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Reason for signing: Approved	Name:PPD Role: Clinical Operations Date of signature: 14-Dec-2018 20:58:13 GMT+0000

Signature Page for CCI

CLINICAL STUDY PROTOCOL

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

Sponsor:	OPKO Health Inc. 4400 Biscayne Boulevard Miami, FL 33137, USA Tel: +1 305 575 4100
Protocol Number:	CP-4-009 Japan Country-Specific
Investigational Product:	MOD-4023
Coordinating Investigator:	PPD , M.D. Ph.D. PPD Division of Endocrinology and Metabolism National Center for Child Health and Development
Safety Medical Officer:	PPD , M.D. PPD Tanaka Growth Clinic, Tokyo, Japan
Protocol Version:	9.0

Confidentiality Statement

This protocol is a confidential communication document of OPKO Health Inc. (OPKO) The recipient of this document agrees not to disclose the information contained herein to others without prior written authorization of OPKO except that this document may be disclosed to appropriate Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) or duly authorized representatives of Regulatory authorities such as Pharmaceuticals and Medical Device Agency (PMDA).

Protocol Signature Page

Protocol Title	A Phase 3, Open-Label, Randomized, Multicenter, 12-Month, Efficacy and Safety Study of Weekly MOD-4023 Compared to Daily Genotropin® Therapy in Japanese Pre-Pubertal Children with Growth Hormone Deficiency
Protocol Number	CP-4-009; Japan Country-Specific
Investigational Product:	MOD-4023
Study Phase	3
Sponsor	OPKO Health Inc. 4400 Biscayne Boulevard Miami, FL 33137, USA Tel: +1 305 575 4100

Sponsor Representatives
We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonisation (ICH) ,Good Clinical Practice (GCP) guidelines and Japanese GCP (J-GCP).

Signature Date

See Electronic Signature
PPD , OPKO

See Electronic Signature
PPD , OPKO

See Electronic Signature
PPD , Quality Assurance, OPKO

Principal Investigator
By signing below, I, the Investigator approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections. 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 OPKO.

Investigator Signature Date

Name Institution City, Country

Protocol Synopsis

Study Title	A Phase 3, Open-Label, Randomized, Multicenter, 12-Month, Efficacy and Safety Study of Weekly MOD-4023 Compared to Daily Genotropin® Therapy in Japanese Pre-Pubertal Children with Growth Hormone Deficiency
Protocol Number	CP-4-009
Investigational Product:	MOD-4023
Clinical Sites	The study will be conducted in approximately 45-55 sites in Japan.
Study Phase	3
Therapeutic Indication	Treatment of children with growth failure due to growth hormone deficiency (GHD).
Study Objectives	Primary • To evaluate the efficacy and safety of weekly MOD-4023 administration compared to daily Genotropin® administration in Japanese pre-pubertal children with GHD. Secondary • To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) profiles of three different doses of MOD-4023 in Japanese pre-pubertal children with GHD.
Study Design	This is a 12-month, open-label, randomized, active controlled, parallel group study comparing the efficacy and safety of weekly MOD-4023 to daily recombinant human growth hormone (r-hGH), Genotropin®. Both drugs will be injected subcutaneously (SC) using a pen device. After a 4 week Screening period (with optional extension of 1 week if needed, for a total of up to 5 weeks) and approval of the study medical monitor, patients meeting all the inclusion criteria and none of the exclusion criteria, will be eligible to participate in the study. At Baseline, eligible patients will be randomized in a 1:1 ratio, to receive either: • MOD-4023 (investigational treatment): weekly MOD-4023 SC injections for 12 months; initially over the first 6 weeks, MOD-4023 will be administered in 3 stepwise escalating doses (0.25 mg/kg/week, 0.48 mg/kg/week and 0.66 mg/kg/week), each for two weeks sequentially. For the remaining 46 weeks, patients will continue to receive MOD-4023 at a dose of 0.66 mg/kg/week. Or • Genotropin® (reference treatment): daily Genotropin® (0.025 mg/kg/day which is equivalent to 0.175 mg/kg/week, divided equally into 7 daily injections over a week) SC injection for 12 months. Patients allocated to the MOD-4023 treatment arm, will initially undergo a stepwise dose escalation over 6 weeks starting with low MOD-4023 dose of 0.25 mg/kg/week for 2 weeks, followed by an intermediate dose of 0.48 mg/kg/week for 2 weeks and then a final dose of 0.66 mg/kg/week for 2 weeks. These MOD-4023 patients will be assigned into one of 4 sampling sub-blocks (as shown in the table below) and undergo population-based PK

and PD sampling to determine concentrations of MOD-4023 and CCI [redacted] In each sub-block, for each dose level, there will be different sampling time collection relative to the second injection of each dose (from pre-dose (-12), 12 (±3), 18 (±3), 36 (±6), 48 (±12), 72 (±12), 96 (±12) and 120 (±12) hours post dose). Six (6) blood samples for PK/PD will be obtained from each patient; 2 samples for 0.25 mg/kg/week dose, 2 for 0.48 mg/kg/week dose, and 2 for 0.66 mg/kg/week dose. At the end of the 6-week dose escalation phase, patients will continue the study for another 46 weeks at dose of 0.66 mg/kg/week. Over this 6 weeks escalation period, patients will be instructed to inject once a week at evening hours/bed time. At the treatment period, patients can choose to stay with evening injection or to switch to morning injection. The time of injection should be consistent until the end of the study.

	0.25 mg/kg/week		0.48 mg/kg/week		0.66 mg/kg/week	
Sub-Block	Sample 1 (Visit 3)	Sample 2 (Visit 3.1)	Sample 3 (Visit 4)	Sample 4 (Visit 4.1)	Sample 5 (Visit 5)	Sample 6 (Visit 5.1)
I	Pre-dose[a]	48[b]	36[c]	120[b]	18[d]	96[b]
II	12[d]	72[b]	Pre-dose[a]	48[b]	36[c]	120[b]
III	18[d]	96[b]	12[d]	72[b]	Pre-dose[a]	48[b]
IV	36[c]	120[b]	18[d]	96[b]	12[d]	72[b]

After the 6-week PK/PD sampling period, the dose of MOD-4023 and Genotropin® will be adjusted every 3 months based on a 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 of adverse events (AEs) or repeated, elevated levels of IGF-1 Standard Deviation Score (SDS)).

The key safety data will be reviewed by an independent and external Data and Safety Monitoring Board (DSMB) at a minimum once every 6 months. The DSMB will also review the number or percentage of patients requiring dose reductions due to IGF-1 above +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® treatment groups). DSMB review will also include a review of the number or percentage of patients requiring dose reductions due to AEs. Following the completion of the12-month treatment period, eligible patients will be consented to enroll into an open-label long term extension (OLE) period, and an amendment to this study protocol will be submitted prior to the first patient completes the 12 months treatment period. Eligible Genotropin®-treated patients will be switched to a MOD-4023 dose of 0.66 mg/kg/week in the OLE. The OLE is planned to continue until MOD-4023 marketing registration in Japan.

Study Procedures

The study will consist of 3 parts; a Screening period, Active Treatment period and Follow Up period, as described below.

[a] 0 to 12 hours before dose.
[b] Time window ±12 hours.
[c] Time window ±6 hours.
[d] Time window ±3 hours.

	Screening Period (Visit 1; Week -4/ Day -28 to Week -1/Day -1) [a] Patients will complete screening procedures to determine eligibility. The Screening period will last up to 4 weeks (with optional extension of 1 week, for a total of 5 weeks) and can be conducted over several visits prior to randomization. Prior to any study-specific investigations, written assent from pediatric patients (if needed, use appropriate 1 of 2 versions according to their education and their age) and consent from the parent(s) or legal guardian(s) will be obtained. The following assessments will be conducted at the screening visits: • Inclusion/Exclusion criteria • Estimated Parental height[b] • Auxology measurements[c], body mass index (BMI) and BMI SDS • Patient's Height SDS and Height Velocity (HV) SDS • Demographics and Medical history, including a description of pituitary deficiencies, concomitant and previous medications • Overall health status assessments – complete physical examination and vital signs • Pubertal status (according to Tanner stages) • Bone age determination with the method of TW2 using a central bone age reader[d] • Assessment of biochemical markers and stimulation tests: - Two different GH stimulation (provocation) tests from the following list: insulin tolerance test (with serum cortisol response to hypoglycemia if insulin stimulation test is chosen); arginine test; clonidine test; glucagon test; L-dopa; and GHRP-2. The minimal duration and number of samples for each test must conform to the specifications in Appendix D.[e] - Analysis of GH serum levels (and glucose and serum cortisol if Insulin tolerance test is performed) may be done by local laboratories and to be provided for study medical monitor review and approval prior to study entry - Assessment of morning cortisol (up to 8 am ±1 hour)[f].

[a] 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 lab results) extra time - equal to the time of patient's unavailability - will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).

[b] It is recommended that the parents' height will be measured at the site. If measured parental height is not available an estimate could be provided by the parent.

[c] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

[d] At Screening Visit, historical bone age assessment might be accepted if they were done no more than 6 months prior to the ICF signature date. If the patient will be eligible, the bone age should be repeated at Visit 2, before the dosing. The Visit 2 scan will be the baseline scan for these patients.

[e] No time limitation for the historical GH stimulation tests.

[f] Morning cortisol assessment will be subject to the investigator judgment.

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[a] or has been diagnosed with adrenal insufficiency). The minimal duration and number of samples for each test must conform to the specifications in Appendix D.

- Assessment of CCI IGF-1 SDS

- Assessment of anti-hGH antibody levels
- Assessments of routine safety laboratory tests: biochemistry, hematology, and urinalysis (see section 5.5.9)
- Assessment of thyroid: TSH, FT4
- Assessment of glucose metabolism: morning fasting insulin and glucose (will be tested as part of biochemistry panel) and HbA1c
- Parameters of lipid metabolism: morning fasting total cholesterol, triglycerides, HDL and LDL
- Head magnetic resonance imaging[b] (MRI) if possible with contrast – after two GH stimulation tests, based on physician recommendation

Approximately 8-42 mL of blood will be drawn from the patients during the screening period.

All lab assessments are done in a central laboratory unless stated otherwise.

Key data and all test results obtained during screening will be reviewed by the study medical monitor and eligibility will be confirmed prior to randomization of each patient.

Active Treatment Period (Baseline to Month 12)

At Baseline (Visit 2/Day 1) or once eligible, eligible patients will be randomized in a 1:1 ratio to MOD-4023 (investigational treatment) or Genotropin® (reference therapy) and will undergo the following assessments[c]:

- Auxology[d] measurements
- AE, local tolerability (injection site reactions assessment) and concomitant medications
- Overall health status assessment, including complete physical examination and vital sign assessments

[a] Insulin tolerance test with serum cortisol response to hypoglycemia is adequate for assessment of adrenal insufficiency and no ACTH/CRH stimulation test is required if such results are available.

[b] MRI to be performed upon physician judgment. In addition, MRI which was conducted within 6 months prior to ICF signature date will be acceptable.

[c] Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

[d] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

- Safety laboratory- biochemistry, hematology and urinalysis, (see section 5.5.9)
- Pubertal status (according to Tanner stages)
- Assessment of thyroid: TSH, FT4
- Assessment of biochemical markers: CCI IGF-1 SDS (applicable for both arms), CCI
- Assessment of MOD-4023 serum levels (applicable for MOD-4023 treatment arm only)
- Parameters of glucose metabolism- morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c
- Parameters of lipid metabolism- morning fasting total cholesterol, triglycerides, HDL and LDL
- Assessment of pre-dose anti-MOD 4023 and anti-hGH antibodies (depending on treatment arm allocation)
- Bone age[a]
- ECG pre-dosing
- Training for patients, parents or legal guardians on patient diary completion and drug administration including on site injection
- Administration of study drug at clinic
- Drug dispensing

Approximately 9-12 mL of blood will be drawn from patients at baseline visit.

During the Treatment period, patients will be scheduled to attend the following clinic visits according to their treatment allocation as shown in the table below. The Baseline Visit (Visit 2/first dose – described above) and Visits 6 to 9 (every three months) will be similar for both treatment arms (except where noted). Visits 3, 4 and 5 will differ between the 2 treatment arms due to the 6-week dose escalation and PK/PD sampling in the MOD-4023 treatment arm.

MOD-4023 Treatment Arm (Investigational)	**Genotropin® Treatment Arm (Reference)**
Visit 2 – Baseline – First dosing	Visit 2 – Baseline – First dosing
Visits 3 and 3.1 – Week 2 First PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation)	Visit 3 – Week 2 Phone interview will be done. Per Appendix I. No clinic visit.
Visits 4 and 4.1 – Month 1/Week 4 Safety (only at Visit 4.1) and second PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation)	Visit 4 – Month 1/Week 4 (±1 week) Clinic visit

[a] Bone age at Visit 2 will be performed in case bone age was not performed at screening. This test should be done prior to the first dose.

Visits 5 and 5.1 – Week 6 Third PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation)	Visit 5 – Week 6 Phone interview will be done per Appendix I. No clinic visit.
Visit 6 – Month 3/Week 13 (±1 week) Clinic visit To be conducted 4 days (-1 day) post dose	Visit 6 – Month 3/Week 13 (±1 week) Clinic visit
Visit 7 and 7.1 – Month 6/Week 26 (±3 weeks) Two clinic visits: - Visit 7 Pre-dose immunogenicity assessments conducted same day as dosing - Visit 7.1 Post-dose assessments conducted 4 days (-1 day) after dose	Visit 7 – Month 6/Week 26 (±1 week) Clinic visit
Visit 8 – Month 9/Week 39 (±1 week) Clinic visit To be conducted 4 days (-1 day) post dose	Visit 8 – Month 9/Week 39 (±1 week) Clinic visit
Visit 9 and 9.1 – EOT Visit – Month 12/Week 52 (±3 weeks) Two clinic visits: - Visit 9 Pre-dose immunogenicity assessments conducted same day as dosing - Visit 9.1 Post-dose assessments conducted 4 days (-1 day) after dose	Visit 9 – EOT Visit – Month 12/Week 52 (±1 week) Clinic visit
Visit 10 – EOS visit – Month 13/Week 56 (+1 week) Phone interview will be done. Per Appendix I. No clinic visit.	Visit 10 – EOS visit – Month 13/Week 56 (+1 week) Phone interview will be done. Per Appendix I. No clinic visit.

Visit windows are relative to the visit, not to the dose, unless specified otherwise.

Assessments for MOD-4023 treatment arm (Visits 3 to 9):

The following assessments will be obtained at the visits 3 and 3.1, 4 and 4.1, and 5 and 5.1.

Visits 3, 4 and 5 will take place at Weeks 2, 4, and 6, respectively, for first PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation). Visits 3.1, 4.1, and 5.1 will take place at Weeks

	2, 4, and 6 respectively, for second PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation – refer to Table 2). For each visit/sub-visit, the patient is expected to visit the clinic twice during the week to obtain two different post-dose PK/PD samples. • Safety evaluation consisting of AE, local tolerability and Concomitant medications at all visits • Complete physical examination and vital sign assessments at visits 3.1, 4.1 and 5.1 only • Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9) at Visit 4.1 only • Assessment of biochemical markers: CCI [redacted], IGF-1 SDS, CCI [redacted] (sampling time per sub-block allocation) • MOD-4023 serum levels (sampling time per sub-block allocation) • Assessment of anti-MOD-4023 antibodies at Visit 4.1 only • Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension) • Weight measurement at Visit 4.1 only. • Training on drug administration, injection site reactions, diary completion, and dosing review (Visits 3.1 and 4.1) • Study drug return and accountability at Visit 4.1 only • Individual dose adjustment and dispensing study drug at Visit 4.1 only Approximately 6 mL of blood will be drawn from the patients at each visit, except for Visit 4.1. At Visit 4.1, approximately 12 mL of blood will be drawn from the patients. **The following assessments will be obtained at Visit 6 (Month 3/Week 13 ± 1week) and Visit 8 (Month 9/Week 39 ±1week):** • Auxology measurements[a] • AE, local tolerability, and concomitant medications • Overall health status assessment, including complete physical examination and vital sign assessments • Safety laboratory: biochemistry, hematology and urinalysis, (see section 5.5.9) • Pubertal status (according to Tanner stages) • Assessment of thyroid: TSH, FT4 • Assessment of biochemical markers: CCI [redacted] IGF-1 SDS • CCI [redacted] • Assessment of anti-MOD-4023 antibodies

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall or equivalent mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

	• Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension) • Study drug return and accountability • Individual dose adjustment and dispensing study drug Approximately 9 mL of blood will be drawn from the patients at those visits. **Visit 7 and Visit 7.1 (Month 6/Week 26 ±3 weeks)** Visit 7 will consist of two clinic visits, Visit 7 (pre-dose) and Visit 7.1 (post-dose), at Week 26 ±3 weeks. Visit 7 must be conducted prior to Visit 7.1. Visit 7 will take place at the clinic prior to dosing at any week during ±3 weeks of Month 6/Week 26. The following pre-dose immunogenicity assessments should be conducted on the same day of dosing: • AE and concomitant medications • Assessment of MOD-4023 serum levels • Assessment of anti-MOD-4023 antibodies Approximately 6 mL of blood will be drawn from the patients at this visit. Visit 7.1 will take place at the clinic 4 days (-1 day) after dose at any week after Visit 7 during the ±3 weeks of Month 6/Week 26. The following post-dose assessments will be conducted 4 days (-1 day) after dose: • Auxology measurements[a] • AE, local tolerability, and concomitant medications • Overall health status assessment, including complete physical examination and vital sign assessments • Safety laboratory: biochemistry, hematology and urinalysis, (see section 5.5.9) • Pubertal status (according to Tanner stages) • Assessment of thyroid: TSH, FT4 • Assessment of biochemical markers: CCI IGF-1 SDS • CCI • Parameters of glucose metabolism- morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c • Parameters of lipid metabolism- morning fasting total cholesterol, triglycerides, HDL and LDL • ECG • Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension) • Study drug return and accountability

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall or equivalent mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

	• Individual dose adjustment and dispensing study drug Approximately 10 mL of blood will be drawn from the patients at this visit. **Visit 9 and Visit 9.1 (Month 12/ Week 52 ±3 weeks) - End of Treatment (EOT) Visit Assessments** Visit 9/EOT will consist of two clinic visits, Visit 9 (pre-dose) and Visit 9.1 (post-dose), at Week 52 ±3 weeks. Visit 9 must be conducted prior to Visit 9.1. Visit 9 will take place at the clinic prior to dosing at any week during ±3 weeks of Month 12/Week 52. The following pre-dose immunogenicity assessments should be conducted on the same day of dosing: • AE and concomitant medications • Assessment of MOD-4023 serum levels • Assessment of anti-MOD-4023 Approximately 6 mL of blood will be drawn from the patients at this visit. Visit 9.1 will take place at the clinic 4 days (-1 day) after dose at any week after Visit 9 during the ±3 weeks of Month 12/Week 52. The following post-dose assessments will be conducted 4 days (-1 day) after dose: • Auxology measurements[a] • AE, local tolerability and concomitant medications • Overall health status assessment, including complete physical examination and vital sign assessments • Safety laboratory biochemistry, hematology and urinalysis (see section 5.5.9) • Pubertal status (according to Tanner stages) • Assessment of thyroid: TSH, FT4 • Hormones and biochemical markers: CCI IGF-1 SDS • Parameters of glucose metabolism- morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c • Parameters of lipid metabolism- morning fasting total cholesterol, triglycerides, HDL and LDL • Assessment of MOD-4023 serum levels • Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension) • Bone age assessment • Study drug return and accountability Approximately 10 mL of blood will be drawn from the patients at this visit.

