follow-up <sup>b</sup>	
Study Day ( $\pm$ in dy/s)	<sup>a</sup> -56 to -1		1/	10 (+4)							EOS <sup>b</sup>		
Study Wk ( $\pm$ in wk/s)	-8 to -1 (+4) <sup>a</sup>		0 (+4 from Eligibility)		4 (+1)	13 ( $\pm$ 1)	26 ( $\pm$ 1)	26 ( $\pm$ 3)	26 ( $\pm$ 3)	39 ( $\pm$ 1)	52 ( $\pm$ 1)	52 ( $\pm$ 1)	56 ( $\pm$ 5 days)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12	13
Study Visit	1		2	3	4	5	6	6a <sup>c</sup>	6b	7	8/10 <sup>d</sup>	8a <sup>c</sup> /10 <sup>d</sup>	9
- urine pregnancy test for girls reporting 1 <sup>st</sup> menstrual cycle													
BA (Greulich-Pyle method using central BA reader)	X		X <sup>k</sup>								X		
Karyotype assessment (girls only) <sup>1</sup>	X												
Randomization		X <sup>m</sup>											
Verification of eligibility <sup>n</sup>		X											
Dispense study drug			X		X	X	X			X	X <sup>o</sup>		
Individual dose adjustment						X	X			X	X <sup>e</sup>		
Training on drug administration			X								X <sup>p</sup>		
Drug administration at clinic			X					X			X <sup>p</sup>	X	
OAT completion at clinic (USA Only)			X										
PAT <sup>q</sup>			X		X								

<sup>k</sup> BA will be done at Visit 2 only in cases where historical bone scans (<6 months prior to screening) were used to fulfill entry criteria. When performed, BA scans will be completed prior to dosing.

<sup>1</sup> Historical karyotype data and chromosomal microarray data are acceptable.

<sup>m</sup> It is recommended that randomization be done within 7 days of the MM eligibility confirmation.

<sup>n</sup> Once all data is available, the investigator will complete an Eligibility Verification Request Form and will forward it to the global study MM for review. Each patient will be enrolled after a written confirmation from the global study MM **prior** to randomization.

<sup>o</sup> If continuing to LT-OLE.

<sup>p</sup> Genotropin<sup>®</sup> patients switching to MOD-4023 in the LT-OLE.

<sup>q</sup> USA Patients Only. PAT will be evaluated during the first 6 full dose administrations (at the site for Visit 2 (for training) and at home for next 5 full dose administrations).

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Study Procedure	Screening		Baseline	Treatment								Follow-up <sup>b</sup>	
Study Day (± in dy/s)	<sup>a</sup> -56 to -1		1/	10 (+4)							EOS <sup>b</sup>		
Study Wk (± in wk/s)	-8 to -1 (+4) <sup>a</sup>		0 (+4 from Eligibility)		4 (+1)	13 (±1)	26 (±1)	26 (±3)	26 (±3)	39 (±1)	52 (±1)	52 (±1)	56 (±5 days)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12	13
Study Visit	1		2	3	4	5	6	6a <sup>c</sup>	6b	7	8/10 <sup>d</sup>	8a <sup>c</sup> /10 <sup>d</sup>	9
PAT return					X	X							
Diary card return					X	X	X			X	X		
QoL questionnaire completion (specific countries)			X								X		
Local tolerability			X	X <sup>r</sup>	X	X	X	X	X	X	X <sup>s</sup>	X <sup>r</sup>	X <sup>t</sup>
Adverse events			X	X	X	X	X	X		X	X	X <sup>r</sup>	X <sup>t</sup>
Prior & concomitant medications	X		X	X	X	X	X	X		X	X	X <sup>r</sup>	X <sup>t</sup>
IP return					X	X	X			X	X		
Fundoscopy			ONLY if there are signs or symptoms indicative of benign intracranial hypertension										
MRI <sup>u</sup> , if possible with contrast or CT (if required) post GH stimulation	X												
<b>Laboratory Assessments</b>													
Hematology <sup>v</sup> , chemistry <sup>w</sup> , & urinalysis <sup>x</sup>	X		X		X	X	X			X	X		

<sup>r</sup> For MOD-4023 arm: assessment will be conducted at the clinic or at the patient's house (according to local regulations), for Genotropin<sup>®</sup> arm: by phone interview.

<sup>s</sup> For Genotropin injections and following administration of MOD-4023, as applicable.

<sup>t</sup> Phone interview, only for those patients who are not participating in the LT-OLE.

<sup>u</sup> Historical MRI or CT is permitted if within 12 months; MRI or CT which was conducted no more than 12 months prior to ICF signature data will be acceptable. For GHD associated with a congenital CNS defect, the MM could allow for use of the historic MRI or CT >12 months old.

<sup>v</sup> For the screening period, additional 4 wks might be added due to technicalities or patient's benign illness.

<sup>w</sup> Hematology: RBC Count; HGB; HCT; MCH; MCHC; MCV; WBC Count and Differential; Platelet Count, PT/INR, PTT (if indicated only).

<sup>x</sup>Chemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LFT, LDH, CPK, alkaline phosphatase; sodium, potassium, calcium, phosphate; BUN, creatinine.

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Study Procedure	Screening		Baseline	Treatment								Follow-up <sup>b</sup>	
				10 (+4)	4 (+1)	13 (±1)	26 (±1)	26 (±3)	26 (±3)	39 (±1)	EOS <sup>b</sup>		
Study Day (± in dy/s)	<sup>a</sup> -56 to -1		1/								52 (±1)	52 (±1)	56 (±5 days)
Study Wk (± in wk/s)	-8 to -1 (+4) <sup>a</sup>		0 (+4 from Eligibility)		4 (+1)	13 (±1)	26 (±1)	26 (±3)	26 (±3)	39 (±1)	52 (±1)	52 (±1)	56 (±5 days)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12	13
Study Visit	1		2	3	4	5	6	6a <sup>c</sup>	6b	7	8/10 <sup>d</sup>	8a <sup>c</sup> /10 <sup>d</sup>	9
GH stimulation (provocation) test <sup>y</sup>	X												
Morning cortisol (at 8am ±1am)	X												
ACTH or CRH stimulation test <sup>z</sup>	X												
SHOX gene evaluation <sup>aa</sup>	X												
IGF-1, IGF-1 SDS, IGFBP-3, and IGFBP-3 SDS	X		X		X	X	X			X	X		
MOD-4023 serum levels <sup>bb</sup>			X	X	X	X		X		X		X	
Thyroid function (TSH, fT4)	X		X			X	X			X	X		
Glucose metabolism <sup>cc</sup>	X		X			X	X			X	X		
Lipid profile <sup>dd</sup>			X			X	X			X	X		
LH, FSH and testosterone <sup>ee</sup>											X		
LH, FSH and estradiol <sup>ff</sup>											X		

<sup>x</sup> Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.

<sup>y</sup> Two (2) different GH stimulation (provocation) tests (ITT, with serum cortisol response to hypoglycemia if insulin stimulation test is chosen OR arginine test/clonidine test/glucagon test (with or without propranolol)/L-dopa plus propranolol.

<sup>z</sup> ACTH or CRH stimulation test will be conducted if morning cortisol is below 190 nmol/L (7 µg/dL), and only if the patient was not previously assessed for the hypothalamus-pituitary-adrenal axis. ITT with serum cortisol response to hypoglycemia is adequate for assessment of adrenal insufficiency and no ACTH stimulation test is required if such results are available. Historical ACTH test is acceptable

<sup>aa</sup> Historical data is acceptable.

<sup>bb</sup> For MOD-4023 arm only.

<sup>cc</sup> Glucose metabolism: fasting glucose and fasting insulin; HbA1c.

<sup>dd</sup> Lipid profile: overnight fasting total cholesterol, LDL cholesterol and triglycerides, HDL and FFA; Lp(a) once every 3 months.

<sup>ee</sup> For male patients that are at the age of 13 years and above.

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Study Procedure	Screening		Baseline	Treatment								Follow-up <sup>b</sup>	
Study Day ( $\pm$ in dy/s)	<sup>a</sup> -56 to -1		1/	10 (+4)							EOS <sup>b</sup>		
Study Wk ( $\pm$ in wk/s)	-8 to -1 (+4) <sup>a</sup>		0 (+4 from Eligibility)		4 (+1)	13 ( $\pm$ 1)	26 ( $\pm$ 1)	26 ( $\pm$ 3)	26 ( $\pm$ 3)	39 ( $\pm$ 1)	52 ( $\pm$ 1)	52 ( $\pm$ 1)	56 ( $\pm$ 5 days)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12	13
Study Visit	1		2	3	4	5	6	6a <sup>c</sup>	6b	7	8/10 <sup>d</sup>	8a <sup>c</sup> /10 <sup>d</sup>	9
Abs to r-hGH (Genotropin arm)			X		X	X	X			X	X		
Abs to r-hGH (all patients)	X												
Abs to MOD-4023			X	X	X	X		X		X		X	

<sup>ff</sup> For female patients that are at the age of 12 years and above.

Effective Date: Date of final electronic approval

**LT-OLE:**

Study Procedure	LT-OLE – Year 1					
	LT-OLE 10 (+4) <sup>a</sup>					
Study Day (± in dy/s)						
Study Wk (± in wk/s)	54	56 (+2)	65 (±2)	78 (±2)	91 (±2)	104 (±4) <sup>b</sup>
Study Month	12.5	13 <sup>c</sup>	15	18	21	24
Study Visit	11 <sup>d</sup>	12	13	14	15	16
Auxology measurements <sup>e</sup>			X	X	X	X
Physical examination and vital signs <sup>f</sup>		X	X	X	X	X
ECG						X <sup>g</sup>
Pubertal status (Tanner stages)						X
Urine pregnancy test for girls reporting 1 <sup>st</sup> menstrual cycle		X	X	X	X	X
BA (Greulich-Pyle method using central BA reader)						X
Dispense study drug		X	X	X	X	X
Individual dose adjustment			X	X	X	X
Diary card return		X	X	X	X	X
Local tolerability	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Prior & concomitant medications	X	X	X	X	X	X
MOD-4023 IP return		X	X	X	X	X
Fundoscopy	ONLY if there are signs or symptoms indicative of benign intracranial hypertension					
<b>Laboratory Assessments</b>						
Hematology <sup>h</sup> , chemistry <sup>i</sup> , & urinalysis <sup>j</sup>			X	X		X

<sup>a</sup> If visit occurs on dosing day (day 14), procedures should be performed prior to dosing.

<sup>b</sup> Pre- and post- dose assessments may be performed on separate days that will be appropriately recorded in the EDC.

<sup>c</sup> For Genotropin<sup>®</sup> patients that switch to MOD-4023 only. For existing MOD-4023 patients: AE and concomitant medication review only by phone interview.

<sup>d</sup> For Genotropin<sup>®</sup> patients that switch to MOD-4023 only.

<sup>e</sup> Actual Ht (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall mounted stadiometer.

<sup>f</sup> Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

<sup>g</sup> ECG will be conducted at 7-12 hours post-dose.

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Study Procedure	LT-OLE – Year 1					
	LT-OLE 10 (+4) <sup>a</sup>					
Study Day (± in dy/s)						
Study Wk (± in wk/s)	54	56 (+2)	65 (±2)	78 (±2)	91 (±2)	104 (±4) <sup>b</sup>
Study Month	12.5	13 <sup>c</sup>	15	18	21	24
Study Visit	11 <sup>d</sup>	12	13	14	15	16
IGF-1, IGF-1 SDS, IGFBP-3, and IGFBP-3 SDS		X	X	X	X	X
MOD-4023 serum levels	X	X	X	X	X	X
Thyroid function (TSH, fT4)			X	X		X
Glucose metabolism <sup>k</sup>			X	X		X
Lipid profile <sup>l</sup>			X	X		X
LH, FSH and testosterone <sup>m</sup>						X
LH, FSH and estradiol <sup>n</sup>						X
Abs to MOD-4023	X	X	X	X	X	X

<sup>b</sup> Hematology: RBC Count; HGB; HCT; MCH; MCHC; MCV; WBC Count and Differential; Platelet Count, PT/INR, PTT (if indicated only).

<sup>c</sup> Chemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; sodium, potassium, calcium, phosphate; BUN, LFT, creatinine.

<sup>j</sup> Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.

<sup>k</sup> Glucose metabolism: overnight fasting glucose and insulin; HbA1c.

<sup>l</sup> Lipid profile: overnight fasting cholesterol, LDL, triglycerides, HDL and FFA; Lp(a)

<sup>m</sup> For male patients that are at the age of 13 years and above.

<sup>n</sup> For female patients that are at the age of 12 years and above.