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall or equivalent mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

	Assessments for Genotropin® Treatment Arm – Visits 3 to 9. At Visit 3 (Week 2) and Visit 5 (Week 6) a phone interview will be conducted according to Appendix I. **No clinic visit.** **The following assessments will be conducted at Visit 4 (±1 week):** • AE, local tolerability and concomitant medications • Overall health status assessment, including complete physical examination and vital signs assessments • Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9) • Hormones and biochemical markers CCI IGF-1 SDS • Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension) • Study drug return and accountability Approximately 7 mL of blood will be drawn from the patients at this visit (No blood samples will be collected at Visits 3 and 5. No clinic visit). **The following assessments will be conducted at Visits 6 (±1 week), 7 (±1 week) and 8 (±1 week):** • Auxology measurements[a] • AE, local tolerability and concomitant medications • Overall health status assessment, including complete physical examination and vital signs assessments • Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9) • Pubertal status (according to Tanner stages) • Assessment of thyroid: TSH, FT4 • Hormones and biochemical markers: CCI IGF-1 serum SDS • Parameters of glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c at Visit 7 only • Parameters of lipid metabolism: morning fasting total cholesterol, triglycerides, HDL and LDL at Visit 7 only • Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension) • Study drug return and accountability • ECG at Visit 7 (Month 6/Week 26 ± 1day) • Individual dose adjustment every 3 months • Dispense study drug

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall or equivalent mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

	• Anti-hGH antibodies Approximately 9 mL of blood will be drawn from the patients at those visits. **Visit 9 (Month 12/Week 52 ±1 week) - End of Treatment (EOT) Visit:** The following assessments will be conducted at visit 9, EOT visit: • Auxology measurements[a] • AE, local tolerability and concomitant medications • Overall health status assessment, including complete physical examination and vital signs assessments • Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9) • Pubertal status (according to Tanner stages) • Assessment of thyroid: TSH, FT4 • Hormones and biochemical markers: CCI IGF-1 SDS • Parameters of glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c • Parameters of lipid metabolism: morning fasting total cholesterol, triglycerides, HDL and LDL • Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension) • Bone age assessment • Study drug return and accountability • Anti-hGH antibodies Approximately 9 mL of blood will be drawn from the patients at this visit. Patients in both arms will be requested to complete a patient diary at home to collect data on AEs, concomitant medications and local tolerability reactions on weekly basis (MOD-4023 after 1 weekly dosing; Genotropin® once a week post 1 dosing). **For MOD-4023 and Genotropin®:** **Follow Up Period (Month 13) - Visit 10 - EOS Visit (Week 56 +1 week)** After 1 month following EOT visit (visit 9), phone interview should be conducted according to Appendix I. This phone interview will be considered as Visit 10 - End Of Study visit.
Study Duration	Study duration for each participating patient will be up to 13 months as follows in the main protocol: Screening period: Up to 1 month (4 weeks + 1 week extension)

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall or equivalent mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

	Active Treatment period: 12 months MOD-4023 Arm: 52 weeks (6 weeks dose escalation + 46 weeks) Genotropin® Arm: 52 weeks Follow Up period: 1 month
Number of Patients	Approximately 44 pre-pubertal children, boys not yet 11 (10 years and 364 days) and girls not yet 10 (9 years and 364 days) years of age, respectively, will be included randomized in a 1:1 ratio to the weekly MOD-4023 arm and the daily Genotropin® comparator arm.
Inclusion Criteria	1. Pre-pubertal child aged ≥ 3 years old, and not yet 10 years for girls (9 years and 364 days) or not yet 11 years for boys (10 years and 364 days), on the date of ICF signature, with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency. 2. Confirmed diagnosis of GHD by 2 different types of GH provocation tests (standardized on growth foundation data): defined as a peak serum GH level of ≤ 6.0 ng/mL or ≤ 16 ng/mL when conducting GHRP-2 provocation test. Prior local laboratory results will be accepted subject to pre-approval by the study medical monitor and if the tests were conducted as specified in the protocol. 3. Bone age (BA) is not older than chronological age and should be less than 10 for girls and less than 11 for boys. 4. Without prior exposure to any r-hGH therapy. 5. Height SD score ≤ -2.0 at screening 6. Impaired height velocity defined as: • Annualized height velocity (HV) below the 25th percentile for CA (HV < -0.7 SDS) and gender according to the local primary care provider standard. • The interval between two height measurements should be at least 6 months, but should not exceed 18 months prior to inclusion. 7. BMI must be within ±2 SDS of mean BMI for the chronological age and sex. 8. Baseline IGF-1 level of at least 1 SDS below the mean IGF-1 level standardized for age and sex (IGF-1 SDS ≤ -1)[a] according to the central laboratory reference values. A single re-test will be allowed (subject to approval from the study medical monitor) if all other criteria are met. 9. Normal creatinine levels according to common practice reference ranges per age. 10. 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. 11. Clinical presentation of normal 46 XX karyotype for girls. 12. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from

[a] According to rounding policy IGF-1 results ≤-0.95 might be acceptable as well

	pediatric patients (when applicable based on age and Japan regulation).
Exclusion Criteria	1. Children with prior history of leukemia, lymphoma, sarcoma or any other forms of cancer. 2. History of radiation therapy or chemotherapy. 3. Malnourished children defined as BMI < -2 SDS for age and sex. 4. Children with suspected psychosocial dwarfism by the discretion of the investigator. 5. Children born small for gestational age (SGA – birth weight and/or birth length < -2 SDS for gestational age). 6. Presence of anti-hGH antibodies at screening. 7. Any clinically significant 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. Children with diabetes mellitus. 9. Known or suspected chromosomal abnormalities including Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Russell-Silver syndrome, SHOX (short stature homeobox) mutations/deletions and skeletal dysplasia's, with the exception of septo-optic dysplasia. 10. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids, sex steroids, with the exception of ADHD drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin [DDAVP]) 11. Children requiring glucocorticoid therapy (e.g. for asthma) that are taking chronically a dose greater than 400 µg/d of inhaled budesonide or equivalent as provided in Appendix J. 12. Major medical conditions and/or presence of contraindication to r-hGH treatment. 13. Known or suspected HIV-positive patient, or patient with advanced diseases such as AIDS or tuberculosis. 14. Drug substance or alcohol abuse. 15. Known hypersensitivity to the components of study medication. 16. Other causes of short stature such as celiac disease, uncontrolled primary hypothyroidism and rickets. 17. The patient and/or the parent/legal guardian are likely to be non-compliant in respect to study conduct. 18. Participation in any other clinical trial within 30 days prior to screening and throughout the entire study period (including administration of investigational agent).
Investigational Product Route and Dosage Form	MOD-4023 is a long-acting modified recombinant human growth hormone (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 multi-dose disposable pre-filled pen. MOD-4023 will be administered as a SC injection once weekly, using a delivery device, into the upper arms, buttocks, thighs or abdomen (8 locations for injection as noted in Figure 1).

	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. During the first 6 weeks of dose escalation phase, the starting dose for the weekly administration will be: 0.25 mg/kg/week for 2 weeks, followed by an intermediate dose of 0.48 mg/kg/week for 2 weeks and then a final dose of 0.66 mg/kg/week for 2 weeks. During the remaining 46 weeks, the starting dose for the weekly administration will be 0.66 mg/kg/week. Over the 6 weeks escalation period, patients will be instructed to inject at evening hours/bed time. Following the 6 weeks escalation period, during the treatment period, patients can choose to stay with evening injections or to switch to morning injections. The time of injection should be consistent until the end of the study.
Reference Drug	Genotropin® is dispensed in a 2-chamber cartridge. The front compartment contains recombinant somatropin, glycine, mannitol, sodium dihydrogen phosphate anhydrous and disodium phosphate anhydrous. The rear compartment contains m-Cresol and mannitol in water for injections. A delivery device (Genotropin® GoQuick pen) will be used for daily (evening/bedtime) SC administration of Genotropin® into the region of the upper arms, buttocks, thighs or abdomen (8 locations). Injection sites should be rotated. Dose regimen for Genotropin®: 0.025 mg/kg/day (or 0.175 mg/kg/w divided equally to 7 injections over a week).
Efficacy Endpoints	**Primary endpoint:** • Annual HV in cm/year after 12 months of treatment. **Secondary endpoints (Auxology/Clinical):** • Annualized HV after 6 months of treatment • Change in height SDS at 6 and 12 months, compared to Baseline • Change in bone maturation (BM) at the end of 12 months, compared to Baseline BA (calculated as BA/CA).
PK / PD Endpoints	**Secondary endpoints (Biochemical):** CCI [redacted] • IGF-1 SDS on day 4(-1) after MOD-4023 dosing across study visits (window only applies to visits 6 to 9) CCI [redacted]
Safety Endpoints	• Incidence of AEs and SAEs • Incidence of anti-MOD-4023 antibody formation (including characterization of the antibodies and neutralizing properties) • Local injection site assessment

	• CCI IGF-1 SDS • Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin level and HbA1c • Thyroid status • Lipid metabolism parameters: morning fasting total cholesterol, LDL, HDL and triglycerides • All other safety hematology and biochemical laboratory parameters • Physical examination • Fundoscopy (normal/abnormal) • Vital signs • ECG
Sample Size	The primary efficacy endpoint is Annual HV in cm/year after 12 months of treatment. Assuming that the mean treatment difference in the HV is -0.8 cm/yr and the common SD is 2.5 cm/yr, a total 44 Patients (22 per treatment) will provide about 90% probability that the point estimate of the mean treatment difference of HV in the CP-4-009 study is greater than -1.8 cm/year (which is the non-inferiority margin in the global trial CP-4-006).
Statistical Analysis	Details on the statistical methods will be provided in a Statistical Analysis Plan (SAP) prior to database lock. The aim of this Phase 3 study is to demonstrate that Annual HV at 12 months for weekly MOD-4023 is comparable to daily r-hGH within the range defined of 1.8 cm/year (non-inferiority margin in CP-4-006 study). Descriptive statistics and confidence intervals (CI) will be used to characterize the results. <u>Primary Efficacy Analysis:</u> The goal of the primary efficacy analysis is to estimate the mean treatment difference between weekly MOD-4023 and daily Genotropin® with respect to the primary efficacy endpoint (HV after 12 months of treatment). Least square means and 95% CI for HV at 12 months will be derived from an Analysis of Covariance (ANCOVA) model, with treatment, gender, as factors (class variables); and peak hGH value during stimulation test, and baseline HV as covariates. The point estimate of the mean difference in HV between treatments will be used to assess comparability. Comparability will be concluded for the primary efficacy endpoint if the point estimate of the mean treatment difference (MOD-4023 – Genotropin®) is ≥ –1.8 cm/year. Missing data will be handled by multiple imputation (using SAS PROC MI), assuming data missing at random. Details will be provided in the SAP. <u>Secondary Analysis</u>: The continuous secondary efficacy endpoints measured at a single post-baseline timepoint will be analyzed in the same manner as the primary endpoint, using the ANCOVA model which may include treatment group, age, and gender, peak hGH value during stimulation test, and the baseline value of the endpoint of interest to generate the least square treatment means. For the secondary endpoints that are measured over time, Mixed-

	effect Model Repeated Measure (MMRM) analysis with similar factors as the ANCOVA model (in the primary analysis) will be used to estimate the time-specific results. This MMRM approach is not intended to test for statistical significance of factors. These secondary analyses are considered to be supportive efficacy analyses. 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.

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GLOSSARY

Abbreviation	Definition
µg	Microgram
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse Event
ALT	Alanine Aminotransaminase (SGPT)
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase (SGOT)
BA	Bone Age
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA	Chronological Age
CI	Confidence Interval
CPK	Creatine Phosphokinase
CRH	Corticotropin Releasing Hormone
CRO	Contract Research Organization
CTP	C-terminal Peptide
D	Day
Day 4 (-1)	Day 3 or 4 post-injection
DBPC	Double-Blind Placebo-Controlled
DDAVP	Desmopressin acetate
dL	Deciliter
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End Of Study
EOT	End Of Treatment
FDA	Food and Drug Administration
FT4	Peripheral Thyroid Hormones
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GHRP	pure growth hormone secretagogue
GRS	Growth Hormone Research Society
HbA1c	Glycated hemoglobin (hemoglobin A1c)
hCG	Human Chorionic Gonadotropin
HCT	Hematocrit
HDL	High Density Cholesterol
HGB	Hemoglobin

Abbreviation	Definition
hGH	Human Growth Hormone
HV	Height Velocity
ICCC	In Country Clinical Caretaker
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
CCI	[redacted]
IGF-1	Insulin-like Growth Factor-I
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
J-GCP	Japanese Good Clinical Practice
Kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LDL	Low Density Cholesterol
LH	Luteinizing Hormone
nmol	Nanomole
M	Meter
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmol	Millimole
MRI	Magnetic Resonance Imaging
OLE	Open-label extension
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Device Agency
QA	Quality Assurance
RA	Regulatory Assurance
RBC	Red Blood Cells
r-hGH	Recombinant Human Growth Hormone
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard deviation
SDS	Standard Deviation Score
SGA	Small for Gestational Age
SHOX	Short stature homeobox
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSH	Thyroid Stimulating Hormone

Abbreviation	Definition
TW2	Tanner-Whitehouse 2
WBC	White Blood Cells
WHO	World Health Organization

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 insulin-like growth factor-I (IGF-1) into the systemic circulation. IGF-1 is instrumental in the promotion of linear growth in children and in the control of metabolism and body composition in adults. These factors are regulated through complex feedback mechanisms involving hGH, insulin-like growth factor-1 binding protein 3 (IGF-BP3) and their complexes (Shalet, Toogood et al. 1998; Bach 2004).

A growth hormone deficiency (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 demographic features 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 35%; there was male predominance in all three categories (Thomas, Massa et al. 2004). The number of new cases has remained fairly constant over the last 2 decades. The Belgian data is comparable to other countries; the prevalence of GHD in the United States 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. Average adult height for untreated patients with severe isolated GHD is 143 cm in men and 130 cm in women. The inability to achieve normal height 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).

1.2 Current Therapy

Recombinant 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 height, 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. In Japan, daily GH treatment is approved at a dose of 0.025 mg/kg/day for

the treatment of GHD pediatric population. Treatment response is assessed by measurement of height and growth velocity and is usually continued until final height, epiphyseal closure, or both have been recorded.

The majority of currently available hGH products require daily SC 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 PK and 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 3 copies of the CTP of the beta chain of human chorionic gonadotropin (hCG); 1 copy at the N-terminus and 2 copies (in tandem) at the C-terminus.

The CTP provides hCG with the required longevity to maintain pregnancy (initial $t_{1/2}$ ~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.

OPKO Biologics' (OPKO) 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 week resulting in similar clinical efficacy as compared to daily injections of r-hGH.

1.3.1 Clinical Studies

MOD-4023 clinical development program includes, apart from the current study, 5 studies which have been completed and 1 which has been initiated. A Phase 1 study (CP-4-001) in healthy adult volunteers, and Phase 2 studies in GHD adults (CP-4-003) and pre-pubertal GHD children (CP-4-004), a Phase 1 study (CP-4-007) in adult Japanese and Caucasian subjects were completed. A Phase 3 pivotal study (CP-4-005) in adult subjects with GHD has

been completed as well and data analysis and an open-label extension (OLE) portion of the study is ongoing.

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 3 doses of MOD-4023 administered on a weekly regimen and 1 exploratory dose on an every other week regimen. MOD-4023 was administered for a period of 4 weeks in adult GHD subjects who were previously on a stable, standard r-hGH treatment for at least 6 months. Fifty-four (54) subjects (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 Phase 2 study (CP-4-004) in pediatric population, which was recently completed, was designed to assess the safety, efficacy and tolerability of 3 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 into 1 of 3 MOD-4023 dose groups or daily r-hGH (Genotropin®) as a comparator. All 4 dose groups demonstrated promising growth response following 6 and 12 months of treatment, as described in detail in the Investigator Brochure (IB). Majority of the patients (43 patients) enrolled in this study continued onto the third year open label extension phase of the trial and are all on MOD-4023 treatment.

A Phase 3 pivotal study (CP-4-005) in adult subjects with GHD has been completed and analysis is ongoing. The study is a randomized, parallel-group, multi-center study consisting of a 26-week double-blind, placebo-controlled (DBPC) period, a 26-week long-term open-label long term extension (OLE, all subjects receive MOD-4023), and a two-week washout period[a]. The starting dose of study drug differed by gender, age and estrogen therapy; Individual dose titration was conducted according to a dose modification plan. Enrolment to this study has been completed.

[a] To obtain blood sample for MOD-4023 antibody assessment and MOD-4023 serum levels

A Phase 3 pivotal study (CP-4-006) in pediatric subjects with GHD has just been initiated and is expected to take 18 – 24 months to complete. This is an open-label, randomized, multicenter, 12 months, efficacy and safety study of weekly MOD-4023 compared to daily Genotropin® therapy. This study is being conducted in up to 30 countries and 191 clinical sites worldwide with a target of 220 patients enrolled and treated.

For additional information on clinical studies please refer to the current version of the Investigator's Brochure (IB).

1.3.2 Study Rationale

In order to submit the product registration dossiers for pre-pubertal GHD in parallel to different global regulatory agencies, including Japan, the Sponsor planned to conduct two Phase III studies, CP-4-006 in global and CP-4-009 in Japan, and to provide integrated analysis to evaluate the consistency of the results between patients in CP-4-006 and Japanese patients in CP-4-009.

A global phase 3 open-label, randomized, multicenter, 12 months, efficacy, and safety study (CP-4-006) of weekly MOD-4023 compared to daily Genotropin® treatment naïve pre-pubertal GHD children has been started in early 2017. In this study, a MOD-4023 dose of 0.66 mg/kg/week will be compared to daily Genotropin® at a dose of 0.025 mg/kg/day. The objectives of the phase 3 study are to demonstrate that weekly dose 0.66 mg/kg MOD-4023 is clinically comparable in terms of safety and efficacy and statistically non-inferior to daily administration Genotropin®. This study design has been agreed with the FDA and EMA. In addition, patients completing the 12 months treatment of the pivotal study will be offered to rollover to an open-label extension (OLE) study with weekly administration of MOD-4023 which will be conducted until MOD-4023 marketing registration.

As for Japan, at the formal consultation meeting held on CCI 2016, PMDA stated CCI [redacted]. Accordingly, the Sponsor agreed to conduct a stand-alone Japan study (CP-4-009) and that the results of CP-4-006 and CP-4-009 will be part of the evaluation data for the complete clinical data package. Since the inclusion/exclusion criteria and the study design will be similar between CP-4-006 and CP-4-009, it is expected that similar efficacy and safety outcomes will be obtained from both studies.

After having the PMDA consultation meeting, the study design of CP-4-009 was confirmed as follows:

- Comparable study design and treatment duration with CP-4-006
    - PK/PD analysis during the first 6 weeks
    - Inclusion /Exclusion criteria should be comparable
- Genotropin® dosage is defined as 0.025 mg/kg/day, the approved dose in Japan
- Following the completion of the12-month treatment period, eligible and accepting patients will be consented to enroll into an open-label extension (OLE) period, and an amendment to study protocol with be submitted prior to the first patient completes the 12 months treatment period. Eligible Genotropin®-treated patients will be switched to

a MOD-4023 dose of 0.66 mg/kg/week in the OLE. The OLE is planned to continue until MOD-4023 marketing registration.

- 40 patients (20 per arm) + 10 % dropout rate

Since this target population is children with GHD, slow dose escalation and PK and PD sampling during the first 6 weeks on treatment are included.

1.3.3 Rationale for Dose Selection

As previously pointed out, MOD-4023 is a new molecular entity with GH mechanism of action, demonstrating reduced receptor affinity and lower specific activity, although with an extended half-life.

The in vitro activity and receptor binding affinity of MOD-4023 was established based on comprehensive characterization studies as part of the preclinical program. MOD-4023, which is comprised of 72.3% net hGH on a molar basis, demonstrated 10-20-fold reduction in affinity to GHR as compared to r-hGH (by Biacore analysis). This was further strengthened by 2 independent cell-based assays indicating that MOD-4023 had a significantly lower biological activity as compared to r-hGH. Based on the in vitro, in vivo and Phase 2 data, it was concluded that any dose comparisons between MOD-4023 and hGH on molecular basis are not reflective of the biological effect of the molecule. Therefore, the selection of MOD-4023 dose for the future clinical study in Japan, or elsewhere, should be determined by safety parameters and the clinical effect, i.e. HV.