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Study Procedure	LT-OLE – Year 2 until study closure				EOS/ET <sup>b</sup>	Follow-up <sup>a</sup> 30 days (±5) following EOS/ET
	Study Day (± in dy/s)	Study Wk (± in wk/s)	Study Month	Study Visit		
	117 (±2)	130 (±2)	143 (±2)	156 (±4)		
	27	30	33	36		
	17, 21...	18, 22...	19, 23...	20, 24...		
Auxology measurements <sup>c</sup>	X	X	X	X	X	
Physical examination and vital signs <sup>d</sup>	X	X	X	X	X	
ECG				X <sup>e</sup>	X <sup>e</sup>	
Pubertal status (Tanner stages)				X	X	
Urine pregnancy test for girls reporting 1 <sup>st</sup> menstrual cycle	X	X	X	X	X	
BA (Greulich-Pyle method using central BA reader)				X	X	
Dispense study drug	X	X	X	X		
Individual dose adjustment	X	X	X	X		
Diary card return	X	X	X	X	X	
Local tolerability	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Prior & concomitant medications	X	X	X	X	X	X
MOD-4023 IP return	X	X	X	X	X	
Fundoscopy	ONLY if there are signs or symptoms indicative of benign intracranial hypertension					
<b>Laboratory Assessments</b>						
Hematology <sup>f</sup> , chemistry <sup>g</sup> , & urinalysis <sup>h</sup>		X		X	X	
IGF-1, IGF-1 SDS, IGFBP-3, and IGFBP-3 SDS		X		X	X	
MOD-4023 serum levels		X		X	X	

<sup>a</sup> Phone interview only.

<sup>b</sup> Pre- and post- dose assessments may be performed on separate days that will be appropriately recorded in the EDC.

<sup>c</sup> Actual Ht (mean of three consecutive measurements per patient per visit) measured on a calibrated wall mounted stadiometer.

<sup>d</sup> Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

<sup>e</sup> ECG will be conducted at 7-12 hours post-dose for ET during year 1. ECG can be conducted at any time for ET from year 2 until EOS.

<sup>f</sup> Hematology: RBC Count; HGB; HCT; MCH; MCHC; MCV; WBC Count and Differential; Platelet Count, PT/INR, PTT (if indicated only).

<sup>g</sup> Chemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; sodium, potassium, calcium, phosphate; BUN, LFT, creatinine.

<sup>h</sup> Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.

Effective Date: Date of final electronic approval

Study Procedure	LT-OLE – Year 2 until study closure				EOS/ET <sup>b</sup>	Follow-up <sup>a</sup> 30 days (±5) following EOS/ET
	Study Day (± in dy/s)	Study Wk (± in wk/s)	Study Month	Study Visit		
	117 (±2)	130 (±2)	143 (±2)	156 (±4)		
	27	30	33	36		
	17, 21...	18, 22...	19, 23...	20, 24...		
Thyroid function (TSH, fT4)		X		X	X	
Glucose metabolism <sup>i</sup>		X		X	X	
Lipid profile <sup>j</sup>		X		X	X	
LH, FSH and testosterone <sup>k</sup>				X	X	
LH, FSH and estradiol <sup>l</sup>				X	X	
Abs to MOD-4023		X		X	X	

<sup>i</sup> Glucose metabolism: overnight fasting glucose and insulin; HbA1c.

<sup>j</sup> Lipid profile: overnight fasting cholesterol, LDL, triglycerides, HDL and FFA; Lp(a)

<sup>k</sup> For male patients that are at the age of 13 years and above.

<sup>l</sup> For female patients that are at the age of 12 years and above.

## APPENDIX B: GROWTH HORMONE STIMULATION TESTS

As stated in the 2000 Growth Hormone Research Society Consensus Guideline: “In a child with clinical criteria for GHD, a peak ***GH concentration less than 10 ng/mL has traditionally been used to support the diagnosis.*** At the present time, a new GH reference standard is being introduced that may require a downward adjustment of the lower limit of normal” (Growth Hormone Research Society Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence (2000))<sup>a</sup>.

The new standard is currently used in the USA and European Union (EU). However, the common clinical practice remains to treat patients with  $GH \leq 10$  ng/mL. The cutoff for this study is in line with this common clinical practice.

**The following GH stimulation tests are recommended, but the final decision regarding which test will be performed will be made by the investigator.**

### ITT

Regular human insulin (0.075-0.15 IU/kg) will be administered intravenously (iv) at time point 0. The test will be interpretable if the blood glucose level decreases below 40 mg/dL. Administration of oral dextrose, sugar containing juice, or iv dextrose will be allowed if the patient develops severe signs of hypoglycemia. ITT is contraindicated in patients with a history of seizures or coronary artery disease.

Blood will be collected at the following intervals: t = 0, 15, 30, 45, 60, and 90 min (6 sampling points) for glucose, hGH and cortisol determination. Additional samples may be obtained during hypoglycemia at the discretion of the investigator.

A normal ACTH reserve is defined as a baseline cortisol level above 190 nmol/L (7 µg/dL) or an increase in peak cortisol level above 500 nmol/L (18 µg/dL).

### Clonidine test

After fasting overnight, clonidine (up to 0.15 mg/m<sup>2</sup> body surface, given orally) will be given at time (t) = 0, and venous blood will be obtained by an indwelling catheter inserted in a cubital vein and kept patent by slow infusion of isotonic saline or with saline flush, heparin lock if necessary. Blood will be collected at the following intervals: t = 0, 30, 60, 90, 120 and 150 min (6 sampling points) for hGH measurement. Caution should be exercised when performing this test, however, as clonidine causes side effects such as tiredness and decreased BP. Thus, BP must be monitored prior to, and up to 30 min after normalization. If BP drops to 20% below baseline, start a normal saline bolus over 1 hour and monitor BP every 15 minutes.

### Arginine test

Soluble 10% arginine hydrochloride (0.5 g/kg) will be given iv from t = 0 to t = 30 min after an overnight fast. Blood samples will be obtained by an indwelling catheter inserted in a cubital vein and kept patent by slow infusion of isotonic saline. Blood will be collected at the

<sup>a</sup> JCEM 2000. Vol. 85 (11): 3990-3993.

following intervals: t = 0, 30, 45, 60 and 90, 120 min (6 sampling points) for hGH measurement.

### Glucagon test

After fasting overnight, glucagon (0.03 mg/kg with a maximal total dose of 1 mg) will be given i.m. or s.c. at time t = 0, and venous blood will be obtained by an indwelling catheter inserted in a cubital vein and kept patent by slow infusion of isotonic saline. Blood will be collected for hGH measurement at 0, 60, 90, 120, 150 and 180 min relative to the time of glucagon administration.

Glucagon test is not recommended for assessing the cortisol status. However, a normal ACTH reserve can be defined as a peak cortisol level above 500 nmol/L (18 µg/dL). If the peak cortisol level reached during the glucagon test (referring to a historical test only) is lower, then an ACTH stimulation test is needed to confirm the diagnosis of hypoadrenalism.

### L-Dopa test

After fasting overnight L-Dopa will be given orally at time-point t=0 at a dose of 125 mg if body weight is less than 15 kg, else 250 mg if body weight is less than 35 kg, else 500 mg if body weight is greater than 35 kg. Since L-Dopa alone is not available in the USA, the combination of Carbidopa/Levodopa can be used which is given as 25/250 mg (if > 15 kg) or 10/100 mg (if <15 kg). Blood samples will be obtained by an indwelling catheter inserted in a cubital vein and kept patent by slow infusion of isotonic saline. Blood will be collected at the following intervals: 0, 30, 60, 90 min.

- Propranolol priming of L-dopa test is **NOT** required

**If any of the above tests are administered in tandem, the last sample of the first test will be the baseline of the second test, decreasing the sample number by 1.**

Any of the tests listed in [Appendix B](#) are acceptable.

- The tests **SHOULD** be performed sequentially, they may **NOT** be simultaneous
  - In case the historical GH stimulation tests were done simultaneously, the data will be evaluated on individual basis and borderline stimulation test results may lead the global study MM to request 1 additional test, as outlined above. In such cases, both global study MM will review the historical and enrollment data before such a request is made.
- **IF** the tests are performed sequentially, the 0 min sample for Agent 2 **MAY** be the final sample timepoint for Agent 1
- As all of the tests outlined in [Appendix B](#) have a minimum of 90 min, the final sample for a 2-agent sequential test should be **NO LESS THAN** 180 min

**APPENDIX C: INSTRUCTIONS FOR OBTAINING HEIGHT MEASUREMENTS**

Use the following instructions when obtaining Ht measurements.

Please repeat the following instructions for 3 consecutive measurement per patient per visit. It is recommended that the Ht measurement will be conducted by the same trained person.

1. Use a wall-mounted calibrated stadiometer, ensure foot plate is in place.
2. Patients should not stretch prior to Ht determination.
3. The patient must be standing without shoes.
4. The patient should be wearing only light clothing so that the patient's pose can be observed.
5. The patient's gaze must be forward and horizontal. (Frankfurt position)
6. Heels must be placed together. If the patient has genu valgum (knock-knee), the knees must be in contact with each other and the heels as close to each other as possible.
7. Heels, buttocks, shoulders, and occiput of the cranium must be in contact with the stadiometer.
8. Upward pressure must be applied to the mandibular rami (jaw).
9. Shoulders should be relaxed and pressure applied to the abdomen to reduce lordosis (spine curvature).
10. The counterweight head rest is lowered until it is in contact with the highest part of the patient's head.
11. Measurement is read at the horizontal level with the counter.
12. Have the patient step away from the stadiometer and repeat the previous steps 2 more times. Repeated determinations must be within 0.2 cm of each other, otherwise the complete measurement needs to be repeated and recorded.
13. Record all measurement, the time of measurement and the observer's name in the CRF.

**APPENDIX D: INSTRUCTIONS FOR OBTAINING X-RAY FILMS****BA Assessment using the Greulich and Pyle Method:**

BA assessment is a procedure frequently employed in pediatric radiology and is a reliable indicator of the skeletal maturity of an individual. The pattern of ossification in the bones of the hand and wrist occurs in a fairly predictable manner and is age specific until the cessation of adolescence when bone elongation is complete. BA assessments and their comparison with CA are important in pediatric endocrinology for diagnosing diseases which result in abnormalities of stature (tall or short) in children. Serial measurements of BA are also critical in determining the effectiveness of established treatments of these diseases as well as use in clinical studies in pediatric populations with new drug candidates for assessment eligibility as well as efficacy and /or safety.

The most common imaging modality for assessment of BA is X-ray of bones of the hand and wrist in a posterior to anterior (PA) view. Assessments are usually done in the left hand and wrist bones to determine the developmental status of individual bones or epiphysis, and a “skeletal age” is ascribed based on the particular indicator or indicators visible on X-ray. The hand radiographs are quite safe and do not expose the patient to any significant radiation exposure with an effective dose of radiation received during a single exposure being below 0.0001-0.001 mSV which is below the exposure one would receive through natural background radiation in 20 min or in 2 min on a transatlantic flight.

The Greulich and Pyle Method is a holistic method based on “The radiographic atlas of skeletal development of the hand and wrist” (second edition, 1959). The atlas contains many standard plates which represent normal bone growth and development of the hand from infancy through adolescence separately for males and females.

For this study, the BA will be assessed by central review using a read model agreed upon with the Sponsor for eligibility and efficacy. The central reviewers will ascribe a BA which corresponds to the appropriate structural features that represent a comparable developmental stage based on the gender of the patient based on the Greulich and Pyle Atlas.

The imaging vendor will provide image acquisition parameters and guidelines to the study sites in order to ensure appropriate acquisition and positioning to facilitate robust reads. Radiographs will be received by the imaging vendor either as DICOM files from digital instruments or as a hard copy film from conventional X-ray instruments. The imaging vendor will digitize the films and blind and mask as needed to ensure that all radiographs will be provided to reviewers in a standardized, de-identified digital format.

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**APPENDIX E: RECOMMENDED INJECTION DAYS**

Day of First Injection	Day of IGF-1 Measurements	Comments	Optional dates for Visit 2 (collection of MOD serum samples and Ab for MOD-4023)
Sunday	Wednesday / Thursday	Not Recommended	Wednesday/Thursday/Friday/Saturday/Sunday – pre dose
Monday	Thursday / Friday	Strongly Recommended	Thursday/Friday/Saturday/Sunday/Monday – pre dose
Tuesday	Friday / <u>Saturday</u>	Recommended	Friday/Saturday/Sunday/Monday/Tuesday – pre dose
Wednesday	Saturday / Sunday	Not Recommended	Saturday/ Sunday/Monday/Tuesday /Wednesday - pre dose
Thursday	<u>Sunday</u> / Monday	Recommended	Sunday/Monday/Tuesday/Wednesday/ Thursday – pre dose
Friday	Monday / Tuesday	Strongly Recommended	Monday/ Tuesday/Thursday/Friday - pre dose
Saturday	Tuesday / Wednesday	Not Recommended	Tuesday/ Wednesday/Thursday /Friday/Saturday - pre dose

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**APPENDIX F: GLYCEMIC TARGETS FOR CHILDREN AND ADOLESCENTS  
WITH TYPE 1 DIABETES**

HbA1C	<7.5%
Plasma glucose before meals	90-130 mg/dL (5.0-7.2 mmol/L)
Plasma glucose at bedtime and overnight	90-150 mg/dL (5.0-8.3 mmol/L)

Source: American Diabetes Association, Standards of Medical Care in Diabetes, January 2015, Volume 38 (Supplement 1), S70–S76.