This assumption was confirmed during the global multicenter 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/week, resulted in comparable IGF-1 and IGF-BP3 profiles to that of Genotropin® administered daily at a dose of 0.034 mg/kg/day. These 2 doses of MOD-4023 were shown to maintain optimal IGF-1 serum levels, with values that were in the mid-range of the gender- and age-adjusted normal range (~0 SDS). The MOD-4023 dose of 0.25 mg/kg/week failed to maintain normal IGF-1 serum levels mainly during the second part of the week, 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 analysis based on the established PK/PD model in pediatric subjects, showing that with increasing doses IGF-1 response is elevated. To examine the magnitude of differences between doses, the entire time course of IGF-1 was simulated for each subject in CP-4-004 (based on their dosing regimen and *post hoc* parameter estimates from the final population PK/PD model), then transformed into IGF-1 SDS units. Mean values for Cohort 3 and Cohort 2 (MOD-4023 dose of 0.66 and 0.48 mg/kg/week) are around 0 SDS IGF-1, and consistently much lower than 0 for Cohort 1 (0.25 mg/kg/week). In accordance with Consensus Guideline 2002 GRS, it is recommended that IGF-1 response should be kept within the mid-range of 0 SDS when treating children with GHD CCI [redacted]

As the population-based PK/PD model revealed no differences between healthy Caucasian and Japanese adults, it assumed that the data and the resulting model obtained from the Phase 2 pediatric clinical trial (CP-4-004) applies to Japanese children and similar PK/PD and response is expected to be obtained and will be presumable confirmed when comparing the MOD-4023 PK-PD of Japanese children to non-Japanese.

MOD-4023 at a dose of 0.66 mg/kg/week to daily Genotropin® at a dose of 0.025 mg/kg/day will likely to provide comparable auxology outcome at 12 months.

2 STUDY OBJECTIVES

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 to daily Genotropin® administration in terms of safety and efficacy in the Japanese population.

Primary Objective:

To evaluate the efficacy and safety of weekly MOD-4023 administration and daily Genotropin® administration in pre-pubertal GHD Japanese children.

Secondary Objective:

To evaluate the PK and PD profiles of 3 different doses of MOD-4023 in pre-pubertal GHD Japanese children.

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 r-hGH, Genotropin®.

Both drugs will be injected SC using a pen device.

To introduce naïve Japanese pediatric GHD patients to the allocated MOD-4023 dose in a gradual manner, a stepwise dose escalation and PK/PD blood sampling will be implemented during first 6-weeks.

After a Screening period lasting for 4 weeks (+ additional 1 week if needed)[a] and approval of the study medical monitor, patients meeting all the inclusion criteria and none of the exclusion criteria, will be eligible to participate in the study. At Baseline, eligible patients will be randomized in a 1:1 ratio[b] to receive:

- MOD-4023 (investigational treatment): weekly MOD-4023 SC injections for 12 months; initially over the first 6 weeks, MOD-4023 will be administered in 3 escalating doses (0.25 mg/kg/week, 0.48 mg/kg/week and 0.66 mg/kg/week), each for 2 weeks. Then for the remaining 46 weeks, patients will continue to receive MOD-4023 at a dose of 0.66 mg/kg/week.
- Genotropin® (reference treatment): daily SC Genotropin® (0.025 mg/kg/day which is equivalent to 0.175 mg/kg/week, divided equally into 7 daily injections over a week) for 12 months.

Patients allocated to the MOD-4023 treatment arm, will initially undergo a stepwise dose escalation over 6 weeks starting with low MOD-4023 dose of 0.25 mg/kg/week for 2 weeks, followed by an intermediate dose of 0.48 mg/kg/week for 2 weeks and then a final dose of 0.66 mg/kg/week for 2 weeks. These patients will be assigned into one of 4 sampling sub-blocks (as shown in Table 2) CCI CCI In each sub-block, for each dose level, there will be different sampling time collection relative to the second injection of each dose (from pre-dose (-12), 12 (±3), 18 (±3), 36 (±6), 48 (±12), 72 (±12), 96 (±12) and 120 (±12) hours post dose). Six (6) blood samples for PK/PD will be obtained from each patient; 2 samples for 0.25 mg/kg/week dose, 2 for 0.48 mg/kg/week dose and 2 for 0.66 mg/kg/week dose. At the end of the 6-week dose escalation phase, patients will continue the study for another 46 weeks at dose of 0.66 mg/kg/week. Over this 6 weeks escalation period, patients will be instructed to inject at evening/bed time hours. Following the 6 weeks escalation period, during the treatment period, patients can choose to stay with evening injection or to

[a] 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 lab results) extra time - equal to the time of patient's unavailability - will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).

[b] Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

switch to morning injection. The time of injection should be consistent until the end of the study.

Following the period above, the dose of MOD-4023 and Genotropin® 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 (section 6.3); dose adjustment will be based on the severity of AEs or repeated and elevated levels of IGF-1 SDS.

The key safety data will be reviewed by an independent DSMB at a minimum once every 6 months.

The total duration of patients' participation in the study will be up to 14 months (up to 5 weeks of Screening, 12 months of active treatment and 1 month of follow up). The study will be conducted at approximately in 45-55 sites in Japan.

Following the completion of the 12-month treatment period, eligible and accepting patients will be consented to enroll into an open-label extension (OLE) period, and an amendment to this study protocol will be submitted prior to the first patient completes the 12 months treatment period. Eligible Genotropin®-treated patients will be switched to a MOD-4023 dose of 0.66 mg/kg/week in the OLE. The OLE is planned to continue until MOD-4023 marketing registration in Japan.

4 STUDY POPULATION

Pre-pubertal children (boys 3-10 (10 years and 364 days) years, girls 3-9 (9 years and 364 days) years), diagnosed with GHD.

4.1 Inclusion Criteria

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

1. Pre-pubertal child aged ≥ 3 years old, and not yet 10 years for girls (9 years and 364 days) or not yet 11 years for boys (10 years and 364 days), on the date of ICF signature, with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency.
2. Confirmed diagnosis of GHD by 2 different types of GH provocation tests (standardized on growth foundation data): defined as a peak serum GH level of ≤ 6.0 ng/mL or ≤ 16 ng/mL when conducting GHRP-2 provocation test.

   Prior local laboratory results will be accepted subject to pre-approval by the study medical monitor and if the tests were conducted according to 1 of the protocols in Appendix D.
3. BA is not older than chronological age and should be less than 10 for girls and less than 11 for boys.
4. Without prior exposure to any r-hGH therapy.
5. Height SD score ≤ -2.0 at screening.
6. Impaired height velocity defined as:
   - Annualized HV below the 25th percentile for CA (HV < -0.7 SDS) and gender according to the local primary care provider standard.
   - The interval between 2 height measurements should be at least 6 months, but should not exceed 18 months prior to inclusion.
7. BMI must be within ±2 SDS of mean BMI for the chronological age and sex.
8. Baseline IGF-1 level of at least 1 SD below the mean IGF-1 level standardized for age and sex (IGF-1 SDS ≤ -1)[a] according to the central laboratory reference values. A single re-test will be allowed (subject to approval from the study medical monitor) if all other criteria are met.
9. Normal creatinine levels according to common practice reference ranges per age.
10. 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.
11. Clinical presentation of normal 46 XX karyotype for girls.
12. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from pediatric patients (when applicable based on age and Japan regulation).

[a] According to rounding policy IGF-1 results ≤-0.95 might be acceptable as well

4.2 Exclusion Criteria

Patients must **NOT** meet any exclusion criteria to be eligible for the study:

1. Children with prior history of leukemia, lymphoma, sarcoma or any other 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 by the discretion of the investigator.
5. Children born small for gestational age (SGA – birth weight and/or birth length < -2 SDS for gestational age).
6. Presence of anti-hGH antibodies at screening.
7. Any clinically significant 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. Children with diabetes mellitus.
9. Known or suspected chromosomal abnormalities including Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Russell-Silver syndrome, SHOX mutations/deletions and skeletal dysplasia's, with the exception of septo-optic dysplasia.
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)).
11. Children requiring glucocorticoid therapy (e.g. for asthma) that are taking chronically a dose greater than 400 µg/d of inhaled budesonide or equivalent as described in Appendix J.
12. Major medical conditions and/or presence of contraindication to r-hGH treatment.
13. Known or suspected HIV-positive patient, or patient with advanced diseases such as AIDS or tuberculosis.
14. Drug, substance, or alcohol abuse.
15. Known hypersensitivity to the components of study medication.
16. Other causes of short stature such as celiac disease, uncontrolled primary hypothyroidism and rickets.
17. The patient and/or the parent/legal guardian are likely to be non-compliant in respect to study conduct.
18. Participation in any other trial of an investigational agent within 30 days prior to screening and throughout the entire study period (including administration of investigational agent).

4.3 Patient Identification

A unique identification number will be assigned by the Electronic Data Capture (EDC) system when an individual patient (if feasible) and parent/legal guardian signs the informed

consent form and starts the screening process. Following eligibility confirmation, the patient will be randomized[a] through the IRT system in a 1:1 ratio to receive either MOD-4023 or Genotropin®.

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 prior to completing 12 months of treatment will not be replaced.

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

- Withdrawal of the patient's/parent's consent (with specific withdrawal reason collected, as possible)
- Occurrence of a malignancy during the course of study (reported as an AE)
- Development of serious inter-current critical illness (reported as an AE)
- Lack of patient compliance (if discontinuation is desired or considered necessary by the investigator or the study medical monitor)
- Severe adverse drug reaction (if discontinuation of study medication is desired by the patient or considered necessary by the investigator or the study medical monitor) (reported as an AE)
- Serious protocol deviation that affects patient safety, and accuracy, and/or validity of data
- Lost to follow-up
- Study enrollment closed prior to full qualification to study or study closure for any other reason by the Sponsor.

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 EOT Visit (Visit 9) and EOS Visit (Visit 10) procedures. Patients should be invited to the site for the EOT Visit (visit 9) within 3-7 days and should be phone interviewed (EOS Visit, Visit 10) one month after the last drug administration. 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 (i.e. patient will cease to receive medication but will continue to come for the follow-up visits) and study withdrawal should

[a]Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

be explained. Patients should be encouraged to continue the follow-up visits and at minimum provide a height measurement at 12 months 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

Schedule of Assessments for this study are shown in Appendix A, Appendix B and Appendix C. No protocol related procedures, including the stopping of prohibited concomitant medications should be performed before the patient (if feasible) and parent/legal guardian provides written informed consent. 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 eCRF.

5.1 Screening Period (Visit 1) – Week -4 /Day -28 to Week -1 /Day -1

The Screening period will last up to 4 weeks[a] and can be conducted over several visits prior to 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 (if needed, use appropriate 1 of 2 versions according to their education and age) 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 the screening visits:

- Inclusion/Exclusion criteria
- Estimated Parental heights [b]
- Patient's Height SDS and HV SDS
- Auxology measurements[c], BMI and BMI SDS
- Demographic and Medical history, including a description of pituitary deficiencies, concomitant and previous medications
- Overall health status assessments – complete physical examination, vital signs.
- Pubertal status (according to Tanner stages)
- Bone age determination with the method of TW2 using a central bone age reader.[d]

[a] 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 lab results) extra time - equal to the time of patient's unavailability - will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks screening period).

[b] It is recommended that parent's height will be measured at the site. If measured parental height is not available an estimate could be provided by the parent.

[c] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

[d] At Screening Visit, historical bone age assessment might be accepted if they were done no more than 6 months prior to the ICF signature date. If the patient will be eligible, the bone age should be repeated at Visit 2, before the dosing. The Visit 2 scan will be the baseline scan for these patients.

- Assessment of biochemical markers and stimulation tests:
  - Two (2) different types GH stimulation (provocation) tests from the following list: insulin tolerance test (with serum cortisol response to hypoglycemia if insulin stimulation test is chosen); arginine test; clonidine test; glucagon test; L-dopa; and GHRP-2. The minimal duration and number of samples for each test must conform to the specifications in Appendix D.
  - Analysis of GH serum levels (and glucose and serum cortisol if Insulin tolerance test is performed) may be done by local laboratories and to be provided for the study medical monitor review and approval **prior to study entry**[a].
  - Assessment of morning cortisol (up to 8am ±1 hour)[b]

    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[c] or has been diagnosed with adrenal insufficiency). The minimal duration and number of samples for each test must conform to the specifications in Appendix D.
  - Assessment of CCI IGF-1 SDS
- Assessment of anti-hGH antibody levels
- Assessments of Routine safety laboratory tests: biochemistry, hematology and urinalysis (see section 5.5.9)
- Assessment of thyroid: TSH, FT4
- Assessment of glucose metabolism: morning fasting insulin and glucose (will be tested as part of biochemistry panel) and HbA1c
- Parameters of lipid metabolism: morning fasting total cholesterol, triglycerides, HDL and LDL
- Head MRI[d] if possible with contrast – to be done only after the two GH stimulation tests based on physician recommendation

Approximately 8-42 mL of blood will be drawn from the patients during the screening period. The total blood volume to be collected during screening period (maximum 5 weeks) is shown. The maximum blood volume per day differs according to the selection of assessments. Based on the pediatric clinical guidance, appropriate blood sampling has to be performed so that the required minimum blood volume is obtained, such as GH stimulation tests and other assessments are taken on different days. All laboratory assessments are done in a central laboratory unless stated otherwise.

[a] No time limitation for the historical GH stimulation tests.
[b] Morning cortisol assessment will be subject to the investigator judgment.
[c] Insulin tolerance test 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.
[d] MRI to be performed upon investigator judgment. In addition, MRI which was conducted within 6 month prior to ICF signature date will be acceptable

Key data and all test results obtained during screening will be reviewed by the Study medical monitor and eligibility will be confirmed by the study medical monitor prior to randomization of each patient.

5.2 Active Treatment Period (Baseline to Month 12)

During Treatment period, patients will be scheduled to attend the following clinic visits according to their treatment allocation as shown in the Table 1. The Baseline visit (first dose) and Visits 6 to 9 (every 3 months) will be similar for both treatment arms (except where noted). Visits 3, 4 and 5 will differ between the 2 treatment arms due to the 6-week dose escalation and PK/PD sampling in the MOD-4023 treatment arm.

Table 1: Overview of Visit Scheduling for both Treatment Arms

MOD-4023 Treatment Arm (Investigational)	Genotropin® Treatment Arm (Reference)
Visit 2 – Baseline – First dosing	Visit 2 – Baseline – First dosing
Visits 3 and 3.1 – Week 2 First PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation)	Visit 3 – Week 2 Phone interview will be done. Per Appendix I. No clinic visit.
Visits 4 and 4.1 – Month 1/ Week 4 Safety (only at Visit 4.1) and second PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation)	Visit 4 – Month 1/ Week 4 (±1 week). Clinic visit
Visits 5 and 5.1 – Week 6 Third PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation)	Visit 5 – Week 6. Phone interview will be done per Appendix I. No clinic visit.
Visit 6 – Month 3/Week 13 (±1 week) Clinic visit To be conducted 4 days (-1 day) post dose	Visit 6 – Month 3/Week 13 (±1 week) Clinic visit
Visit 7 and 7.1 – Month 6/Week 26 (±3 weeks) Two clinic visits: - Visit 7 Pre-dose immunogenicity Assessments conducted same day as dosing - Visit 7.1 Post-dose assessments conducted 4 days (-1 day) after dose	Visit 7 – Month 6/Week 26 (±1 week) Clinic visit
Visit 8 – Month 9/Week 39 (±1 week) Clinic visit To be conducted 4 days (-1 day) post dose	Visit 8 – Month 9/Week 39 (±1 week) Clinic visit
Visit 9 and 9.1 – EOT visit – Month 12/Week 52 (±3 weeks) Two clinic visits: - Visit 9 Pre-Dose Immunogenicity Assessments conducted same day as dosing - Visit 9.1 Post-dose assessments conducted 4 days (-1 day) after dose	Visit 9 – EOT visit- Month 12/Week 52 (±1 week) Clinic visit
Visit 10 – EOS visit – Month 13/Week 56 (+1 week) Phone interview will be done per Appendix I. No clinic visit.	Visit 10 – EOS visit – Month 13/Week 56 (+1 week) Phone interview will be done per Appendix I. No clinic visit.

Visit windows are relative to the visit, not to the dose, unless specified otherwise.

5.2.1 Visit 2 (Day 1/Baseline) – Both Treatment Arms

At Baseline (Visit 2) or once eligible, eligible patients will be randomized in a 1:1 ratio to MOD-4023 (investigational treatment) or Genotropin® (reference therapy)[a].

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

- Auxology measurements[b]
- AE, local tolerability and concomitant medications
- Overall health status assessment, including complete physical examination and vital signs assessments
- Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9)
- Pubertal status (according to Tanner stages)
- Assessment of thyroid: TSH, FT4
- Assessment of biochemical markers: CCI IGF-1 SDS (applicable for both arms), CCI
- Assessment of MOD-4023 serum levels (applicable for MOD-4023 treatment arm only)
- Parameters of glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c
- Parameters of lipid metabolism: morning fasting total cholesterol, triglycerides, HDL and LDL
- Assessment of pre-dose anti-MOD 4023 and anti-hGH antibodies (depending on treatment arm allocation)
- Bone age[c]
- ECG pre-dosing
- Training for patients, parents or legal guardians on drug administration
- Administration of study drug at clinic
- Dispense study drug and patient diary

Approximately 9-12 mL of blood will be drawn from patients at baseline visit.

[a] Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

[b] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

[c] Bone age at Visit 2 will be performed in case bone age was not performed at screening. This test should be done prior the first dose.

5.2.2 Treatment Period - MOD-4023 Treatment Arm – Visits 3 to 9

5.2.2.1 Visits 3 and 3.1, 4 and 4.1, 5 and 5.1 (Weeks 2, 4 and 6)

Visits 3, 4 and 5 will take place at Weeks 2, 4, and 6, respectively, for first PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation). Visits 3.1, 4.1 and 5.1 will take place at Weeks 2, 4, and 6, respectively, for second PK/PD sampling post 2nd dose for each dose level (according to sub-block PK/PD allocation – refer to Table 2). For each visit/sub-visit, the patient is expected to visit the clinic twice during the week to obtain two different post-dose PK/PD samples.

The following assessments will be conducted at these visits:

- Safety evaluation consisting of AE, local tolerability and concomitant medication at all visits
- Complete physical examination and vital signs assessments at visits 3.1, 4.1 and 5.1 only
- Safety evaluation consisting of safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9) at Visit 4.1 only
- Assessment of biochemical markers: CCI , IGF-1 SDS, CCI
- MOD-4023 serum levels (sampling time per sub-block allocation)
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension)
- Weight measurement at Visit 4.1 only.
- Study drug return and accountability (Visit 4.1 only)
- Training on drug administration, injection site reactions, diary completion, and dosing review (Visits 3.1 and 4.1)
- Assessment of Anti-MOD-4023 at Visit 4.1 only
- Dispense study drug and patient diary at Visit 4.1 only

Approximately 6 mL of blood will be drawn from the patients at each visit, except for Visit 4.1.

At Visit 4.1, approximately 12 mL of blood will be drawn from the patients.

5.2.2.2 Visit 6 (Month 3/Week 13 ±1 week) and Visit 8 (Month 9/Week 39 ±1 week)

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

- Auxology measurements[a]
- AE, local tolerability and concomitant medications

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

- Overall health status assessment, including complete physical examination and vital signs assessments
- Safety laboratory- biochemistry, hematology and urinalysis (see section 5.5.9)
- Pubertal status (according to Tanner stages)
- Assessment of thyroid: TSH, FT4
- Assessment of biochemical markers: CCI, IGF-1 SDS
- Assessment of MOD-4023 serum levels
- Assessment of anti-MOD-4023 antibodies.
- Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension)
- Study drug return and accountability
- Individual dose adjustment and dispensing study drug and patient diary

Approximately 9 mL of blood will be drawn from the patients at those visits.

5.2.2.3 Visit 7 and Visit 7.1 (Month 6/Week 26 ±3 weeks)

Visit 7 will consist of two clinic visits, Visit 7 (pre-dose) and Visit 7.1 (post-dose), at Week 26 ±3weeks. Visit 7 must be conducted prior to Visit 7.1.

Visit 7 will take place at the clinic prior to dosing at any week during ±3 weeks of Month 6/Week 26. The following pre-dose immunogenicity assessments should be conducted on the same day of dosing:

- AE and concomitant medications
- Assessment of MOD-4023 serum levels
- Assessment of anti-MOD-4023

Approximately 6 mL of blood will be drawn from the patients at this visit.