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**APPENDIX G: 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.

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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 minimizes 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 minimize 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 patients 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 patients 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 patients 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 patients and information regarding provisions for treating and/or compensating patients 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 patients 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.

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**Privacy and Confidentiality**

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

**Informed Consent**

25. Participation by individuals capable of giving informed consent as patients 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 patients 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 patients 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 patients 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 authorized 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 authorized representative. The potential subject's dissent should be respected.
30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or

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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 authorized 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 patients 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 authorized 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 patients 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 patients 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 authorized 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 H: EXAMPLE INJECTION SITE ASSESSMENT TABLE (LOCAL REACTIONS) AND PAIN ASSESSMENT**

**Assessment by the PI and Medical Staff**

Assessment of local tolerability will be performed by examining the injection sites by the Investigator or designated personnel to evaluate if a reaction is present at the time of every visit according to the below.

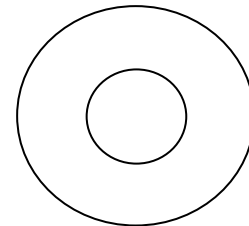
Observations of local injection site reactions will be recorded on the appropriate eCRF pages. If an injection site reaction meets the criteria for “abnormal” defined above, it will be considered and assessed as an AE.

The Investigator is encouraged to properly photo the local injection site if the reaction is considered as abnormal and was assessed as an AE and to properly record it in the patient’s medical file. Photographs of injection site reactions may be taken and used to document any clearly observed clinical effect of MOD-4023 or Genotropin<sup>®</sup>, but will not be formally evaluated.

**Redness**

**Grade Description**

0	NONE	No visible redness
1	MILD	0 to 2 cm redness
2	MODERATE	2 to 5 cm redness
3	SEVERE	Greater than 5 cm redness

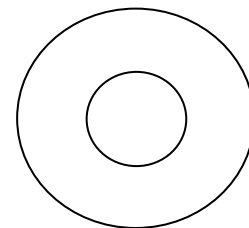


Redness will be assessed by a member of the study staff. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe.

**Bruising**

**Grade Description**

0	NONE	No visible bruising
1	MILD	0 to 2 cm bruising
2	MODERATE	2 to 5 cm bruising
3	SEVERE	Greater than 5 cm bruising

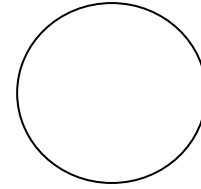


Bruising will be assessed by a member of the study staff. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe.

Effective Date: Date of final electronic approval

**Swelling****Grade Description**

0	NONE	No swelling detected
1	MILD	Palpable “firmness” only
2	MODERATE	< 4 cm swelling
3	SEVERE	> 4 cm swelling



Swelling will be assessed by a member of the study staff. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe.

**Itching****Grade Description**

0	NONE
1	MILD
2	MODERATE
3	SEVERE

The patients will be asked the degree of itching they are experiencing. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe.



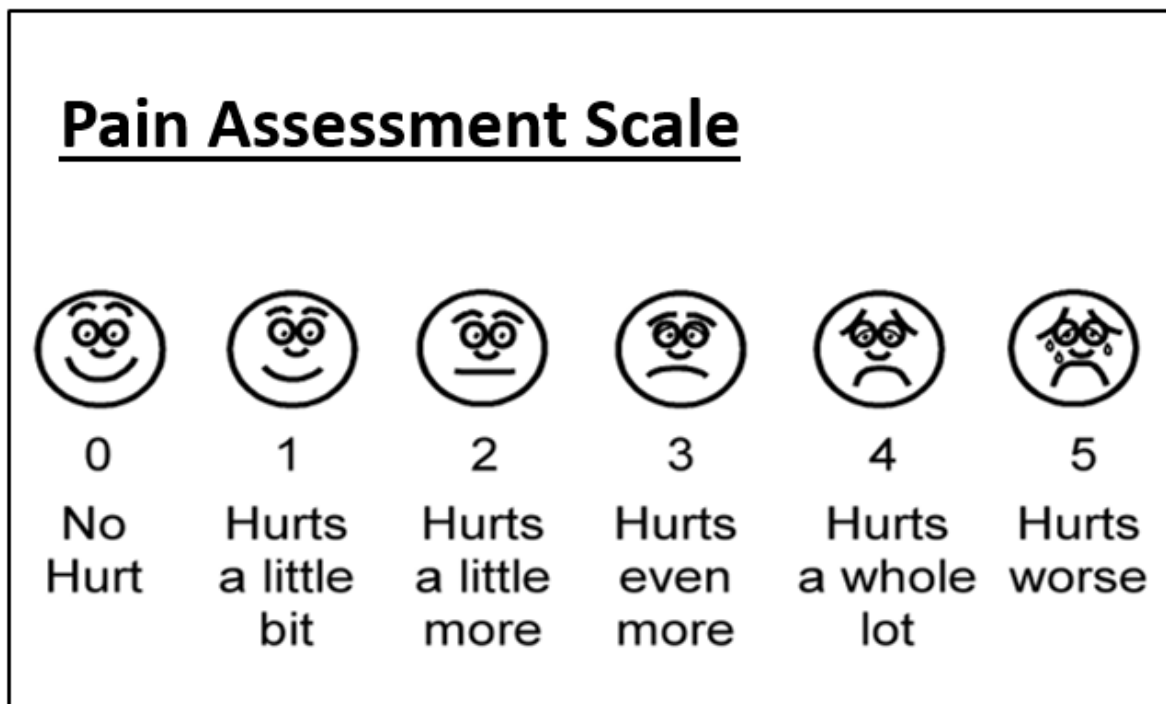
**Pain**

For patients, injection site pain will be evaluated by the Investigator or designated personnel if the injection is given at the medical center, and by the parent/legal guardian if the injection is given at home. The pain will be evaluated using the Pain Rating Scale (below). In addition, each patient and parent/guardian will be queried during study visits regarding possible injection site pain.

The patients should be trained to record any injection site reaction in their diaries.

Pain score above or equal to 4 is considered as an AE.

**Pain Assessment**



The patients will be asked to point to the face that best describes the pain they are experiencing (in the patient diary) and circle the corresponding number.

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**APPENDIX I: EXAMPLE PHONE INTERVIEW FOR VISITS DONE AT HOME.**

*Please note that this questionnaire is subject to change. Please refer to the Ethics approved patient documents for use at each specific clinical site.*

**Phone interview will be done by the investigator or designated personnel and the following questions will be addressed by the patient and his legal guardian/parents**

Name of person conducting phone interview:

\_\_\_\_\_

Role (per Delegation of Responsibilities

Log): \_\_\_\_\_

Please explain the necessity of the call.

We are calling you today to check how you feel; we would like to ask you a few questions, if this is OK with you.

If the patient/parents/legal guardian refuses to answer complete the following steps:

Not interested

Complete a protocol deviation in the EDC.

If the patient/parents/legal guardian are willing to speak, please ask the following questions:

1. From your last visit, do you feel any different?  Yes  No

If yes, please specify and record appropriate AEs (if required) in the patient records and EDC:

\_\_\_\_\_

2. From your last visit, have you taken any new medications or have any existing medications changed?  Yes  No

If yes, please specify and record appropriate con. meds. or changes to existing con. meds. in the patient records and EDC:

\_\_\_\_\_

3. Have any changes in injection sites occurred in the past weeks?  Yes  No

If yes, please specify and record appropriate AEs (if required) in the patient records and EDC:

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**APPENDIX J: CLINICALLY COMPARABLE DOSES OF INHALED  
CORTICOSTEROIDS**

Kelly et al., Annals of Pharmacotherapy 2009 March, Volume 43.

Mometasone fu  
Triamcinolone s  
CFC-MDI = chl  
inhaler; MDI = r  
\*Child age is 5-  
\*Doses are not  
\*Child doses an  
propionate, be

**APPENDIX K: LIST OF CENTRAL TECHNICAL FACILITIES****General Safety Europe:**

1. Covance – Central Lab  
7, rue Moïse Marcinhes  
1217 Meyrin  
Switzerland  
Tel: (+41) 58.822.7000  
Fax: (+41) 58.822.6999

2. Endocrine Research Laboratory  
Medizinische Klinik – Innenstadt Klinikum der Universität (Dr. Bidlingmaier)  
Ziemssenstraße 1, 80336 Munich, Germany  
Tel.: (+49) 89.5160.2277

3. Institute of Laboratory Medicine  
Clinical Chemistry and Molecular Diagnostics  
University Hospital Leipzig  
Liebigstr. 27 (postal address)  
Paul-List-Str. 13-15 (delivery address)  
D-04103 Leipzig  
Germany  
Tel.: (+49) 341.9722241  
(+49) 341.9722450  
Fax: (+49) 341.9722249  
(+49) 341.9722414

4. Labo Medische Genetica  
Department of Medical Genetics  
University and University Hospital of Antwerp  
Prins Boudewijnlaan 43/6  
2650 Edegem  
Belgium  
Phone: (+32) 3.275.9706  
Phone: (+32) 3.275.9719  
Fax: (+32) 3.275.9723

**General Safety US:**

1. Covance USA  
8211 SciCor Drive  
Indianapolis, IN 46214-2985  
USA  
Tel: (+1) 317.271.1200  
Fax: (+1) 317.273.403

2. LabCorp Center for Esoteric Testing  
1447 York Court  
Burlington, NC 27215  
USA  
Tel.: (+1) 336.584.9525  
Fax: (+1) 336.436.0568

Effective Date: Date of final electronic approval

**3. Intertek Pharmaceutical Services**

10420 Wateridge Circle

San Diego, CA 92121

USA

Tel.: (+1) 858.558.2599

(+1) 858.210.3413

Fax: (+1) 858.558.2600

**General Safety APAC:****1. Covance – Singapore**

1, International Business Park

#05-12A/B The Synergy

Singapore 609917

Tel.: (+65) 6560.8793

Fax: (+65) 6565.5901

**2. PPD Central Lab (Singapore)**

61, The Galen, #02-11/14

Science Park 2

Singapore 117525

Tel.: (+65) 6594.6200

Effective Date: Date of final electronic approval

**APPENDIX L: QOL QUESTIONNAIRE**

The QoLISSY questionnaire will be completed at Visits 2 and 8 by patients with the support of their parents/caregiver.

For patients between the age of 3-7 and 0 days, a Parent Questionnaire will be used.

For patients above and including the age of 7 and 0 days, a Child Questionnaire will be encouraged to be used.

The questionnaires are provided in the following order.

The QoLISSY questionnaire will only be filled in the following countries using a validated translated tool:

USA, Australia, New Zealand, Belarus, Russia, Ukraine, France, United Kingdom (UK), Germany, Spain, Italy, Argentina, Chile, Brazil.

Effective Date: Date of final electronic approval

IDENTIFIER/ SUBJECT NUMBER: \_\_\_\_\_

**Parent Questionnaire (for patients below the age of 7 and 0 days)**

Date: \_\_\_\_\_ Name: \_\_\_\_\_

Full name of your child: \_\_\_\_\_

Dear Parent,

We would like to invite you to help us find out more about how your child feels related to his/her height.

- Please answer the following questions. There are no right or wrong answers. It is important that you answer ALL the questions and also that we can see your answers clearly.
- When you think of your answer please think about the last week. If a question is difficult to answer please try it nevertheless by choosing the closest answer – you can also write a note on the last page.
- If you have any difficulties or concerns please write them down on the last page.

**This is how it works:**

Please read every question carefully. What answer comes to your mind first? Choose the box that fits your answer best and mark the box as in the example below.

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Sometimes we would like to know **HOW STRONGLY** or **HOW OFTEN** your child thinks or feels something, and sometimes we would like to know how your child’s height affects you. When you think about your answer, please try to remember your child’s experiences or your experiences over the last week.

**Example:**

Pre-dose						
	My child likes pizza	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input checked="" type="radio"/>

If your child loves eating pizza, then you would mark the box that says “Extremely/always“.

If you find it impossible to answer a question then you can skip that question and go on to the next one. However, please try to answer all the questions.