Visit 7.1 will take place at the clinic 4 days (-1 day) after dose at any week after Visit 7 during the ±3 weeks of Month 6/Week 26. The following post-dose assessments will be conducted 4 days (-1 day) after dose:

- Auxology measurements[a]
- AE, local tolerability, and concomitant medications
- Overall health status assessment, including complete physical examination and vital sign assessments
- Safety laboratory: biochemistry, hematology and urinalysis, (see section 5.5.9)

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

- Pubertal status (according to Tanner stages)
- Assessment of thyroid: TSH, FT4
- Assessment of biochemical markers: CCI IGF-1 SDS
- Assessment of MOD-4023 serum levels
- Parameters of glucose metabolism- morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c
- Parameters of lipid metabolism- morning fasting total cholesterol, triglycerides, HDL and LDL
- ECG
- Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension)
- Study drug return and accountability
- Individual dose adjustment and dispensing study drug and patient diary

Approximately 10 mL of blood will be drawn from the patients at this visit.

5.2.2.4 Visit 9 and Visit 9.1 (Month 12/Week 52 ±3 weeks) – End of Treatment (EOT) Visit Assessments

Visit 9/EOT will consist of two clinic visits, Visit 9 (pre-dose) and Visit 9.1 (post-dose), at Week 52 ±3 weeks. Visit 9 must be conducted prior to Visit 9.1.

Visit 9 will take place at the clinic prior to dosing at any week during ±3 weeks of Month 12/Week 52. The following pre-dose immunogenicity assessments should be conducted on the same day of dosing:

- AE and concomitant medications
- Assessment of MOD-4023 serum levels
- Assessment of anti-MOD-4023

Approximately 6 mL of blood will be drawn from the patients at this visit.

Visit 9.1 will take place at the clinic 4 days (-1 day) after dose at any week after Visit 9 during the ±3 weeks of Month 12/Week 52. The following post-dose assessments will be conducted 4 days (-1 day) after dose:

- Auxology measurements[a]
- AE, local tolerability and concomitant medications
- Overall health status assessment, including complete physical examination and vital signs assessments
- Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9)

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

- Pubertal status (according to Tanner stages)
- Assessment of thyroid: TSH, FT4
- Assessment of MOD-4023 serum levels
- Hormones and biochemical markers: CCI IGF-1 SDS
- Parameters of glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c
- Parameters of lipid metabolism: morning fasting total cholesterol, triglycerides, HDL and LDL
- Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension),
- Bone age assessment
- Study drug return and accountability

Approximately 10 mL of blood will be drawn from the patients at this visit.

5.2.3 Treatment Period - Genotropin® Treatment Arm – Visits 3 to 9

At Visit 3 (Week 2) and Visit 5 (Week 6) a phone interview will be conducted according to Appendix I. **No clinic visit**.

5.2.3.1 Visit 4 (Month 1/Week 4 ±1week)

The following assessments will be conducted at Visit 4:

- AE, local tolerability, and concomitant medications
- Overall health status assessment, including complete physical examination and vital sign assessments
- Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9)
- Biochemical markers: CCI IGF-1 SDS
- Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension)
- Study drug return and accountability
- Dispense study drug and patient diary

Approximately 7 mL of blood will be drawn from the patients at this visit (No blood samples will be collected at Visits 3 and 5. No clinic visit).

5.2.3.2 Visit 6 (Month 3/Week 13 ±1week), Visit 7 (Month 6/ Week 26 ±1week), and Visit 8 (Month 9/Week 39 ±1week)

The following assessments will be conducted at Visits 6, 7 and 8:

- Auxology measurements[a]
- AE, local tolerability and concomitant medications
- Overall health status assessment, including complete physical examination and vital signs assessments
- Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9)
- Pubertal status (according to Tanner stages)
- Assessment of thyroid: TSH, FT4
- Hormones and biochemical markers: CCI IGF-1 SDS
- Parameters of glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c at visit 7 only
- Parameters of lipid metabolism:- morning fasting total cholesterol, triglycerides, HDL and LDL at visit 7 only
- Fundoscopy (ONLY if there are signs or symptoms indicative of benign intracranial hypertension)
- Study drug return and accountability
- ECG at Visit 7 (Month 6/Week 26 ± 1day)
- Individual dose adjustment every three months
- Dispense study drug and patient diary
- Anti-hGH antibodies

Approximately 9 mL of blood will be drawn from the patients at those visits.

5.2.3.3 Visit 9 (Month 12/Week 52 ±1week) - End of Treatment Visit

The following assessments will be conducted at Visit 9, EOT visit:

- Auxology measurements[b]
- AE, local tolerability and concomitant medications
- Overall health status assessment, including complete physical examination and vital signs assessments
- Safety laboratory: biochemistry, hematology and urinalysis (see section 5.5.9)
- Pubertal status (according to Tanner stages)
- Assessment of thyroid: TSH, FT4

[a] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall or equivalent mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

[b] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall or equivalent mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.

- Hormones and biochemical markers: CCI IGF-1 SDS
- Parameters of glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), morning fasting insulin and HbA1c
- Parameters of lipid metabolism: morning fasting total cholesterol, triglycerides, HDL and LDL
- Fundoscopy (ONLY if there are signs or symptoms indicative of increased intracranial hypertension)
- Bone age assessment
- Study drug return and accountability
- Anti-hGH antibodies

Approximately 9 mL of blood will be drawn from the patients at this visit.

5.2.4 Follow up Period (Month 13) - Visit 10 - EOS Visit (Week 56 +1 week): Both Treatment Arms

After 1 month following EOT Visit, phone interview should be conducted according to Appendix I. This phone interview will be considered as Visit 10- End of Study Visit.

5.3 Efficacy Assessments and Endpoints

5.3.1 Height and Annual HV

Height measurements must be performed according to Appendix E with a calibrated 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 independent readings will be recorded for each visit in the eCRF.

Height will be measured in centimeters.

The Height SDS will be derived from the age and gender according to the local primary care provider standard.

Annualized HV will be calculated in centimeters as the change in height from Visits 2 to 9 (after 12 months of treatment), using the actual elapsed days.

5.3.2 Bone Age

Bone age will be determined by X-ray according to TW2 using central bone age reader at Screening (Visit 1), and/or Visit 2[a] (Baseline) and Visit 9 (Month 12). X-ray films of the left hand and wrist will be taken as outlined in Appendix F and will be sent to a qualified central reader. The central reader will be blinded to the chronological age, drug allocation and name of the patients. X-ray films will hold only an identification number and gender. Details of the

[a] Bone age assessment should be performed at Visit 2 only if not performed at screening

central bone age reader and the procedure for blinding and shipping of X-rays will be provided to the investigator.

5.4 Assessments and Endpoints

CCI

[redacted]

5.4.1.3 Biochemical markers: CCI

CCI

[redacted]

For patients allocated to MOD-4023 treatment arm, CCI will be evaluated during the first 6 weeks of dose escalation phase as described in section 5.4.1.2.

5.5 Safety Assessments and Endpoints

Safety assessments will be based on changes from baseline of clinical AEs (including injection site reaction) reported by the patient or observed by the investigator, concomitant medication use, treatment compliance, vital signs, ECG, physical examination and laboratory assessments (hematology, biochemistry, glucose metabolism, lipid metabolism, endocrinology, IGF-1 levels, immunogenicity and urinalysis).

5.5.1 AEs

AEs, including injection site reactions, will be assessed at all study visits throughout the study (except at pre-dose Visits 7 and 9 for injection site reaction). In addition, patients will be requested to complete a patient diary at home to collect data on AE, concomitant medications and local site reactions.

Any AEs that occur throughout the study will be recorded. Any new AE that occur 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.

5.5.2 Local 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) 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 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 observed at the time of visit or reported during phone call and moderate to severe in intensity.
- Injection site reaction between the last and present visit, and/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 ≥ 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 the Pain Assessment Scale (Appendix G). In addition, each patient and parent/guardian will be queried during study visits regarding possible injection site pain.

- Pain score ≥4 should be reported as an AE

Photographs of Injection Site Reactions

If possible with any case of an abnormal local site reaction assessed and recorded as an AE, the investigator will document the local site reaction by photo that will be kept signed and dated in the patient medical record.

5.5.3 Concomitant Medication Use

Use of concomitant medication will be recorded at all study visits.

5.5.4 Treatment Compliance

Study drug return accountability will be performed at Visits 4 (for the Genotropin® arm), Visit 4.1 (for MOD-4023 arm) and Visits 6, 7, 8 and 9 (for both arms).

5.5.5 Vital Signs

Vital signs measurements will include body temperature, respiration, blood pressure and heart rate after the patient has sat quietly for at least 5 minutes and using the same arm throughout the study where possible.

5.5.6 Physical Examination

A complete physical examination will be performed and will include appearance, eyes, ears, nose, head, throat, neck, chest, lungs, heart, abdomen, extremities, skin and musculoskeletal system. Clinically significant findings at screening will be reported as medical history and as AEs after the Screening Visit. Weight will be measured, ideally fasted in the morning, without shoes and having removed all outwear such as jackets, sweaters or sweatshirts and heavy pocket items.

5.5.7 ECG

ECG (preferably 12-lead) will be performed on Visit 2 (pre-dose) and Visit 7 for both Genotropin® and MOD-4023 arms (no time limitation).

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 clinically significant findings are detected by the investigator, a local 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 clinical significance to the patient rests with the investigator and reported as normal /abnormal in the eCRF.

5.5.8 Fundoscopy

Fundoscopic 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 myalgia's). Fundoscopy will be performed according to standard of care and confirmed by an ophthalmology evaluation if necessary.

5.5.9 Laboratory Assessments

All routine clinical laboratory assessments will be performed by local central laboratory (LSI Medience Corporation) according to the schedule in Appendix A, Appendix B and Appendix C. The laboratory evaluations will include:

1. GH stimulation (provocation) tests: insulin tolerance test (with serum cortisol response to hypoglycemia if insulin stimulation test is chosen)/arginine test/clonidine test/glucagon test /L-dopa/ GHRP-2. Will be performed at Screening Visit.
2. Morning cortisol at Screening Visit, if applicable.
3. ACTH or CRH stimulation test at Screening Visit (If morning cortisol is below 190 nmol/L (7 µg/dL).
4. 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, at all study visits except for Visits 3, 3.1, 4 (MOD-4023 arm), 5, 5.1, 7 (MOD-4023 arm) and Visit 9 (MOD-4023 arm).
5. Serum biochemistry: glucose, total protein, albumin, total bilirubin, ALT (SGPT), AST (SGOT), GGT, LDH, CPK, alkaline phosphatase, sodium, potassium, calcium, phosphate, BUN, creatinine, at all study visits except for Visits 3, 3.1, 4 (MOD-4023 arm), 5, 5.1, 7 (MOD-4023 arm) and Visit 9 (MOD-4023 arm).
6. Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein at all study visits except for Visits 3, 3.1, 4 (MOD-4023 arm) 5, 5.1, 7 (MOD-4023 arm) and Visit 9 (MOD-4023 arm).
7. Lipid metabolism: morning fasting total cholesterol, LDL, HDL and triglycerides at Screening, Baseline, Visit 7 and Visit 9 (Genotropin® arm) and Visit 7.1 and Visit 9.1 (MOD-4023 arm).
8. Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), fasting insulin and HbA1C at Screening, Baseline, Visit 7 and Visit 9 (Genotropin® arm) and Visit 7.1 and Visit 9.1 (MOD-4023 arm).
9. Assessment of thyroid: TSH, FT4 at all study Visits except for Visits 3, 3.1, 4, 4.1, 5, 5.1, Visit 7 (MOD-4023 arm) and Visit 9 (MOD-4023 arm).
10. Immunogenicity (will be performed by Intertek, San Diego): antibodies to MOD-4023 at Visits 2 (Baseline, pre-dose), 4.1, 6, 7 (pre-dose), 8 and Visit 9 (pre-dose) (MOD-4023 arm only).

Antibodies to hGH at Visit 2 (Baseline, pre-dose) and Visits 6, 7, 8 and Visit 9 (Genotropin® arm only).

11. Immunogenicity: antibodies to hGH (will be performed by University Hospital Leipzig, Leipzig, Germany) at Screening Visit (both arms).

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

If a patient discontinues prematurely from the study for the reasons specified in section 4.4, the same procedures planned for EOT Visit (Visit 9- 12 months / Week 52) and EOS Visit (Visit 10 - 13 months / Week 56) will be conducted (Patients should be invited to EOT Visit (visit 9) within 3-7 days and should be phone interviewed (EOS Visit, Visit 10) one month after the last drug administration). Other procedures and evaluations will be completed as deemed necessary by the investigator.

6 INVESTIGATIONAL PRODUCT

6.1 Investigational Product

6.1.1 Identity of Investigational Product

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 device used in this study has not been approved or certified in Japan.

The formulation includes CCI

6.1.2 Reference Therapy

Genotropin® is a daily GH, which will be used as the reference therapy in this study.

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

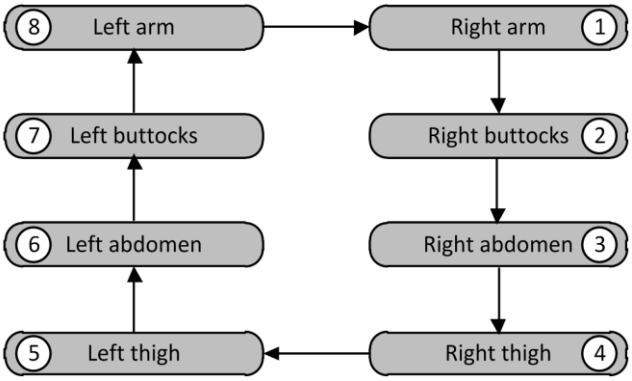
The pen device is intended to assist self-injecting adult and pediatric patients, healthcare professionals and caregivers with the daily SC injection of the r-hGH, primarily self-administered at home or in a healthcare environment.

Dose regimen for Genotropin®: 0.025 mg/kg/day (or 0.175 mg/kg/w divided equally to 7 injections over a week).

6.2 Study Drug Administration

MOD-4023 will be administered as a SC injection once weekly. Over the 6 weeks of the escalation period, patients will be instructed to inject at evening hours/bed time. At the treatment period, patients can choose to stay with evening injection or to switch to morning injection. The time of injection should be consistent until the end of the study. MOD-4023 will be administered using the pen into the upper arms, buttocks, thighs or abdomen (8 locations for injection). It is recommended that all 8 injection sites are used successively, using a different injection site at each subsequent injection. It is recommended that the same injection site should be used only after all other injection sites have been rotated (see recommended rotation scheme below).

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 ≤72 h 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 week. If the dose is more than 72 hours late, the patient will not take a dose for the whole week and will continue taking the study medication on the regular day the following week.

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.

The patient should notify site staff about the delayed injection or the missed dose and be instructed by the site when the next visit is scheduled.

In case the delayed injection is in the week when an onsite visit is planned, the site should confirm that the visit date follows the proper post injection interval (for example: 3-4 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 week should be rescheduled, to meet the required post dosing interval.

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. Split dose from the same pen: This may occur when the prescribed dose exceeds the maximum dose which can be selected according to the pen amount. The maximum dose per injection for the MOD-4023 24 mg pen is 12 mg and the maximum dose injection for the MOD-4023 60 mg pen is 30 mg. The patient's first injection would be the maximum dose and the second injection would be the remaining dose of the full prescribed dose.

   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 from 2 pens (the current pen and a new pen): This may occur when the amount of medication remaining in the pen is not sufficient for the full prescribed dose.

For example, if the full prescribed dose is 25.0 mg and the volume left in the current pen is 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 completes the patient diary for each of the 2 injections administered. When the second injection is from a new pen, the new pen must be primed accordingly to the Instructions for Use provided.

Further details are provided in the Patient Diary.

Missed, delayed, or split doses should be reported in the Patient Diary and the appropriate eCRF.

6.3 Dose Modification Plan

During study conduct, the dose of MOD-4023 and Genotropin® will be assessed every 3 months based on patient's body weight. Doses will be determined by the EDC 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).

6.3.1 Dose Decrease

For patients on MOD-4023, the dose will be decreased based on 2, repeated day 4(-1) levels of IGF-1 > +2.0 SDS. For patients on Genotropin®, the dose may be decreased based on repeated IGF-1 levels > +2 SDS.

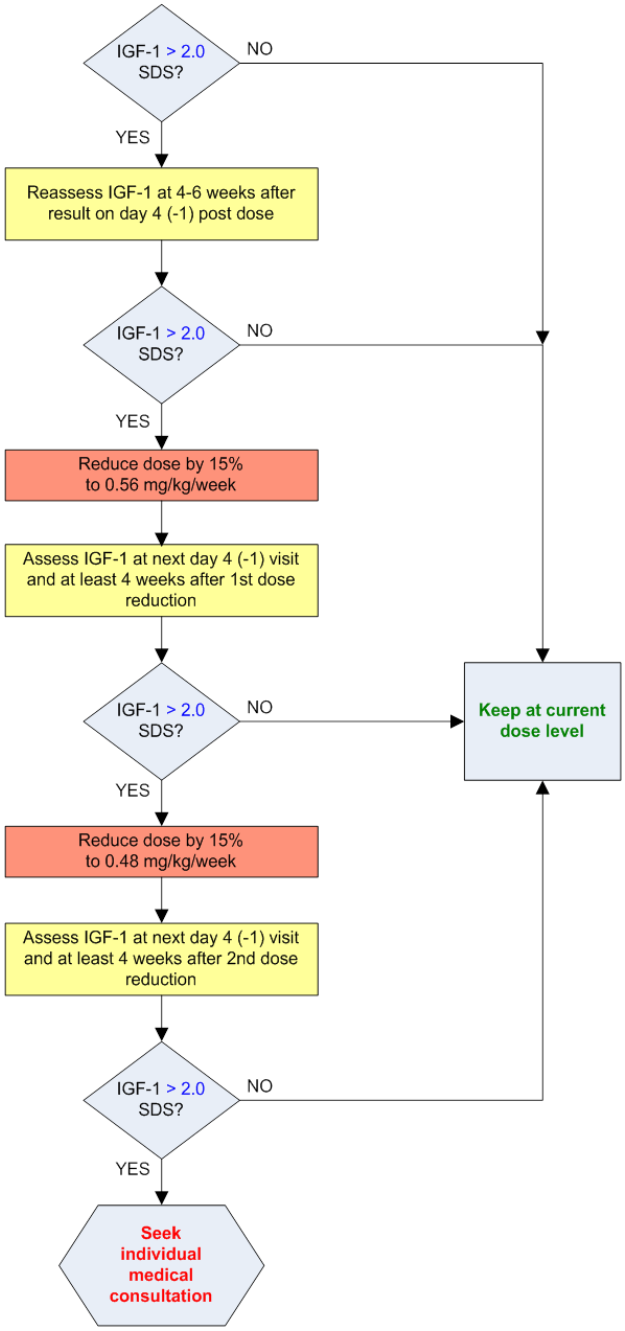
If a patient has an IGF-1 level above +2.0 SDS, they will be requested to return for an unscheduled visit within 4-6 weeks after the >+2.0 SDS result, on day 4(-1) post dose, for MOD-4023 treated patients, or any day for Genotropin®. If their IGF-1 level is still above +2.0 SDS, the most recent dose will be reduced by 15% (i.e. to 0.56 mg/kg for MOD-4023; 21µg/kg/day for Genotropin®). The patient will be treated with the new dose for at least 4 weeks before a subsequent IGF-1 determination can result in a further dose modification. If the next scheduled visit is less than 4 weeks 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 week minimum time period), IGF-1 will be resampled. If the IGF-1 is still above +2.0 SDS, the dose will be reduced an additional 15% to 0.48 mg/kg for MOD-4023 and to 18 µg/kg/day for Genotropin® arm. If the IGF-1 is still above +2.0 SDS following 2 dose reductions (at least 4 weeks after second dose reduction), the medical monitor (with the assistance of the DSMB if necessary) will decide on course of treatment on an individual basis. This information is summarized in Figure 2 below.

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

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

The key safety data will be reviewed by an independent and external DSMB at least once every 6 months. The DSMB will also include review of number or percentage of patients requiring dose reductions due to IGF-1 above +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® arms). DSMB review will also include review of number or percentage of patients requiring dose reductions due to AEs.