Effective Date: Date of final electronic approval



The following section is about possible restrictions your child might experience because of his/her height:

1.1	My child's height prevents him/her from doing things that other children his/her age do.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.2	Because of my child's height (s)he has problems everyday.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.3	Because of my child's height (s)he has more trouble reaching things than others his/her age.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.4	Because of my child's height (s)he depends on others.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.5	My child has to look up at most children his/her age when (s)he talks to them.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.6	It bothers my child that other children his/her age can go on fairground rides and (s)he can't.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>

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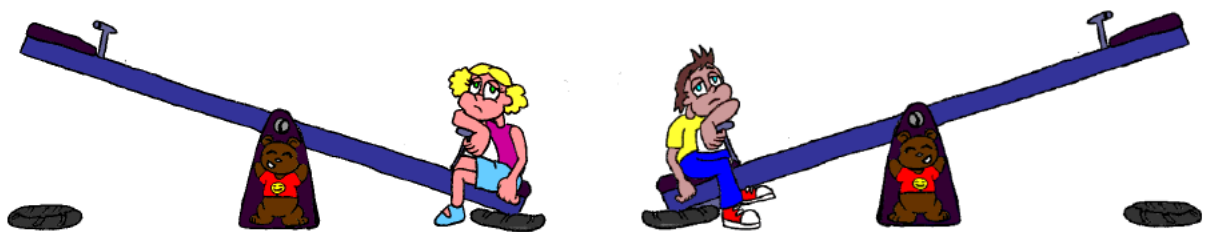
In this part we would like to know what it is like for your child to be with other people (e.g. family, friends, classmates, strangers)

2.1	Being asked about his/her height at school bothers him/her.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
2.2	My child feels small around others his/her age.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
2.3	Others mistake him/ her for being younger than (s)he is.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
2.4	Because of his/her height (s)he gets laughed at and teased.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
2.5	Because of his/her height (s)he is treated differently.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
2.6	My child's height is the only thing others notice about him/her.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
2.7	Because of his/her height (s)he has problems getting the clothes (s)he likes.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
2.8	It hurts my child to be left out of things because of his/her height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>

Effective Date: Date of final electronic approval

This part is about your child's feelings and emotions.

3.1	Because of his/her height my child feels different from others his/her age.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.2	(S)he is fed up with comments about his/ her height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.3	Because of his/her height (s)he is shy.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.4	He/she is happy with his/her height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.5	(S)he is insecure because of his/her height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.6	(S)he is sad because of his/her height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.7	Despite his/her height, my child feels comfortable with the way (s)he is.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.8	His/her height bothers him/her.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>



Effective Date: Date of final electronic approval

IDENTIFIER/ SUBJECT NUMBER: \_\_\_\_\_

**Child Questionnaire (for patients above and including the age of 7  
and 0 days)**

Date: \_\_\_\_\_ Name: \_\_\_\_\_

Date of birth: \_\_\_\_\_ First name: \_\_\_\_\_ ID: \_\_\_\_\_

Hi!

We are interested in how you feel about yourself and we would like to invite you to help us find out. The questions relate to your life in general, your height and your strengths and difficulties.

- Please answer the following questions. There are no right or wrong answers: the most important thing is that you tell us *HOW YOU FEEL*. It is important that you answer *ALL* the questions and also that we can see your marks clearly.
- When you think of your answer please think about the past week. If a question is difficult to answer please try it nevertheless by choosing the closest answer – you can also write a note on the last page.
- If you have any difficulties or concerns please write them down on the last page.

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This is how it works:

Please read every sentence below carefully. What answer comes to your mind first? Choose the box that fits your answer best and mark it with an X.

Sometimes we would like to know **HOW STRONGLY** you think or feel something, and sometimes **HOW OFTEN** you think or feel something. When you think of your answer please try to remember the last week, meaning the last seven days.

**Example:**

**Thinking about last week:**

	Not at all/ never	Slightly/ seldom	Moderately/ quite often	Very/ often	Extremely/ always
I like pizza	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

If you love eating pizza, then you would mark the box that says “Extremely/always“.





**Let us begin with problems you might have with your height.**

1.1	My height prevents me from doing things that other children my age do.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.2	Because of my height I have problems everyday.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.3	Because of my height I have more trouble reaching things than others my age.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.4	Because of my height I depend on others.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
1.5	I have to look up at others my age when I talk to them.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>

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			Moderat			
1.6	It bothers me that others my age can go on fairground rides that I can't.	Not at all/ never	Slightly/ seldom	ely/ quite often	Very/ very often	Extreme ly/ always
		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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**In this part we would like to know what it is like for you to be with other people (such as your family, friends, classmates, strangers).**

2.1	Being asked about my height at school bothers me.	Not at		Moderat	Very/	Extreme
		all/	Slightly/	ely/	quite	ly/
		never	seldom	often	often	always
		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2.2	I feel small around others my age.	Not at		Moderat	Very/	Extreme
		all/	Slightly/	ely/	quite	ly/
		never	seldom	often	often	always
		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2.3	Others mistake me for being younger than I am.	Not at		Moderat	Very/	Extreme
		all/	Slightly/	ely/	quite	ly/
		never	seldom	often	often	always
		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2.4	Because of my height I get laughed at or teased.	Not at		Moderat	Very/	Extreme
		all/	Slightly/	ely/	quite	ly/
		never	seldom	often	often	always
		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2.5	Because of my height I am treated differently.	Not at		Moderat	Very/	Extreme
		all/	Slightly/	ely/	quite	ly/
		never	seldom	often	often	always
		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2.6	My height is the only thing others notice about me.	Not at	Slightly/	Moderat	Very/	Extreme
		all/	seldom	ely/	quite	ly/
		never	seldom	often	often	always
		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>



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		never	<input type="radio"/>	quite	often	always
		<input type="radio"/>		often	<input type="radio"/>	<input type="radio"/>
				<input type="radio"/>		
				Moderat		
2.7	Because of my height I have problems getting the clothes I like.	Not at all/ never	<input type="radio"/>	Slightly/ seldom	<input type="radio"/>	quite often/ always
			<input type="radio"/>			
				Moderat		
2.8	It hurts to be left out of things because of my height.	Not at all/ never	<input type="radio"/>	Slightly/ seldom	<input type="radio"/>	quite often/ always
			<input type="radio"/>			
				Moderat		
				ely/	Very/	Extreme
				quite	very	ly/
				often	often	always
			<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