Figure 2: Dose Adjustment Scheme (example is for MOD-4023)



Scheme and percent reduction is applicable for the MOD-4023 and Genotropin® arm as well and in case AEs are defined as “severe” and drug related.

6.4 Method of Assigning Patients to Treatment Groups

Eligible patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups, MOD-4023 or GH Genotropin® (reference therapy) for 12 months.

Randomization will be performed through the IRT system. The treatment codes for each patient will be held according to EDC.

6.5 Shipment and Storage Condition of Investigational Product

Shipment, Storage, Dispensing and Return of the Investigational Product and the reference drug will be managed through the IRT system.

The investigational drug will be packed and shipped at 2-8°C in appropriate boxes with temperature loggers.

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 and how to keep record of how much study drug was returned, used and unused by each patient.

All investigational products 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.

6.6 Accountability and Compliance of Investigational Product

The investigator must maintain complete and adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products (MOD-4023 and Genotropin®) will be accounted for using a drug accountability form/record. The investigator is responsible that all investigational products accountability records are accurate and available for review by the study monitor, Sponsor or designee or the relevant regulatory authority.

At the last study visit, all used and unused MOD-4023/Genotropin® study drugs (pen) 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 approval.

Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of used and unused investigational product and expired laboratory kits (e.g., at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Sponsor. All destruction must be adequately documented.

6.7 Prior and Concomitant Therapy

6.7.1 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, start and stop dates, and the dose.

6.7.2 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 investigational products (within 30 days prior to ICF signing)

6.7.3 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 adverse events. 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.

6.7.4 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® 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 investigational product 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 investigational product treatment) of the concomitant disease present at Baseline visit (after initiation of investigational product 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 signs 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 clinical significance

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 countermeasures 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.

The investigator will document in his/her opinion the relationship of the AE to study treatment using the criteria outlined in Table 3.

Table 3: AE Relationship Criteria

Relationship	Criteria
Not related	• The temporal sequence of the AE onset relative to administration of the investigational product is not reasonable. • Disease or other drugs provide plausible explanations. • Dechallenge (if performed) is negative or ambiguous.
Unlikely related	• The temporal sequence of the AE onset relative to the administration of the investigational product is reasonable. • Could also be explained by disease or other drugs. • Dechallenge (if performed) is positive or uncertain. • Rechallenge (if performed) is negative.
Possibly related	• The temporal sequence of the AE onset relative to administration of the investigational product is reasonable. • Unlikely to be attributed to disease or other drugs. • Dechallenge (if performed) is positive.
Related	• The temporal sequence of the AE onset relative to administration of the investigational product is reasonable. • Cannot be explained by disease or other drugs. • Dechallenge (if performed) is positive and pharmacologically/ pathologically plausible. • Rechallenge (if feasible) is positive. • The AE shows a pattern consistent with previous knowledge of the investigational product or product class, i.e., pharmacologically or phenomenologically recognized/plausible or an objective and specific medical disorder.

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's or Sponsor's opinion on the relationship to the investigational product and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause)
- a life-threatening adverse event
- 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-AE (e.g. cosmetic surgery) 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 following 30 days of last study drug administration and is considered to be related (possibly) to the investigational product or study participation should be recorded and reported immediately.

A **life-threatening** AE 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 AE

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 investigational product 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 adverse event 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. Because knowledge of treatment assignment is needed to complete the determination, the Sponsor's designee will provide the final determination as to whether an SAE is a SUSAR.

7.5 Notification about Serious or Unexpected AEs

Initial notification

Each SAE must be reported by the investigator to the Sponsor or designee (OPKO Miami pharmacovigilance), to the study medical monitor and to Japan Safety Group (ICCC) 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 considered unexpected by the Sponsor or designee and is thought to be possibly related to the study drug, a Safety Associate shall urgently request further information from the investigator through the project

leader. This is essential for collecting information to report to the competent regulatory authority (RA).

SAE Reporting and Contact Information

All SAEs will be entered initially on the AE eCRF in EDC and an email notification should be sent to: the study medical monitor, OPKO Miami Pharmacovigilance Group and Japan Safety Group. In addition, the investigator will complete the CP-4-009 SAE Report Form that will be outside the EDC system. This form will be available for completion electronically as a pdf or may be printed for completion. The completed SAE Report Form will then be scanned and a copy sent to the study medical monitor, Japan Safety Group mailbox and to OPKO Miami Pharmacovigilance Group mailbox per the below specified contact information.

1. Medical Monitor:

   PPD
   PPD Tanaka Growth Clinic
   2-36-7, Yohga, Setagaya-ku
   Tokyo, Japan 158-0097
   TEL：P FAX：P
   E-mail： CP4009_medical_monitor@opko.com

2. OPKO Miami Pharmacovigilance Unit:

   PPD
   4400 Biscayne Blvd
   Miami, FL 33137
   Email: PPD
   Phone: PPD

3. Japan Safety Group (ICCC: EPS International Holdings Co., Ltd.)

   PPD
   PPD
   1-8 Tsukudo-cho, Shinjuku-ku
   Tokyo, Japan, 160-0821
   Email: PPD
   Phone: PPD

The investigator must complete the CP-4-009 SAE Report Form in English; assess the relationship to study treatment and submit to the above contacts via the email address specified within 24 hours to OPKO Miami Pharmacovigilance as well as to the study medical monitor and Japan Safety Group as above specified.

Follow-Up of SAEs / SUSARs

Follow-up information is to be submitted on a new SAE Report Form. The new form should clearly state that it is a follow-up to the previously reported SAE and include 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 follow up report may also include copies of site's case reports, autopsy reports and other documents, when requested and applicable.

Accompanying documentation, such as copies of study site's case reports, autopsy reports and other documents when applicable, should be summarized on the SAE form and a copy of the source document should be emailed to Japan Safety Group and to the study medical monitor. The above mentioned Japanese documentations should be translated by the Japan Safety Group to English, if required, and provided to OPKO Pharmacovigilance Group. 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 head of the study sites and to the PMDA 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

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

Once emailed, the SAE form and accompanying documentation should be placed in the SAE section of the investigator's file. If supplementary information on a SAE has to be sent, the SAE form to be used must be marked as "follow-up report".

SAEs and Non-SAE Reporting Period

SAEs / SUSARs that occur during the study will continue to be followed until their satisfactory resolution or stabilization.

All AEs (including SAEs) must be followed until resolution or stabilization and until 30 days after the patient last drug administration. In exceptional cases, it may be defined as "ongoing without further follow-up" by the investigator and Sponsor's decision.

7.6 Independent 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 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 approximately once every 6 months. DSMB will also include review of number or percentage of patients requiring dose reductions due to IGF-1 above +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® cohorts). DSMB will also include review of number or percentage of patients requiring dose reductions due to AEs.

7.7 Medication Errors

Medication errors may result from the administration of the investigational product 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 investigational product
- 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 study participant are to be captured in the EDC system.

7.8 Medical Device Complaint

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, must be reported by the investigator to the Sponsor, and the device must not be used. This includes potential incidents or malfunctions associated with the use of a medical device product. 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.

If the device complaint is considered unexpected by the Sponsor, Sponsor or its designated ICCC shall urgently request further information from the investigator through the project leader. In addition, all potential incidents or malfunctions will be reported to the head of the study sites and to the PMDA as required by local regulations and ICH-GCP guidelines.

8 STATISTICAL ANALYSIS

8.1 Sample Size Consideration

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

Assuming that the mean treatment difference is -0.8 cm/yr and the common SD is 2.5 cm/yr, a total 40 patients (20 per treatment) will provide about 90% probability that the point estimate of the mean treatment difference of HV in CP-4-009 is greater than -1.8 cm/year (which is the non-inferiority margin in the global trial CP-4-006).

8.2 Analyzed Population Sets

8.2.1 Full Analysis Set

The Full Analysis Set will include all randomized patients.

8.2.2 Per Protocol Set

The Per Protocol Set will be all randomized patients who completed the study per protocol and who did not have any major protocol deviations.

8.2.3 Safety Analysis Set

The safety analysis set will include all patients who have received at least one dose of study treatment.

8.3 Handling of Missing Data

Multiple Imputation (using SAS PROC MI) assuming data missing at random will be used to impute missing observations in the primary efficacy analysis. Sensitivity analyses will be performed to evaluate the effect of missing data. Details on the method used to handle missing data and all sensitivity analyses for missing data will be provided in the SAP.

8.4 Endpoints

8.4.1 Primary Efficacy Endpoint

- HV in cm/year after 12 months of treatment.

8.4.2 Secondary Efficacy Endpoints

Auxology/Clinical endpoints:

- Annualized height velocity after 6 months of treatment
- Change in height SDS at 6 and 12 months, compared to Baseline
- Change in bone maturation (BM) at the end of 12 months, compared to Baseline (BM calculated as BA/CA)

8.4.3 Secondary PK/PD Endpoints

Biochemical endpoints:

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- IGF-1 SDS on day 4(-1) after MOD-4023 dosing across study visits (window only applies to Visits 6 to 9)

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8.4.4 Safety Outcomes

- Incidence of AEs and SAEs
- Incidence of anti-MOD-4023 antibody formation (including characterization of the antibodies and neutralizing properties)
- Local injection site assessment
- IGF-1 serum levels and SDS
- Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin level, HbA1c
- Thyroid status
- Lipid metabolism parameters: morning fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
- All other safety hematology and biochemical laboratory parameters
- Physical examination
- Fundoscopy (normal/abnormal)
- Vital signs
- ECG

8.5 Statistical Analysis

The planned final analysis will be done after all patients complete 12 months treatment. Details of applicable statistical methods will be provided in a SAP prior to database lock. The primary analysis set for all the efficacy analyses will be the Full Analysis Set.

8.6 Efficacy Analysis

The aim of the Phase 3 study is to demonstrate that in terms of the primary efficacy endpoint, Annual HV at 12 months, weekly MOD-4023 is comparable to daily r-hGH within the range

defined of 1.8 cm/year (non-inferiority margin in CP-4-006 study). Descriptive statistics and confidence intervals will be used to characterize the results.

Primary Efficacy Analysis:

The goal of the primary efficacy analysis is to estimate the mean treatment difference between weekly MOD-4023 and daily Genotropin® with respect to the primary efficacy endpoint (HV after 12 months of treatment). Least square means and 95% CI for HV at 12 months will be calculated from an ANCOVA model, with treatment, gender, as factors (class variables); and peak hGH value during stimulation test, and baseline HV as covariates. The point estimate of the mean difference in HV between treatments will be used to assess comparability. Comparability will be concluded for the primary efficacy endpoint if the point estimate of the mean treatment difference (MOD-4023 – Genotropin®) is ≥ –1.8 cm/year.

Missing data will be handled by multiple imputation (by using SAS PROC MI), assuming data missing at random. Details will be provided in the SAP.

Secondary Analysis:

The continuous secondary efficacy endpoints measured at a single post-baseline timepoint will be analyzed in the same manner as the primary endpoint, using the ANCOVA model which may include treatment group, age, and gender, peak hGH value during stimulation test, and the baseline value of the endpoint of interest to generate the least square treatment means. For the secondary endpoints that are measured over time, MMRM analysis with similar factors as the ANCOVA model (in the primary endpoint) will be used to estimate the time specific results. This MMRM approach is not intended to test for statistical significance of factors. These analyses are considered to be supportive efficacy analyses.

8.6.1 Safety Analysis

All safety analyses will be conducted using the Safety Analysis Set. 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.

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9 ETHICS

9.1 IRB

Prior to initiation of the study, the sponsor or its designated ICCC will submit the study protocol and amendments, sample ICF and any other documents that may be requested to the IRB for review and approval. The Head of the study site will request that the IRB to 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. The investigator must agree to make any required progress reports to the Head of the study site, as well as reports of SAEs, serious medical device (pen) complaint, life-threatening conditions, or death. The sponsor or its designated ICCC must report those information to the IRB as required by local regulations.

9.2 Ethical Conduct of the Study

All clinical work conducted under this protocol is subject to ICH-GCP and J-GCP guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB 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 or designee's SOPs and the following guidelines:

- ICH-GCP: Consolidated Guideline (ICH of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Brazil, 2013 (Appendix H).
- Local country guidelines for conducting clinical trials

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). The Sponsor will make reasonable efforts to have the investigators agreement in regards to these changes. All protocol modifications must be submitted to the IRB 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 trial patients, or when the changes involve only logistical or administrative aspects of the trial. No approval will be required for notifications.

9.4 Patient Information and Consent

Prior to screening for the study each patient and parents/legal guardians 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 J-GCP, the FDA (21 CFR 50.25) and ICH-GCP will be followed. Written consent will be obtained from parents/legal guardian of each patient to be involved in the clinical trial by using the IRB approved ICF prior to the conduct of any study-related activity. In addition to this, the investigators will try to obtain assents from patients. Parents/legal

guardian of each patient will be given a copy of the written ICF. The parents/legal guardian of patients will also be instructed that they are free to withdraw their consent and discontinue their children's participation in the study at any time without prejudice. Each patient's chart will include the signed ICF for study participation obtained from their parents/legal guardian as well as assents if obtained. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file for the required period of time. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

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 file or can be made available to the investigator and to the IRB 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, by sending a letter to the physician if required by the local authorities.

9.7 Personal Data Protection

The Sponsor complies with the principle of the patient's right to protection against invasion of privacy. Throughout this trial, all data will be identified only by an identification number and/or date of birth.

The 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 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 ICCC maintain a quality assurance (QA) system with written SOPs to ensure that clinical trials are conducted and data are generated, documented and reported in compliance with the protocol, GCP, J-GCP and applicable regulatory requirements.

10.1 Audits and Inspections

The investigator/the Head of the study site should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor QA 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. The study monitor will advise the investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP, J-GCP and all applicable regulatory requirements. Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRF will be reviewed for completeness with corresponding source documents and patient medical records. 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 study 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 meet with the study monitor during these on-site visits, cooperate in providing the documents for inspection and respond to inquiries.

10.2.1 Source Documents

The Head of the study site will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB 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 site's 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 was signed, participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

10.2.2 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 laboratory.

10.4 Data Management

An eCRF will be used for the current study and a data management plan (DMP) will be prepared by the Sponsor and/or it 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 Medical Dictionary for Regulatory Activities (MedDRA, 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 45 - 55 sites will participate in this study.

Required Documents Prior to Study Initiation

Prior to the start of this study, all pre-investigational requirements must be met by the investigator and study site. These may include:

- Appropriate IRB documentation properly signed and dated by the required Head of the study site (i.e., the submission package)
- Signed copy (original) of the approved protocol
- Completed and signed statement of investigator
- A signed Clinical Trial Agreement
- Curriculum vitae for the investigator and sub-investigators[a]
- IRB name and address; and membership list
- Letter of approval from the IRB for both protocol (identified by protocol title and number) and informed consent form (identified by protocol title and number)
- Copy of the IRB -approved written ICF to be used in the study (that has also been approved by the Sponsor)
- Provisions for direct access to source/data documents if necessary for trial-related monitoring, audits, IRB review and regulatory inspection
- If applicable, medical license of participating investigator and / or sub-investigator

Upon satisfactory receipt of all required regulatory documents, Sponsor will arrange that study drugs be delivered to the study site. Supply of all other study materials will be the responsibility of OPKO 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 will prepare an Investigator's Study File (ISF). This file should be used for all trial related documents. The investigator will be responsible for keeping the investigator's file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

[a] Can be collected at Site Initiation Visit

11.2 Clinical Trial Supplies

The Sponsor and/or designated representative will be responsible for supplying IP clinical trial supplies through the IRT system. IP clinical supplies inventory will be managed through the IRT system. Other clinical trial supplies (i.e. ancillaries, lab supplies, etc.) will be managed outside of the IRT system. The investigator will be responsible for inventory and accountability of all clinical trial supplies at his/her 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.

Clinical trial supplies include, however, are not limited to: laboratory supplies, study drugs and ancillary items.

11.3 ISF

The ISF will be prepared by the investigator and/or designee by the time of the initiation visit. All documents required for the conduct of the study as specified in the ICH-GCP guidelines and J-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 and RAs.

11.4 Study Completion

This study is expected to end when the last enrolled patient completes Visit 10- EOS visit. 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 serious adverse event reported
- Copies of protocol amendments and IRB as well as relevant health authority approval/notification (if applicable)

11.5 Final Report

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

11.6 Retention of Study Records

Per the J-GCP the investigator and the head of the study site/or designee 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 and the head of the study site/or designee is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed of the individual who will be assuming this responsibility.

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

11.7 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 and birthdates.

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

All information supplied by OPKO 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 OPKO, shall not be disclosed to others without the written consent of OPKO 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 used by OPKO. This information may be disclosed as deemed necessary by OPKO. To allow the use of this information derived from this study, the investigator is obliged to provide OPKO with complete test results and all data developed in this study.

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APPENDIX A: SCHEDULE OF ACTIVITIES – MOD-4023 TREATMENT ARM –VISITS 1 – 5.1

Study Procedure	Screening	Baseline	Treatment Period - Dose escalation phase (6 weeks)					
Study Month	-1 to Day -1	0	0.5		1		1.5	
Study Week	-4[a] to Day -1	1	2		4		6	
Study Visit	1	2	3	3.1	4	4.1	5	5.1
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographic & medical history including parent's height	X							
MRI (if required) post GH stimulation[b]	X							
BMI and BMI SDS	X							
Auxology measurements[c]	X[d]	X						
Weight measurement						X		
Physical examination and vital signs	X	X		X		X		X
ECG		X pre-dose						
Pubertal status (according to Tanner stages)	X	X						
BA (TW2 using central bone age reader)	X[e]	X[f]						
Fundoscopy			ONLY if there are signs or symptoms indicative of benign intracranial hypertension					
Verification of eligibility[g]	X							
Randomization		X[g]						
Training on drug administration, injection site reactions, patient diary completion, and dosing review		X		X		X		
Drug administration at clinic		X						
Dispense study drug and patient diary		X				X		
Patient diary, study drug return & accountability						X		
Local tolerability (Injection site reactions)		X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X
Prior & concomitant medications	X	X	X	X	X	X	X	X

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] MRI to be performed upon investigator judgment. In addition, MRI which was conducted within 6 month prior to ICF signature date will be acceptable
[c] Actual height (mean of 3 consecutive measurements) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.
[d] Including Patient's Height SDS and HV SDS
[e] For Screening visit, historical BA assessment might be accepted if they were done no more than 6 months prior to the ICF signature date. If the patient will be eligible, the BA should be repeated at Visit 2, before the dosing. The Visit 2 scan will be the baseline scan for these patients.
[f] BA assessment should be performed at Visit 2 only if not performed at screening.
[g] Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

Study Procedure	Screening	Baseline	Treatment Period - Dose escalation phase (6 weeks)					
Study Month	-1 to Day -1	0	0.5		1		1.5	
Study Week	-4[a] to Day -1	1	2		4		6	
Study Visit	1	2	3	3.1	4	4.1	5	5.1
Laboratory Assessments								
Hematology[b], Biochemistry[c], & Urinalysis[d]	X	X				X		
Thyroid Assessment (TSH, FT4)	X	X						
Glucose metabolism[e]	X	X						
Lipid profile[f]	X	X						
GH stimulation (provocation) test[g]	X							
Morning cortisol (up to 8am ±1hr)[h]	X							
ACTH or CRH stimulation test[i]	X							
[redacted] IGF-1 SDS[j]	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X
MOD-4023 serum levels		X	X	X	X	X	X	X
Antibodies to hGH	X							
Antibodies to MOD-4023		X pre-dose				X		
Blood volume (mL)[l]	8-42	9-12	6	6	6	12	6	6

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] Hematology: RBC; HGB; HCT; MCH; MCHC; MCV; WBC, Count and Differential; Platelet Count
[c] Biochemistry: total protein, albumin, total bilirubin; ALT AST, GGT, LDH, CPK, alkaline phosphatase; glucose; sodium, potassium, calcium, phosphate; BUN, creatinine;
[d] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein
[e] Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel) and insulin; HbA1c
[f] Lipid profile: morning fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
[g] 2 different GH stimulation (provocation) tests (insulin tolerance test, with serum cortisol response to hypoglycemia if insulin stimulation test is chosen OR arginine test/clonidine test/glucagon test /L-dopa/ GHRP-2). Prior local laboratory results, will be accepted subject to pre-approval by Sponsor medical monitor and if the tests were conducted as specified in the protocol.
[h] Morning cortisol assessment will be subject to the investigator judgment.
[i] 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. Insulin Tolerance test with serum cortisol response to hypoglycemia is adequate for assessment of adrenal insufficiency and no ACTH or CRH stimulation test is required if such results are available
[j] Frequency of sampling from Visits 3 – 5.1 as per assigned sub-block
[k] Frequency of sampling from Visits 3 – 5.1 as per assigned sub-block
[l] The total blood volume to be collected during screening (maximum 5 weeks) is shown. The maximum blood volume per day differs according to the selection of assessments. Based on the pediatric clinical guidance, blood sampling must be performed so the required minimum blood volume is obtained, and such GH stimulation tests and other assessments are taken on different days.