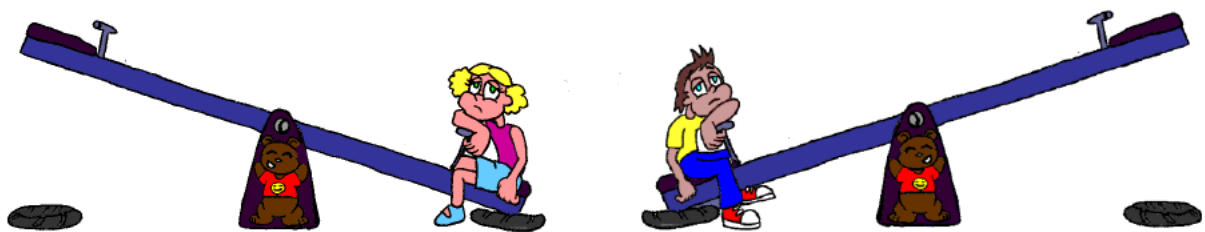
Effective Date: Date of final electronic approval

**This part is about your emotions and how you feel about your height.**

3.1	Because of my height I feel different from others my age.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.2	I am fed up with comments about my height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.3	Because of my height I am shy.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.4	I am happy with my height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.5	I am insecure because of my height.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	Moderately/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extremely/ always <input type="radio"/>
3.6	I am sad because of my	Not at	Slightly/ <input type="radio"/>	Moderately/ <input type="radio"/>	Very/ <input type="radio"/>	Extremely/ <input type="radio"/>

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height.	all/ never <input type="radio"/>	seldom <input type="radio"/>	ely/ quite often <input type="radio"/>	very often <input type="radio"/>	ly/ always <input type="radio"/>
			Moderat		
3.7 Despite my height, I feel comfortable with the way I am.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	ely/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extreme ly/ always <input type="radio"/>
			Moderat		
3.8 My height bothers me.	Not at all/ never <input type="radio"/>	Slightly/ seldom <input type="radio"/>	ely/ quite often <input type="radio"/>	Very/ very often <input type="radio"/>	Extreme ly/ always <input type="radio"/>



Effective Date: Date of final electronic approval

**APPENDIX M: PARTICIPANT ASSESSMENT TOOL (PAT)**

**Patient Questionnaire** (only to be completed by the pen user)

Please complete a new questionnaire each time you take your dose of medicine.  
If splitting your dose between 2 different pens please complete a new questionnaire for each pen.  
It is important that the answers are given by the person who actually operated the pen.

Subject number

Subject ID

What day did you use the pen?

Date

What is the pen kit number?

Pen kit number

Have you used this pen before now? (ie. the pen is already in use)

Yes  No

**1** Who actually gave the injection?

- Subject       A Healthcare Professional  
 A relative or friend  
 Someone else (please specify)

I had help from: \_\_\_\_\_

**2** Were the instructions clear enough for you to use without getting any help?

Yes       No      I had help from: \_\_\_\_\_

Please check which instruction step(s) you had trouble with, below.

- | Preparing                                   | Priming  | Injecting                                     |
|---|--|---|
| <input type="checkbox"/> 4 - Check medicine | <input type="checkbox"/> 8 - Set priming dose  | <input type="checkbox"/> 14 - Inject medicine |
| <input type="checkbox"/> 5 - Attach needle  | <input type="checkbox"/> 9 - Move air bubbles  |   |
|   | <input type="checkbox"/> 10 - Press button     |   |
|   | <input type="checkbox"/> 11 - Check for liquid | <input type="checkbox"/> Other                |

Please state why: \_\_\_\_\_

**3** Which area did you try to inject?

- Thigh       Abdomen       Arm       Buttock

Effective Date: Date of final electronic approval

4 How many injections did you take from this pen today?

1 injection

2 injections

3 injections

4 injections

Please state why:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

5 Did the dose window show '0' when you finished your injection(s), as shown below?

Injection 1

 Yes No

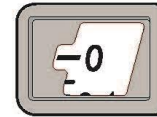
Injection 2

 Yes No

Injection 3

 Yes No

Injection 4

 Yes No

6 Do you believe that a full dose was injected?

Injection 1

 Yes No

Injection 2

 Yes No

Injection 3

 Yes No

Injection 4

 Yes No

If you answered "No" in question 6 above:

7 At what step(s) did the problem occur?

- Preparing the pen
- Priming the pen
- Setting the dose
- Injecting
- After injection
- Other

Please give a brief description of the problem:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

*Thank you for your participation.*

Effective Date: Date of final electronic approval

## APPENDIX N: OBSERVER ASSESSMENT TOOL (OAT)

### Observer Questionnaire

#### Introduction to the assessment

Start the assessment by handing the study materials as outlined in the Subject Study Medication Dosing Booklet and Instructions to the subject or caregiver (user), after they have been trained as outlined in the protocol.

Inform the user that there is no need to hurry. There is no benefit to achieving a shorter time. Doing the procedure CORRECTLY is most important—not speed.

Inform the user that you are there to observe and provide guidance and the onus is on the user to be able to perform the injection without physical assistance. A reason for your physical intervention may be for example to prevent an avoidable injury.

The user should read or refer to the Instructions for Use (IFU)—as much as needed.

If splitting the dose between 2 different pens please complete a new questionnaire for each pen.

In some cases more than 1 injection from the same pen may be needed.

Please record all injections from the same pen on this questionnaire.

#### In the event of an unsuccessful injection

If the pre-filled pen fails to operate, or if the user cannot use the pen so that the injection cannot be performed, document this as a failure in the form (on next page) and provide the user with another pen, but do not provide physical assistance.

Record the injection with the replacement pen on a fresh observer questionnaire. A pen failure should be dealt with as a device complaint (see Protocol Medical Device Complaint Reporting Requirements).

#### Providing assistance to the user

If the user is able to successfully administer the dose but requires your help to complete the injection, document the specifics below, including asking the user if after the injection they are now confident that they will be able to inject unassisted at home.

If not, provide additional training until you have addressed their confusion or concerns and they confirm their understanding as to how to successfully administer the study drug.

Turn over for questions 

Effective Date: Date of final electronic approval

### Observer Questionnaire

Turn over for instructions 

Subject ID

Assessment date

Pen kit number

Signature:

**1** Based on your observations, did the user successfully inject into an acceptable injection site? Please report all injections from this pen.

**Injection 1**

Yes

No

**Injection 2**

Yes

No

**Injection 3**

Yes

No

**Injection 4**

Yes

No

For unsuccessful attempts please provide details of the errors  
(e.g. – pen failed to operate; user was unable to perform a step.)

[Free text]

**2** Where a successful injection was made—did the user need any specific help to achieve it?

Yes

No

Please record the details of all such help provided.

(e.g. – what was the task or step that they could not complete; what additional instruction was required; were they able to complete the injection after the instruction, etc.)

[Free text]

Signature Page for CP-4-006 Protocol US v5.0

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