APPENDIX B: SCHEDULE OF ACTIVITIES – MOD-4023 TREATMENT ARM (VISITS 6 - 10)

Study Procedure	Active treatment period				EOT		EOS
Study Month	3	6		9	12		13
Study Week	13 (±1Weeks)	26 (±3Weeks)		39 (±1Weeks)	52 (±3Weeks)		56 (+1week)
Study Visit	6[a]	7[b]	7.1[c]	8[d]	9[e]	9.1[f]	10
Auxology measurements[g]	X		X	X		X	
Physical examination and vital signs	X		X	X		X	
ECG			X				
Pubertal status (according to Tanner stages)	X		X	X		X	
BA (TW2 method using central bone age reader)						X	
Fundoscopy	ONLY if there are signs or symptoms indicative of benign intracranial hypertension						
Individual dose adjustment	X		X	X			
Dispense study drug and patient diary	X		X	X			
Patient diary, study drug return & accountability	X		X	X		X	
Local tolerability (Injection site reactions)	X		X	X		X	
AEs	X	X pre-dose	X	X	X pre-dose	X	
Prior & concomitant medications	X	X pre-dose	X	X	X pre-dose	X	
Phone interview per Appendix I							X
Laboratory Assessments							
Hematology[h], Biochemistry[i], & Urinalysis[j]	X		X	X		X	
CCI IGF-1 SDS	X		X	X		X	
CCI	X	X pre-dose	X	X	X pre-dose	X	
Thyroid Assessment: (TSH, FT4)	X		X	X		X	
Glucose metabolism[k]			X			X	
Lipid profile[l]			X			X	
Antibodies to MOD-4023	X	X pre-dose		X	X pre-dose		
Blood volume (mL)[m]	9	6	10	9	6	10	0

[a] Visit will be conducted 4 days (-1) post dose (Day 3 or 4 post-injection).
[b] Blood Sampling, AE and concomitant medication will be conducted on dosing day (predose/Visit 7)
[c] Visits 7 and 9 post-dose assessments will be conducted 4 days (-1) after that week's injection.
[d] Visit will be conducted 4 days (-1) post dose (Day 3 or 4 post-injection).
[e] Blood Sampling, AE and concomitant medication will be conducted on dosing day (predose/Visit 9)
[f] Visit will be conducted 4 days (-1) post dose (Day 3 or 4 post-injection).
[g] Actual height (mean of 3 consecutive measurements) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items
[h] Hematology: RBC; HGB; HCT; MCH; MCHC; MCV; WBC, Count and Differential; Platelet Count
[i] Biochemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; glucose; sodium, potassium, calcium, phosphate; BUN, creatinine;
[j] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein
[k] Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel) and insulin; HbA1c
[l] Lipid profile: morning fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
[m] Based on the pediatric clinical guidance, blood sampling must be performed so the required minimum blood volume is obtained, and such GH stimulation tests and other tests are taken on different days.

APPENDIX C: SCHEDULE OF ACTIVITIES – GENOTROPIN® TREATMENT ARM

Study Procedure	Screening	Baseline	Active treatment period									EOT	EOS
Study Month	-1 to Day -1	0	0.5		1		1.5		3	6	9	12	13
Study Week	-4[a] to Day -1	1	2		4 (±1)		6		13 (±1w)	26 (±1w)	39 (±1w)	52 (±1w)	56 (+1w)
Study Visit	1	2	3[b]	3.1	4	4.1	5	5.1	6	7	8	9	10
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographic & medical history including parent's height	X												
MRI (if required) post GH stimulation[c]	X												
BMI and BMI SDS	X												
Auxology measurements[d]	X[e]	X							X	X	X	X	
Physical examination and vital signs	X	X			X				X	X	X	X	
ECG		X pre-dose								X			
Pubertal status (according to Tanner stages)	X	X							X	X	X	X	
BA (TW2 method using central bone age reader)	X[f]	X[g]										X	
Fundoscopy					ONLY if there are signs or symptoms indicative of benign intracranial hypertension								
Verification of eligibility[h]	X												
Randomization		X[h]											
Training on drug administration, injection site reactions, diary completion, and dosing review		X											
Drug administration at clinic		X											
Individual dose adjustment									X	X	X		

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] No clinic Visit 3 for Genotropin® arm only phone interview
[c] MRI to be performed upon investigator judgment. In addition, MRI which was conducted within 6 month prior to ICF signature date will be acceptable
[d] Actual height (mean of 3 consecutive measurements) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.
[e] Including Patient's Height SDS and Height Velocity (HV) SDS
[f] At screening visit, historical BA assessment might be accepted if they were done no more than 6 months prior to the ICF signature date. If the patient will be eligible, the BA should be repeated at Visit 2, before the dosing. The Visit 2 scan will be the baseline scan for these patients.
[g] BA assessment should be performed at Visit 2 only if not performed at screening.
[h] Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

Study Procedure	Screening	Baseline	Active treatment period									EOT	EOS
Study Month	-1 to Day -1	0	0.5		1		1.5		3	6	9	12	13
Study Week	-4[a] to Day -1	1	2		4 (±1)		6		13 (±1w)	26 (±1w)	39 (±1w)	52 (±1w)	56 (+1w)
Study Visit	1	2	3[b]	3.1	4	4.1	5	5.1	6	7	8	9	10
Dispense study drug and patient diary		X			X				X	X	X		
Patient diary, study drug return & accountability					X				X	X	X	X	
Local tolerability (Injection site reactions)		X			X				X	X	X	X	
AEs		X			X				X	X	X	X	
Prior & concomitant medications	X	X			X				X	X	X	X	
Phone interview per Appendix I			X				X						X
Laboratory Assessments													
Hematology[c], Biochemistry[d], & Urinalysis[e]	X	X			X				X	X	X	X	
GH stimulation (provocation) test[f]	X												
Morning cortisol (up to 8am ±1hr)[g]	X												
ACTH or CRH stimulation test[h]	X												
CCI IGF-1 SDS	X	X			X				X	X	X	X	
Thyroid Assessment: (TSH, FT4)	X	X							X	X	X	X	
Glucose metabolism[i]	X	X								X		X	
Lipid profile[j]	X	X								X		X	
Antibodies to hGH	X	X pre dose							X	X	X	X	
Blood volume (mL)[k]	8-42	9-12	0		7		0		9	9	9	9	0

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] No clinic Visit 3 for Genotropin® arm only phone interview
[c] Hematology: RBC; HGB; HCT; MCH; MCHC; MCV; WBC, Count and Differential; Platelet Count
[d] Biochemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; glucose; sodium, potassium, calcium, phosphate; BUN, creatinine;
[e] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein
[f] Two different GH stimulation (provocation) tests (insulin tolerance test, with serum cortisol response to hypoglycemia if insulin stimulation test is chosen OR arginine test/clonidine test/glucagon test /L-dopa
[g] Morning cortisol assessment will be subject to the investigator judgment.
[h] 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. Insulin Tolerance test with serum cortisol response to hypoglycemia is adequate for assessment of adrenal insufficiency and no ACTH or CRH stimulation test is required if such results are available
[i] Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel) and insulin; HbA1c
[j] Lipid profile: morning fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
[k] Based on the pediatric clinical guidance, blood sampling must be performed so the required minimum blood volume is obtained, and such GH stimulation tests and other tests are taken on different days.

APPENDIX D: STIMULATION TESTS

GH Stimulation Tests

After the nationwide standardization of GH measurement kits in 2005, a peak GH concentration equal to or less than 6ng/mL (16 ng/mL in GHRP-2 test) is the diagnostic criteria for GHD in Japan when the kits use recombinant hGH as standards (Tanaka, T. Horm Res 2005;64(suppl 2):6-11). However, the considerable variations were observed again by the annual nationwide control survey, GH value by Beckman should be judged after calculation by the correction formula (Katsumata N. Endocr J 2016;63:933-936).

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

Insulin Tolerance Test

Regular human insulin (0.1 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, 60, and 90 min (5 sampling points ± 5 min) for glucose, hGH (except 15 min) and cortisol determination (except 15 min).

At the 15 min time point glucose levels should be measured at bedside by a simple glucose meter. 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 (5 µg/dL) or an increase in peak cortisol level above (18 µg/dL).

Clonidine test

After fasting overnight, clonidine (0.1 mg/m^2 body surface, given orally, 0.15 mg maximum) 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 and 120 (5 sampling points ± 5 min) for hGH measurement. Caution should be exercised when performing this test, however, as clonidine causes side effects such as tiredness and decreased blood pressure. Thus, blood pressure 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 BPs every 15 minutes.

Arginine test

Soluble 10% arginine hydrochloride (0.5 g/kg) will be given iv from time 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 following intervals: t = 0, 30, 60 and 90, 120 min (5 sampling points ± 5 min) for hGH measurement

Glucagon test

After fasting overnight, glucagon (0.03 mg/kg with a maximal total dose of 1 mg) will be given intramuscularly (im) 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 (± 5 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 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 10 mg/kg (maximum 500 mg). Blood samples will be obtained by an indwelling catheter. Blood will be collected at the following intervals: 0, 30, 60, 90 and 120 min (5 sampling points ± 5 min).

GHRP-2 test

After fasting overnight, GHRP-2 (2 µg/kg, maximum 100 µg) will be administered iv at t=0. Blood will be collected for hGH measurement at 0, 15, 30, 45 and 60 min (± 5 min) relative to the time of GHRP-2 administration.

CRH and ACTH Stimulation Tests

CRH Stimulation Test

CRH at a dose of 1.5 µg/kg (maximum 100 µg) will be given iv at time point 0. Blood will be collected at the following intervals: t=0, 30, 60, 90 and 120 min (5 sampling points ± 5 min) for ACTH and cortisol determination.

ACTH Stimulation Test

After fasting overnight, ACTH (Cortrosyn, Daiichi-Sankyo Company, Ltd, Japan) at dose of 1 µg/1.73 m^2 body surface will be given iv at time point 0. Blood will be collected at the following intervals: 0, 30 and 60 min (3 sampling points ± 5 min) post injection for cortisol level determination.

APPENDIX E: INSTRUCTIONS FOR OBTAINING HEIGHT MEASUREMENTS

Height will be measured in cm.

Verify the stadiometer is calibrated prior to height measurement.

Use the following instructions when obtaining height measurements.

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

1. Use a wall or equivalent mounted calibrated stadiometer.
2. Patients should not stretch prior to height 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 two 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 F: INSTRUCTIONS FOR OBTAINING X-RAY FILMS

BA Assessment using the Tanner-Whitehouse 2 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 chronological age are important in pediatric endocrinology for diagnosing diseases which result in abnormalities of stature (tall or short) in children. Serial measurements of bone age are also critical in determining the effectiveness of established treatments of these diseases as well as use in clinical trials 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 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 minutes or in two minutes on a transatlantic flight.

For this study, the bone age 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 Tanner-Whitehouse 2 Method (Murata M. Japanese specific BA standard on the TW2. Clin Pediatr Endocrinol 1993; (Suppl 3):35-41).

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

APPENDIX G: INJECTION SITE ASSESSMENT TABLE (LOCAL REACTIONS) AND PAIN ASSESSMENT

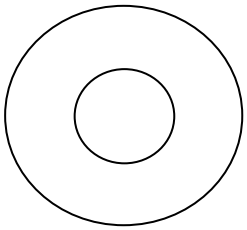
Assessment by the PI and Medical Staff

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 will be taken and used to document any clearly observed clinical effect of MOD-4023 or Genotropin® but will not be formally evaluated.

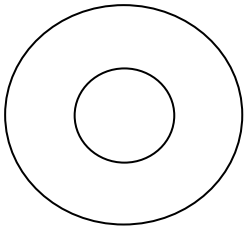
Redness



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.

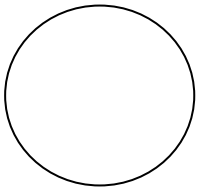
Bruising



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.

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.

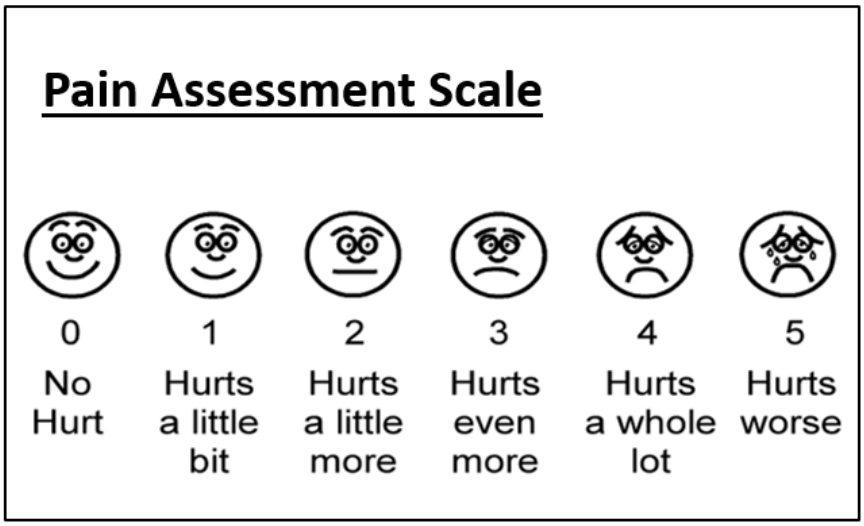
Pain

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 Assessment 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 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.

APPENDIX H: DECLARATION OF HELSINKI (2013)

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

Preamble

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

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

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

General Principles

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

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

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

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

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

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

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of

personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that 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 subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

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

    Vulnerable Groups and Individuals
19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

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

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

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

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally 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 subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally 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 subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally 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 subjects must be registered in a publicly accessible database before recruitment of the first subject.

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

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally 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.

APPENDIX I: PHONE INTERVIEW

Phone Interview for Genotropin® arm will be conducted on Visit 3 and Visit 5.

Phone Interview will be conducted on Visit 10 (EOS Visit) for both arms.

During the OLE, Phone Interviews will be conducted at the following visits:

- Visit 11 and Visit 12 for existing MOD-4023 patients only
- Visit 13 for all patients
- Follow Up Visit for all patients

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

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.

In case the patient/parents/legal guardiuan refuse to answer- Please mark "not intersted" and complete a protocol deviation.

1. From your last visit, do you feel any different? Y/N

If yes, please specify.

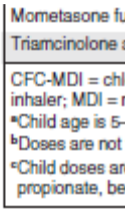
2. Are you taking any new medications? Y/N

If yes, please specify.

3. Have any changes in injection sites occurred in the past week/since the last injection drug administration?

If yes, please specify.

APPENDIX J: CLINICALLY COMPARABLE DOSES OF INHALED CORTICOSTEROIDS



Mometasone fu
Triamcinolone

CFC-MDI = chl
inhaler; MDI = r
[a]Child age is 5-
[b]Doses are not
[c]Child doses ar
propionate, be

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

APPENDIX K: OPEN-LABEL EXTENSION PROTOCOL

Signature Page for VV-TMF-98259 v3.0

Reason for signing: Approved	Name: PPD Role: PPD Date o Dec-2018 04:16:00 GMT+0000

Reason for signing: Approved	Name: PPD Role: Quality Assurance Date of signature: 13-Dec-2018 18:46:26 GMT+0000

Reason for signing: Approved	Name: PPD Role: Clinical Operations Date of signature: 13-Dec-2018 18:57:29 GMT+0000

Signature Page for [redacted]

CLINICAL SUB-STUDY PROTOCOL

EXTENSION STUDY OF THE PHASE 3, OPEN-LABEL, RANDOMIZED, MULTICENTER, 12-MONTH, EFFICACY AND SAFETY STUDY OF WEEKLY MOD-4023 COMPARED TO DAILY GENOTROPIN® THERAPY IN JAPANESE PRE-PUBERTAL CHILDREN WITH GROWTH HORMONE DEFICIENCY

Sponsor: OPKO Health, Inc.
4400 Biscayne Blvd
Miami, FL 33137
USA

Protocol Number: CP-4-009

CTN Number: 29-0329

Safety Medical Officer: PPD, MD

Statistician: PPD Ph.D.
Research Global Point

PROTOCOL SYNOPSIS

SUB-STUDY TITLE	Extension Study of the Phase 3, Open-Label, Randomized, Multicenter, 12-month,Efficacy and Safety Study of Weekly MOD-4023 Compared to Daily Genotropin® Therapy in Japanese Pre-Pubertal Children with Growth Hormone Deficiency
PROTOCOL NO.	CP-4-009
CTN NUMBER	29-0329
CLINICAL SITES	The study will be conducted at CP-4-009 active clinical sites with qualified and interested patients.
STUDY PHASE	3
THERAPEUTIC INDICATION	Treatment of children with growth failure due to growth hormone deficiency (GHD).
STUDY OBJECTIVE	To demonstrate the safe switch of patients who have completed 12 months treatment with daily Genotropin ® to weekly MOD-4023, and to document long term safety and efficacy of weekly MOD-4023 treatment in an open-label extension (OLE).
STUDY DESIGN	The study will consist of a single-arm, open-label extension (OLE) study with weekly MOD-4023 injections. Patients who have successfully completed 12 months of treatment in study CP-4-009 and meet the OLE inclusion/exclusion criteria of this protocol will be eligible to rollover into this OLE study. Patients who received Genotropin® for 12 months during the main study CP-4-009, will be switched to receive a dose of 0.66 mg/kg per week of MOD-4023 (no less than one day after cessation of Genotropin® treatment). Patients who have received MOD-4023 for 12 months during the main study will continue in the OLE with the same dose (mg/kg/wk) of MOD-4023. During the OLE study, the MOD-4023 dose will be adjusted based on the patients' body weight every three months. The dose may be decreased 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). During the OLE dose reduction for IGF-1 level >+2.0 SDS will be made following consultation with the Study MM on an individual patient basis. The key safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) once every 6 months. The study will be conducted, subject to Sponsor, Regulatory Authority and IRB approvals.
STUDY PROCEDURES	After successful completion of 12 months of treatment in the CP-4-009 main study and meeting the OLE inclusion/exclusion criteria of this protocol, and upon receipt of necessary Regulatory and IRB approvals, patients will be eligible to rollover into the

	OLE study with MOD-4023. An informed consent/assent will be obtained from patients and/or parents or legal/authorized guardian for this extension study. Patients who do not qualify to continue in the trial or who are not interested in continuing into the OLE should complete the End of Treatment (EOT) Visit, which is equivalent to visit 9/9.1, and should complete a phone interview for visit 10 within 4 weeks (+1 week) to complete End of Study Assessments according to the CP-4-009 main study protocol schedule of activities. Patients who received MOD-4023 during the main CP-4-009 study will continue in the OLE with the same dose (mg/kg/week) of MOD-4023, adjusted for body weight. For these patients, study visits will take place every three months on day 4 (-1 day) post-dose. Pre-dose assessments will be taken at month 6 and month 12 during the first year. These patients will consent to the OLE preferably during Visit 8 (week 39) of the main study to ensure availability of MOD-4023 at their first visit of the OLE study. Informed consent can also be obtained at main study Visit 9/9.1/OLE Baseline Visit 9.2 (week 52). MOD-4023 patients will continue treatment and receive study drug at OLE Visit 9.2, skip Visit 10 (close out or end of main study), and have phone interviews at OLE Visits 11, 12, and 13 as described in the schedule of activities. Visits will occur every 3 months thereafter beginning at Visit 14. All patients will be provided with a patient diary throughout the trial as described in the Schedule of Activities (Appendix A). Patients who received Genotropin® during the CP-4-009 main study will complete the main study assessments and will be switched to MOD-4023 at Visit 9. Dosing of MOD-4023 treatment at 0.66 mg/kg/wk will begin 1 day and no more than 2 weeks after cessation of Genotropin® treatment (at Visit 9/OLE Visit 9.2). These patients will consent to the OLE preferably during Visit 8 of the main study to ensure availability of MOD-4023 at their first visit of OLE study (main study Visit 9/OLE Visit 9.2). Patients will skip Visit 10 (close out or end of main study) and have additional onsite subsequent visits at Visit 11 (Month 12.5, Day 10 post first MOD-4023 dose [10+4 days]), Visit 12 (1 month post first MOD-4023 dose (Month 1 [±1wk]), and Visit 14 (Month 3 [±1wk]). A phone interview will occur at OLE Visit 13 (Month 2 [±1wk]). Visits will occur every three months thereafter, until study closure. All patients will be provided with a patient diary throughout the trial as described in the Schedule of Activities (Appendix A of the OLE Sub-Protocol). For all patients switching from Genotropin® to MOD-4023, the following assessments will be performed at OLE Visit 9.2:

	• MOD-4023 and associated diaries 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 pen device, and diary completion. • Local tolerability assessment after first dose administered at site. • Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche). Patients who experience a delay for any reason between completion of the main study and entry into the OLE may have to temporarily stop treatment. If initiation/re-initiation of treatment occurs less than 90 days after Visit 9 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 OLE after confirmation of availability of all required baseline OLE assessments (Visit 9). In addition to the onsite training, dose administration of MOD-4023, and local tolerability assessment, the following tests and assessments below must be repeated at the time of the unscheduled visit at the site: • Overall health status assessment, including complete physical examination and vital sign assessments. • Safety laboratory tests: chemistry, hematology and urinalysis. • Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin, HbA1c. • Assessment of thyroid: TSH, FT4. • Parameters of lipid metabolism: morning fasting total cholesterol, LDL, triglycerides, and HDL. • Assessment of anti-MOD-4023 Ab for all patients. • Assessment of biochemical markers: CCI IGF-1 SDS. • Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche). <u>OLE Treatment – Year 1</u> During the first year of OLE treatment, the following assessments will be conducted on Day 4 (-1 day) post dose during onsite visits for patients making the switch from Genotropin® to MOD-4023 (Visits 11 – 12): • Safety laboratory tests: chemistry, hematology, and urinalysis (only Visit 12).

	• Overall health status assessment, including complete physical examination and vital signs assessment. • 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: CCI [redacted] calculate the related IGF-1 SDS (only Visit 12). • CCI [redacted]. • Assessment of anti-MOD-4023 Ab. • Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension). • Dispense study drug and patient diary (only Visit 12).[a] • Patient diary review, study drug return & accountability (only Visit 12). For patients making the switch from Genotropin® to MOD-4023, a phone interview will be conducted at Visit 13. Existing MOD-4023 patients will have a phone interview at Visits 11, 12, and 13 as indicated in the schedule of activities to ask about AEs and concomitant medications. These visits will be completed using the questionnaire in Appendix I of the main study protocol. The following assessments will be conducted on day 4 (-1 day) post-dose for all patients during the first year of OLE treatment at months three (Visit 14), six (Visit 15), nine (Visit 16), and twelve (Visit 17): • Pre-dose assessment of MOD-4023 serum levels and anti-MOD-4023 Ab (Visit 15 and Visit 17 only). • Safety laboratory tests: chemistry, hematology, and urinalysis • Auxology measurements: Height (average of 3 consecutive measurements) and body weight measurements (see Appendix E in the main study protocol for height instructions) • 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: CCI [redacted] calculate the related IGF-1 SDS

[a] Patient Diary will be re-issued for further completion.

	• CCI . • Post-dose assessment of anti-MOD-4023 Ab (Visit 14 and Visit 16 only). • Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension). • Dispense study drug and patient diary. • Patient diary review, study drug return & accountability. • Assessment of thyroid function: TSH, FT4 (except Visit 16). • Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin, HbA1c (except Visit 16). • Parameters of lipid metabolism: morning fasting cholesterol, triglycerides, high density lipoprotein (HDL), and low density lipoprotein (LDL) (except Visit 16). <u>OLE Treatment – Year 2 until study closure</u> Following completion of the first year of OLE treatment the following assessments will be conducted for all patients on day 4 (-1 day) post-dose every three months : • Auxology measurements: Height and body weight measurements. • 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). • Dispense study drug and patient diary. • Patient diary review, study drug return & accountability. The following assessments will be conducted for all patients on day 4 (-1 day) post-dose every six months: • Assessment of biochemical markers: CCI related IGF-1 SDS calculation • Safety laboratory tests: chemistry, hematology and urinalysis. • Assessment of thyroid function: TSH, FT4. • Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin, HbA1c.

	• Parameters of lipid metabolism: morning fasting cholesterol, triglycerides, HDL, and LDL. • Assessment of MOD-4023 serum levels. • Assessment of anti-MOD-4023 Ab. <u>OLE Treatment – Annually from Year 1 until study completion</u> Additional assessments will be performed once a year, on day 4 (or -1 day) post-dose at month 12 (OLE Visit 17) and Year 2 onward: • ECG • Bone age • Pubertal status (according to Tanner stages) • For males that are 13 years and older: LH, FSH and testosterone will be analyzed. For females that are 12 years and older: LH, FSH and estradiol will be analyzed (from OLE treatment year 2 until study closure). • Pre-dose and post-dose assessment of MOD-4023 serum levels annually • Pre-dose assessment of Abs to MOD-4023 annually Year 1 (including end of study (EOS) during year 1): ECG should be conducted around the time of maximum concentration (Tmax) (7-12 hours post-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. An ECG must still be obtained even if patients do not take the final dose. For EOS from 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 4 weeks [± 1 week] after ET visit in order to obtain safety related information (local tolerability, AEs, prior and concomitant medications).
STUDY DURATION	Patients will continue with weekly MOD-4023 treatment until study closure or discontinuation rules have been met. The OLE study will continue until marketing approval.
NUMBER OF PATIENTS	Up to 44 boys and girls who have been randomized and treated in the main study CP-4-009 and have completed 12 months of treatment will be eligible to continue in the OLE study of MOD-4023 therapy.

INCLUSION CRITERIA	1. Completion of the main study (12 months of treatment) with adequate compliance and adherence to the visit schedule and without major protocol deviation according to the main study protocol. 2. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from pediatric patients.
EXCLUSION CRITERIA	1. 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®]). 2. Change in medical condition during the treatment period (such as, but not limited to, occurrence of a malignancy during the course of study, development of a serious inter-current critical illness, a severe adverse drug reaction, etc.) 3. Unresolved drug related (MOD-4023 or Genotropin®) SAE from the treatment period as per MM judgement.
STATISTICAL ANALYSIS	STATISTICS: 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: morning blood fasting glucose, fasting insulin level, HbA1c; • Thyroid (endocrinology) status; • Parameters of Lipid metabolism/profile; morning fasting total cholesterol, triglycerides, HDL and LDL; • All other safety hematology, biochemical parameters and urinalysis; • Physical examination; • Fundoscopy results - if performed (normal/abnormal); • Vital signs; • ECG. 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 OLE year 1 and to previous values from OLE year 2 onwards). Biochemical Endpoints • CCI IGF-1 SDS levels on day 4 (-1) after MOD-4023 dosing across study visits. The assessment of safety and efficacy (auxology/clinical and biochemical endpoints) during the 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 OLE will be provided.
PATIENT DIS-CONTINUATION RULES	Specific discontinuation criteria during the OLE: • When the patient's annualized growth rate is ≤ 2 cm/12 months, and Girls with a BA of ≥15 years and boys with a BA of ≥17 years. • Positive urine pregnancy test or confirmed pregnancy. In case of pregnancy, the study drug should be discontinued, and the 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 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.

TABLE OF CONTENTS

GLOSSARY

Abbreviation	Definition
Ab	Antibody
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	Adverse Event
ALT	Alanine Aminotransaminase (SGPT)
AST	Aspartate Transaminase (SGOT)
BA	Bone Age
BM	Bone Maturation
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CA	Chronological Age
CI	Confidence Interval
cm	Centimeter
CPK	Creatinine Phosphokinase
CS	Clinically Significant
day 4(-1)	Day 3 or 4 Post-injection
DDAVP	Desmopressin
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
FT4	Free Thyroxine
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GH	Growth Hormone
GHD	Growth Hormone Deficiency
HbA1C	Glycated Hemoglobin (Hemoglobin A1C)
HCT	Hematocrit
HDL	High Density Lipoproteins
HGB	Hemoglobin
hGH	Human Growth Hormone

Abbreviation	Definition
HV	Height Velocity
HV SDS	Height Velocity Standard Deviation Score
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor-1
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator's Site File
kg	Kilogram
LDH	Lactate Dehydrogenase
LDL	Low Density Cholesterol
LH	Luteinizing Hormone
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram
mL	Milliliter
MM	Medical Monitor
ng	Nanogram
No.	Number
OLE	Open Label Extension
PEN	Single patient use, multi-dose, disposable pre-filled pen containing 20 or 50 mg/mL MOD-4023
PI	Principal Investigator
QA	Quality Assurance
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
SDS	Standard Deviation Score
SUSAR	Suspected Unexpected Serious Adverse Reaction
t	Time
Tmax	Time Of Maximum Concentration
TSH	Thyroid Stimulating Hormone

Abbreviation	Definition
UK	United Kingdom
USA	United States of America
WBC	White Blood Cells
WHO	World Health Organization
wk	Week

1 INTRODUCTION

1.1 Overview

Long term safety and efficacy of MOD-4023 has been demonstrated in an ongoing phase 2 study in which 48 pediatric GHD patients have been treated long term since the study intiation in 2013. Patients who have completed 12 months treatment in the main study of CP-4-009 will be offered to switch to once a week adminstration of MOD-4023 (from the daily Genotropin® group) or continue with the weekly MOD-4023.

1.2 Study Rationale

Over 80% of the patients that started in the phase 2 CP-4-004 study for the treatment of pediatric growth hormone deficiency are in the fourth and fifth years of dosing with the weekly MOD-4023. Robust efficacy of MOD-4023 continues year after year and safety profile of MOD-4023 in the treatment of pediatric GHD patients has been unremarkable.

Patients who enroll in the CP-4-009 study are of the similar exclusion/inclusion criteria as those patients who have been treated in the CP-4-004 clinical trial with MOD-4023. There is adequate evidence of long term efficacy and safety of weekly MOD-4023 treatment to support the continuation of treating pediatric GHD patients who are and would be enrolled in the CP-4-009 study. The proposed extension of CP-4-009 clinical trial will enable the collection of continuous efficacy and long term safety data of weekly treatment with MOD-4023 in Japanese pediatric growth hormone deficiency patients.

The second objective of this extension study is to evaluate the safety switch of daily growth hormone treatment to weekly MOD-4023 treatment in Japanese pediatric GHD patients. In the CP-4-009 study, half of the patients (estimated to be 22) are treated with daily Genotropin®. Data collected from patients who would be switched in this study, will provide information to assist endocrinologists in assessing the risk and benefit of patients who consider switching from current daily rhGH treatment to weekly MOD-4023.

1.3 Rationale for Study Dose

In part, the extension study is to allow patients who have been treated with MOD-4023 at the weekly dose of 0.66 mg/kg, to continue the same treatment until the product becomes available in the market and to collect long term safety data. The other objective is to offer patients who have been randomized to daily rhGH to be treated with weekly MOD-4023. The dose of 0.66 mg/kg has been demonstrated to be safe and effective in the CP-4-004 clinical trial in pediatric GHD patients for over four years, including switches from daily Genotropin® injection to 0.66 mg/kg/week in 11 patients. As well this dose is being used in a multi-national pediatric study CP-4-006 which was initiated in April 2017.

2 STUDY OBJECTIVE

To demonstrate the safe switch of patients who have completed 12 months treatment with daily Genotropin® to weekly MOD-4023, and to document long term safety and efficacy of weekly MOD-4023 treatment in an open-label extension (OLE).

3 STUDY DESIGN

The study will consist of a single-arm, open-label extension (OLE) study with weekly MOD-4023 injections.

Patients who have successfully completed 12 months of treatment in study CP-4-009 and meet the OLE inclusion/exclusion criteria of this protocol will be eligible to rollover into this OLE study. Patients who received Genotropin® for 12 months during the main study CP-4-009, will be switched to receive a dose of 0.66 mg/kg/week of MOD-4023 (no less than one day after cessation of Genotropin® treatment). Patients who received MOD-4023 for 12 months during the main study will continue in the OLE with the same dose (mg/kg/wk) of MOD-4023.

During the OLE study, MOD-4023 dose will be adjusted based on the patients' body weight every three 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). During the OLE dose reduction for IGF-1 level >+2.0 SDS will be made following consultation with the Study MM on an individual patient basis

The key safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) once every 6 months.

The study will be conducted, subject to Sponsor, Regulatory Authority and IRB approvals. Study drug will be available until study discontinuation or marketing approval.

4 STUDY POPULATION

Pediatric GHD patients who completed the 12 months of treatment in accordance with the CP-4-009 main study are eligible to enter into this open label extension study.

4.1 Inclusion Criteria for the OLE Study

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

1. Completion of the main study (12 months of treatment) with adequate compliance and adherence to the visit schedule and without major protocol deviation according to the main study protocol.
2. Willing and able to provide written informed consent of the parent or legal guardian of the patient and written assent from pediatric patients.

4.2 Exclusion Criteria for the OLE Study

1. 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 Attention-Deficit/Hyperactivity Disorder (ADHD) drugs or hormone replacement therapies (thyroxin, hydrocortisone, testosterone, estrogen/progesterone, desmopressin [DDAVP®]).
2. Change in medical condition during the treatment period (such as, but not limited to, occurrence of a malignancy during the course of study, development of a serious inter-current critical illness, a severe adverse drug reaction, etc.).
3. Unresolved drug related (MOD-4023 or Genotropin®) SAE from the study CP-4-009 as per Global Study MM judgement.

4.3 Patient Identification

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

4.4 Removal, Replacement or Early Withdrawal of Patients from Therapy or Assessment

The patient's participation in this OLE study may be discontinued due to the reasons indicated in the main study protocol Section 4.4. Additional specific discontinuation criteria during the OLE are listed below:

- When the patient's annualized growth rate is ≤ 2 cm/12 months, and Girls with a BA of ≥15 years and boys with a BA of ≥17 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 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.

4.5 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 recommend to terminate the study.

5 INVESTIGATIONAL PLAN AND STUDY PROCEDURES

A schedule of activities for this study is shown in Appendix A of this OLE protocol. No OLE protocol related procedures, including the cessation of prohibited concomitant medications should be performed before patients provide written[a] 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 OLE Study Procedures

Visit 10 – EOS Visit (Month 13/Wk 56 (+1 week)) – Only for patients not continuing on into the OLE study.

Patients not continuing in the OLE study will be contacted 4 weeks (+ 1 week) after Visit 9 (inclusive of 9.1) in order to obtain safety related information (see questionnaire in Appendix I of the main study protocol).

OLE Rollover Period

After successful completion of 12 months of treatment in the CP-4-009 main study and meeting the OLE inclusion/exclusion criteria of this protocol, and upon receipt of necessary Regulatory and IRB approvals, patients will be eligible to rollover into the OLE study with MOD-4023 treatment. An informed consent/assent will be obtained from patients and/or parents or legal/authorized guardian for this extension study.

Patients who do not qualify to continue in the trial or who are not interested in continuing into the OLE should complete the End of Treatment Visit, which is equivalent to visit 9/9.1, and should complete a phone interview for visit 10 within 4 weeks (+1 week) to complete End of Study Assessments according to the CP-4-009 main study protocol schedule of activities.

Patients who received MOD-4023 during the main CP-4-009 study will continue in the OLE with the same dose (mg/kg/week) of MOD-4023, adjusted for body weight. For these patients, study visits will take place every three months on day 4 (-1 day) post-dose. Pre-dose assessments will be taken at month 6 and month 12 during the first year. These patients will consent to the OLE preferably during Visit 8 (week 39) of the main study to ensure availability of MOD-4023 at their first visit of the OLE study. If necessary, informed consent can be obtained at main study Visit 9/9.1/OLE Visit 9.2 (week 52/OLE Baseline). MOD-4023 patients will continue treatment and receive study drug at OLE Visit 9.2, skip Visit 10 (close out or end of trial) main study, and have a phone interview at OLE Visits 11, 12, and 13 as described in the schedule of activities. Visits will occur every 3 months thereafter beginning at Visit 14. All patients will be provided with a patient diary throughout the trial as described in the Schedule of Activities.

Patients who received Genotropin® during the CP-4-009 main study will complete the main study assessments and will be switched to MOD-4023 at Visit 9. Dosing of MOD-4023 treatment at 0.66 mg/kg/week will begin 1 day after cessation of Genotropin® treatment (at Visit 9/OLE Visit 9.2). Patients should start MOD-4023 one day after cessation and no more than 2 weeks after cessation of Genotropin®. These patients will consent to the OLE preferably during Visit 8 of the main study to ensure availability of MOD-4023 at their first

[a] Illiterate patients should provide their consent in a method that is accepted according to local regulations.

visit of OLE study (Visit 9/OLE Visit 9.2). Patients will skip visit 10 (close out or end of trial of the main study) and have additional onsite subsequent visits at Visit 11 (Month 12.5, Day 10 post first MOD-4023 dose [10+4 days]), Visit 12 (1 month post first MOD-4023 dose (Month 1 [±1wk]), and Visit 14 (Month 3 [±1wk]). A phone interview will occur at OLE Visit 13 (Month 2 [±1wk]). Visits will occur every three months thereafter, until study closure. All patients will be provided with a patient diary throughout the trial as described in the Schedule of Activities.

For all patients switching from Genotropin® to MOD-4023, drug will be dispensed and the following assessments will be performed at OLE Visit 9.2:

- MOD-4023 and associated diaries 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 pen device and diary completion.
- Local tolerability after first dose administered at site.
- Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche).

Patients who experience a delay for any reason between completion of the main study and entry into the OLE may have to temporarily stop treatment. If initiation/re-initiation of treatment occurs less than 90 days after Visit 9, 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 OLE after confirmation of availability of all required baseline OLE assessments (Visit 9). In addition to the onsite training, dose administration of MOD-4023, and local tolerability assessment, the following tests and assessments below must be repeated at the time of the unscheduled visit at the site:

- Overall health status assessment, including complete physical examination and vital sign assessments.
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin, HbA1c.
- Assessment of thyroid: TSH, FT4.
- Parameters of lipid metabolism: morning fasting total cholesterol, LDL, triglycerides, and HDL.
- Assessment of anti-MOD-4023 Ab for all patients .
- Assessment of biochemical markers: CCI IGF-1 SDS.
- Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche).

OLE TREATMENT – YEAR 1

During the first year of OLE treatment, the following assessments will be conducted on Day 4 (-1 day) post dose during onsite visits for patients making the switch from Genotropin® to MOD-4023 (Visits 11 – 12):

- Safety laboratory tests: chemistry, hematology, and urinalysis (only Visit 12)
- Overall health status assessment, including complete physical examination and vital signs assessment
- 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: CCI calculate the related IGF-1 SDS (only Visit 12)
- CCI
- Assessment of anti-MOD-4023 Ab.
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).
- Dispense study drug and patient diary (only Visit 12).[a]
- Patient diary review, study drug return & accountability (only Visit 12).

For patients making the switch from Genotropin® to MOD-4023, a phone interview will be conducted at Visit 13.

Existing MOD-4023 patients will have a phone interview at Visits 11, 12, and 13 as indicated in the schedule of activities to ask about AEs and concomitant medications. These visits will be completed using the questionnaire in Appendix I of the main study protocol.

The following assessments will be conducted on day 4 (-1 day) post-dose for all patients during the first year of OLE treatment at months three (Visit 14), six (Visit 15), nine (Visit 16), and twelve (Visit 17):

- Pre-dose assessment of MOD-4023 serum levels and anti-MOD-4023 Ab (Visit 15 and Visit 17 only).
- Safety laboratory tests: chemistry, hematology, and urinalysis
- Auxology measurements: Height (average of 3 consecutive measurements) and body weight measurements (see Appendix E in the main protocol for height instructions)
- Overall health status assessment, including complete physical examination and vital signs assessment
- Individual dose adjustment based on weight
- AEs, local tolerability, and concomitant medications.

[a] Patient Diary will be re-issued for further completion.

- Urine pregnancy test at every visit once a female patient reports first menstrual cycle (menarche).
- Assessment of biochemical markers: CCI calculate the related IGF-1 SDS
- CCI
- Post-dose assessment of anti-MOD-4023 Ab (Visit 14 and Visit 16 only).
- Fundoscopy (if there are signs or symptoms indicative of benign intracranial hypertension).
- Dispense study drug and patient diary.
- Patient diary review, study drug return & accountability.
- Assessment of thyroid function: TSH, FT4 (except Visit 16).
- Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin, HbA1c (except Visit 16).
- Parameters of lipid metabolism: morning fasting cholesterol, triglycerides, high density lipoprotein (HDL), and low density lipoprotein (LDL) (except Visit 16).

OLE TREATMENT – YEAR 2 UNTIL STUDY CLOSURE

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

- Auxology measurements: Height and body weight measurements.
- 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).
- Dispense study drug and patient diary.
- Patient diary review, study drug return & accountability.

The following assessments will be conducted for all patients on day 4 (-1 day) post-dose every six months:

- Assessment of biochemical markers: CCI related IGF-1 SDS calculation
- Safety laboratory tests: chemistry, hematology and urinalysis.
- Assessment of thyroid function: TSH, FT4.
- Parameters of glucose metabolism: morning fasting glucose, morning fasting insulin, HbA1c.

- Parameters of lipid metabolism: morning fasting cholesterol, triglycerides, HDL, and LDL.
- Assessment of MOD-4023 serum levels.
- Assessment of anti-MOD-4023 Ab.

OLE TREATMENT – ANNUALLY FROM YEAR 1 UNTIL STUDY CLOSURE/COMPLETION

Additional assessments will be performed once a year, on day 4 (or -1 day) post-dose at month 12 (OLE Visit 17) and Year 2 onward:

- ECG
- Bone age
- Pubertal status (according to Tanner stages)
- For males that are 13 years and older: LH, FSH and testosterone will be analyzed. For females that are 12 years and older: LH, FSH and estradiol will be analyzed (from OLE treatment year 2 until study closure).
- Pre-dose and post-dose assessment of MOD-4023 serum levels annually
- Pre-dose assessment of Abs to MOD-4023 annually

Year 1 (including end of study (EOS) during year 1): ECG should be conducted around the time of maximum concentration (Tmax) (7-12 hours post-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. An ECG must still be obtained even if patients do not take the final dose.

For EOS from 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 4 weeks [± 1 week] after EOS/ET visit in order to obtain safety related information (local tolerability, AEs, prior and concomitant medications).

5.2 Early Discontinuation Study Visit

If, during the OLE, a patient discontinues prematurely from the study for the reasons specified in Section 4.4, the same procedures for OLE End of Study (EOS)/ET will be conducted.

5.3 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.

5.4 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 metabolism, thyroid function, CCI, immunogenicity and urinalysis). AEs and concomitant medication use will be assessed at every visit. Adverse events that meet the definition of a serious adverse event (SAE) must be reported within 24 hours of awareness to the sponsor and designee. SAE evaluation and reporting is detailed in the main study protocol (section 7.2). Physical examination and safety laboratory assessments will be performed according to the schedule of activities in Appendix A.

TREATMENT COMPLIANCE

OLE Study drug return accountability and patient diary will be reviewed at each visit for treatment compliance from previous visits (except scheduled telephone visits).

ECG

During the OLE, ECG (preferably 12-lead) will be performed annually every 12 months until study closure.

Year 1 (including end of study (EOS) during year 1): ECG should be conducted around the time of maximum concentration (Tmax) (7-12 hours post-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. An ECG must still be obtained even if patients do not take the final dose.

For EOS from 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.

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.

LABORATORY ASSESSMENTS

All routine clinical laboratory assessments will be performed by local central laboratory (LSI Medience Corporation) according to the schedule in Appendix A of this OLE protocol. 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.

2. Serum biochemistry: glucose, total protein, albumin, total bilirubin, ALT (SGPT), AST (SGOT), GGT, LDH, CPK, alkaline phosphatase, sodium, potassium, calcium, phosphate, BUN, creatinine.
3. Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.
4. Lipid metabolism: morning fasting cholesterol, LDL, triglycerides, and HDL.
5. Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel), fasting insulin and HbA1C.
6. Assessment of thyroid: TSH, FT4.
7. Immunogenicity (will be performed by Intertek, San Diego): antibodies to MOD-4023 for all patients during the OLE.
8. CCI for all patients during the OLE.
9. CCI for all patients during the OLE (will be performed by Intertek, San Diego).
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.

5.5 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 weeks 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 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 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.

6 INVESTIGATIONAL PRODUCT (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 CCI

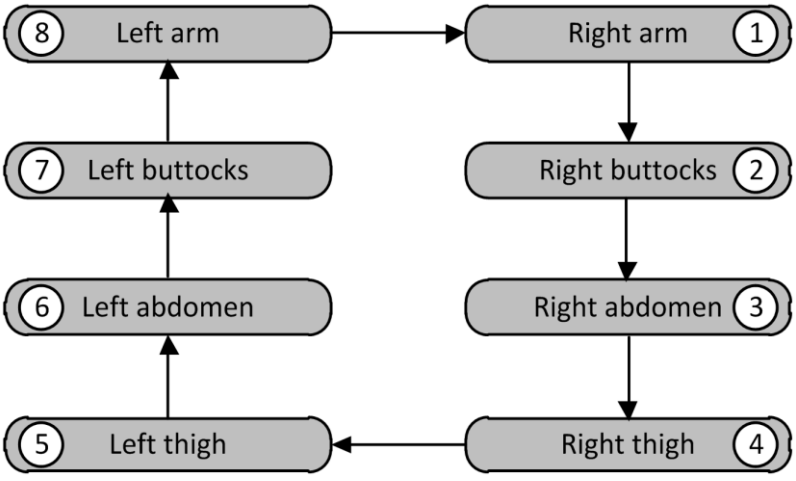
6.2 Reference Therapy

Genotropin® is a daily GH, which will be used as the reference therapy during the main study, but not used in the OLE study. No additional dosing with Genotropin® is allowed after the patient completes the main study Visit 9 and should be switched to MOD-4023 according to this protocol. If the patient wishes to continue on Genotropin® after the main study is completed, they will not be allowed to participate in the OLE study.

6.3 Study Drug Administration

MOD-4023 will be administered as a SC injection 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 in Figure 1).

Figure 1 Recommended rotation of injection sites for MOD-4023



The starting MOD-4023 dose for the administration will be 0.66 mg/kg/wk. All patients on Genotropin® that complete the main study and continue into the OLE will start treatment with MOD-4023 at 0.66 mg/kg/wk.

If a patient misses the weekly scheduled dose of MOD-4023, the patient should inject the dose as soon as possible as long as it is less than or equal to 72 hours from the time of the patient's usual injection. If more than 72 hours have passed, then the patient should skip the

injection. In either case, the patient should return to the regular injection day the following week.

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 week 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 CCI 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 week should be rescheduled, to meet the required post dosing interval.

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. Split dose from the same PEN: This may occur when the prescribed dose exceeds the maximum dose which can be selected according to the PEN amount. The maximum dose per injection for the MOD-4023 24 mg pen is 12 mg and the maximum dose injection for the MOD-4023 60 mg pen is 30 mg. The patient's first injection would be the maximum dose and the second injection would be the remaining dose of the full prescribed dose.

   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 from 2 PENS (the current PEN and a new PEN): This may occur when the amount of medication remaining in the pen is not sufficient for the full prescribed dose.

   For example, if the full prescribed dose is 25.0 mg and the volume left in the current PEN is 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 completes the patient diary for each of the 2 injections administered. When the second injection is from a new PEN the new pen must be primed accordingly to the Instructions for Use provided.

Further details are provided in the Patient Diary.

Missed, delayed, or split doses should be reported in the Patient Diary and the appropriate eCRF.

6.4 Dose Modification Plan

The dose of MOD-4023 will be assessed every 3 months and adjusted based on patient's body weight. Doses will be calculated by the Electronic Data Capture (EDC) system and will be rounded – either up or down – to the closest PEN increment (0.2 mg increments in 20 mg/mL pens and 0.5 mg increments in 50 mg/mL pens).

Doses may be decreased for safety reasons (which will be based on the severity of AEs or repeated, elevated levels of IGF-1 SDS).

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.

During the OLE dose reduction for IGF-1 level >+2.0 SDS will be made following consultation with the Study MM on an individual patient basis.

If AEs are defined as "severe" AND drug-related, dose reduction will be initiated upon discussion with the Study MM and DSMB.

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

The key safety data will be reviewed by an independent and external DSMB approximately every 6 months during the 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. DSMB review will also include review of number or percentage of patients requiring dose reductions due to AEs.

7 STATISTICS

7.1 Data Analysis

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: morning blood fasting glucose, fasting insulin level, HbA1c;
- Thyroid (endocrinology) status;
- Parameters of lipid metabolism/profile; morning fasting total cholesterol, triglycerides, HDL and LDL;
- All other safety hematology, biochemical parameters and urinalysis;
- Physical examination;
- Fundoscopy results - if performed (normal/abnormal);
- Vital signs;
- ECG.

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 OLE year 1 and to previous values from OLE year 2 onwards).

Biochemical Endpoints

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

The assessment of safety and efficacy (auxology/clinical and biochemical endpoints) during the 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 OLE will be provided.

8 STUDY ADMINISTRATION

8.1 Participating Centers

Approximately 25-35 sites will participate in the OLE study. A list of all participating sites will be kept in the electronic study master file.

8.2 Study Completion

The goal for the OLE study is for every patient to complete the first year of the OLE (a completion of 24 months on IP). The OLE study will continue until product approval, to collect additional safety and efficacy information. Study completion will be defined when regulatory approval and post-marketing data collection is defined or if the sponsor decides to terminate the study early.

9 OLE SECTIONS PERTAINING TO MAIN STUDY PROTOCOL

The OLE phase of the study is a continuation of the main study with patients rolling into the OLE with no or minimum interruption of treatment. This protocol serves to describe the purpose, treatment criteria, and procedures specifically for the OLE phase of the clinical trial. The below sections and Appendix of the main study continue to be relevant to the OLE as they are considered to have the same information for both the main study and the OLE study. Please reference the main study protocol for more information on the sections below.

- Section 1.1 Growth Hormone Deficiency
- Section 1.2 Current Therapy
- Section 1.3 – Investigational Therapy
    - 1.3.1 – Clinical Studies (only)
- Section 5.3 Efficacy Assessments and Endpoints
- Section 5.5 Safety Assessments and Endpoints
    - 5.5.1 – AEs
    - 5.5.2 – Local Injection Site Reactions
    - 5.5.3 – Concomitant Medication Use
    - 5.5.5 – Vital Signs
    - 5.5.6 – Physical Examination
    - 5.5.8 – Fundoscopy
- Section 6.5 Shipment and Storage Condition of Investigational Product
- Section 6.6 Accountability and Compliance of Investigational Product
- Section 6.7 Prior and Concomitant Therapy
- Section 7.0 Safety and Pharmacovigilance
- Section 7.1 Adverse Event
- Section 7.2 Serious Adverse Event
- Section 7.3 Definition of an Unexpected AE
- Section 7.4 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)
- Section 7.5 Notification about Serious or Unexpected AEs
- Section 7.6 Independent DSMB
- Section 7.7 Medication Errors
- Section 7.8 Medical Device Complaint
- Section 8.6 Efficacy Analysis
- Section 9.0 Ethics
- Section 9.1 IRB
- Section 9.2 Ethical Conduct of the Study

- Section 9.3 Protocol Revisions and/or Deviations
- Section 9.4 Patient Information and Consent
- Section 9.5 Patient Insurance
- Section 9.6 Informing the General Practitioner
- Section 9.7 Personal Data Protection
- Section 10.0 Quality Control and Quality Assurance
- Section 10.1 Audits and Inspections
- Section 10.2 Study Monitoring
- Section 10.3 Quality Laboratory Standards
- Section 10.4 Data Management
- Section 11.0 Study Administration
- Section 11.2 Clinical Study Supplies
- Section 11.3 ISF
- Section 11.5 Final Report
- Section 11.6 Retention of Study Records
- Section 11.7 Confidentiality and Publication
- Section 12.0 References
- Appendix E: Instructions for Obtaining Height Measurements
- Appendix F: Instructions for Obtaining X-Ray Films
- Appendix G: Injection Site Assessment Table (Local Reactions) and Pain Assessment
- Appendix H: Declaration of Helsinki (2013)
- Appendix I: Phone Interview
- Appendix J: Clinically Comparable Doses of Inhaled Corticosteroids

APPENDIX A: STUDY FLOW CHART / SCHEDULE OF ACTIVITIES

OLE:

Study Procedure	OLE – Year 1							
Study Day (± in dy/s)		**OLE 10 (+4)[a]**						
Study Wk (± in wk/s)	**52**	**54 (±1)**	**56 (±1)**	**60 (±1)**	**65 (±1)**	**78 (±2)[b]**	**91 (±2)**	**104 (±2)[b] 2 years**
Study Month (OLE Study Month)	**12**	**12.5**	**13 (1 mth)**	**14 (2 mth)**	**15 (3 mth)**	**18 (6 mth)**	**21 (9 mth)**	**24 (12 mth)**
Study Visit	**9.2[c]**	**11[d]**	**12[d]**	**13**	**14**	**15**	**16**	**17**
Auxology measurements [e]					X	X	X	X
Physical examination and vital signs		X	X		X	X	X	X
ECG								X[f]
Pubertal status (Tanner stages)								X
Urine pregnancy test for girls reporting 1st menstrual cycle	X	X	X		X	X	X	X
BA (TW2 method using central bone age reader)								X
Dispense study drug and patient diary	X		X[g]		X	X	X	X
Individual dose adjustment					X	X	X	X
Patient diary review, study drug return & accountability			X		X	X	X	X
Local tolerability	X	X	X		X	X	X	X
AEs		X	X		X	X	X	X
Prior & concomitant medications		X	X		X	X	X	X

[a] If visit occurs on dosing day (day 14), procedures should be performed prior to dosing.
[b] Pre- and post- dose assessments may be performed on separate days that will be appropriately recorded in the EDC.
[c] If continuing to the OLE, study drug (MOD-4023) and patient diary must be dispensed during the same time as the main study Visit 9/9.1.
[d] Patients switching from Genotropin® will have an onsite visit, and existing MOD patients will have a phone interview at this visit.
[e] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.
[f] ECG will be conducted at 7-12 hours post-dose.
[g] Patient Diary will be re-issued for further completion.

Study Procedure	OLE – Year 1							
Study Day (± in dy/s)		**OLE 10 (+4)[a]**						
Study Wk (± in wk/s)	**52**	**54 (±1)**	**56 (±1)**	**60 (±1)**	**65 (±1)**	**78 (±2)[b]**	**91 (±2)**	**104 (±2)[b] 2 years**
Study Month (OLE Study Month)	**12**	**12.5**	**13 (1 mth)**	**14 (2 mth)**	**15 (3 mth)**	**18 (6 mth)**	**21 (9 mth)**	**24 (12 mth)**
Study Visit	**9.2[c]**	**11[d]**	**12[d]**	**13**	**14**	**15**	**16**	**17**
Phone Interview per Appendix I		X[h]	X[h]	X				
Fundoscopy		ONLY if there are signs or symptoms indicative of benign intracranial hypertension						
Laboratory Assessments								
Hematology [i], chemistry [j], & urinalysis[k]			X		X	X	X	X
CCI IGF-1 SDS			X		X	X	X	X
CCI		X	X		X	X[l]	X	X[l]
Thyroid function (TSH, fT4)					X	X		X
Glucose metabolism [m]					X	X		X
Lipid profile [n]					X	X		X
LH, FSH and testosterone [o]								X
LH, FSH and estradiol [p]								X
Abs to MOD-4023		X	X		X	X[q]	X	X[q]
Blood volume (mL)	N/A	3	9	0	9	13	9	16

[h] No phone interview for Genotropin® patients that switch to MOD-4023. For existing MOD-4023 patients: AE and concomitant medication review only required by phone interview at this visit.
[i] Hematology: RBC Count; HGB; HCT; MCH; MCHC; MCV; WBC Count and Differential; and Platelet Count
[j] Chemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; sodium, potassium, calcium, phosphate; BUN, creatinine.
[k] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.
[l] Pre-dose and post-dose assessment of MOD-4023 serum levels.
[m] Glucose metabolism: morning fasting glucose and insulin; HbA1c.
[n] Lipid profile: morning fasting cholesterol, LDL, triglycerides, and HDL.
[o] For male patients that are at the age of 13 years and above.
[p] For female patients that are at the age of 12 years and above.
[q] Pre-dose assessment of Abs to MOD-4023.

Study Procedure	OLE – Year 2 until study closure					Follow-up
Study Day (± in dy/s)					EOS/ET[r]	4 Weeks (±1 Week) following EOS/ET
Study Wk (± in wk/s)	117 (±2)	130 (±2) 2.5 years	143 (±2)	156 (±4) 3 years		
Study Month	27	30	33	36		
Study Visit	18, 22…	19, 23…	20, 24…	21, 25…		
Auxology measurements [s]	X	X	X	X	X	
Physical examination and vital signs	X	X	X	X	X	
ECG				X[t]	X[t]	
Pubertal status (Tanner stages)				X	X	
Urine pregnancy test for girls reporting 1st menstrual cycle	X	X	X	X	X	
BA (TW2 method using central bone age reader)				X	X	
Dispense study drug and patient diary	X	X	X	X		
Individual dose adjustment	X	X	X	X		
Patient diary review, study drug return & accountability	X	X	X	X	X	
Local tolerability	X	X	X	X	X	
AEs	X	X	X	X	X	
Prior & concomitant medications	X	X	X	X	X	
Phone Interview per Appendix I						X
Fundoscopy	ONLY if there are signs or symptoms indicative of benign intracranial hypertension					
Laboratory Assessments						
Hematology [u], chemistry [v], & urinalysis[w]		X		X	X	
CCI IGF-1 SDS		X		X	X	
CCI		X		X[x]	X[x]	
Thyroid function (TSH, fT4)		X		X	X	
Glucose metabolism [y]		X		X	X	

[r] Pre- and post- dose assessments may be performed on separate days that will be appropriately recorded in the EDC.
[s] Actual height (mean of three consecutive measurements per patient per visit) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.
[t] ECG will be conducted at 7-12 hours post-dose for EOS during year 1. ECG can be conducted at any time for EOS from year 2 until EOS.
[u] Hematology: RBC Count; HGB; HCT; MCH; MCHC; MCV; WBC Count and Differential; and Platelet Count
[v] Chemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; sodium, potassium, calcium, phosphate; BUN, creatinine.
[w] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.
[x] Pre-dose and post-dose assessment of MOD-4023 serum levels annually (and at EOS/ET).
[y] Glucose metabolism: morning fasting glucose and insulin; HbA1c.

Study Procedure	OLE – Year 2 until study closure					Follow-up
Study Day (± in dy/s)					EOS/ET[r]	4 Weeks (±1 Week) following EOS/ET
Study Wk (± in wk/s)	117 (±2)	130 (±2) 2.5 years	143 (±2)	156 (±4) 3 years		
Study Month	27	30	33	36		
Study Visit	18, 22…	19, 23…	20, 24…	21, 25…		
Lipid profile [z]		X		X	X	
LH, FSH and testosterone [aa]				X	X	
LH, FSH and estradiol [bb]				X	X	
Abs to MOD-4023		X		X[cc]	X[cc]	
Blood volume (mL)	0	9	0	16	16	0

[z] Lipid profile: morning fasting cholesterol, LDL, triglycerides, and HDL.
[aa] For male patients that are at the age of 13 years and above.
[bb] For female patients that are at the age of 12 years and above.
[cc] Pre-dose assessment of Abs to MOD-4023 annually (and at EOS/ET).