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Safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children

[redacted]

EUDRACT NUMBER: 2011-004553-60

Drug Code No.:	**MOD-4023**
Drug Class:	**Long Acting Human Growth Hormone**
Investigational Phase:	**Phase 2**
Protocol No.:	**CP-4-004**
Protocol Version/Date:	**Final 1.0/ 27 October 2011**
Protocol Version/Date:	**Final Version 2.0/ 15 May 2012, Global Amendment 1**
Protocol Version/Date:	**Final Version 3.0/ 26 June 2012, Global Amendment 2**
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Protocol Version/Date:	**Final Version 8.0 / 3 April 2016, Global Amendment 7**
Protocol Version/Date:	**Final Version 9.0 / 25 April 2016, Global Amendment 8**
Protocol Version/Date:	**Final version 10.0 / 03 Oct 2017, Global Amendment 9**

[redacted]

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CONFIDENTIALITY STATEMENT

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PREVIOUS VERSIONS

Version 1.0/ 27 October 2011
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Version 6.0 /01 September 2013
Version 7.0 / 26 January 2015
Version 8.0 / 3 April 2016
Version 9.0 / 25 April 2016

Protocol Synopsis

STUDY TITLE:	Safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children.
PROTOCOL NUMBER:	CP-4-004
CLINICAL STUDY LOCATION:	The main study is conducted in 7 countries (Hungary, Bulgaria, Belarus, Ukraine, Russia, Greece and USA), and at 14 sites. The extension study is conducted in all countries except Bulgaria and Greece.
STUDY PHASE:	Phase 2
THERAPEUTIC INDICATION:	MOD-4023 is a long-acting modified recombinant human growth hormone which utilizes the C-terminal peptide (CTP) technology indicated for treatment of children with growth failure due to growth hormone deficiency.
PRIMARY STUDY OBJECTIVES:	**The primary objective is:** To compare the safety, efficacy, and tolerability of three MOD-4023 doses to that of a commercially available standard daily recombinant human growth hormone (r-hGH) formulation, in pre-pubertal children with growth failure due to insufficient secretion of endogenous growth hormone.
SECONDARY STUDY OBJECTIVE:	**The secondary objectives are**: 1. To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) profiles of 3 different doses of MOD-4023 in pre-pubertal growth hormone deficient (GHD) children. 2. To select the optimal dose of MOD-4023 for the subsequent phase 3 study on the basis of safety and efficacy.
NUMBER OF PATIENTS:	Estimated recruitment will be up to 56 patients (up to 14 patients/cohort) into the Main Study. Patients will be divided into two subgroups: Up to 40 patients with peak serum GH levels after stimulation test [redacted] ng/ml and up to 16 patients with peak serum GH levels after stimulation test [redacted] and [redacted] ng/ml. Patients who completed 12 months of treatment in the Main Study and continued to the 12-month Open Label Extension (OLE) period will be eligible to continue into the Long-Term OLE (LT-OLE) period and Long-Term OLE PEN (LT-OLE-PEN) periods until marketing approval in their country, subject to an annual notification to local EC/IRB of continuation of study, where applicable.
DURATION OF STUDY:	The duration of the Main Study is expected to be 12 months for each patient. The OLE period duration will be based on the initial extension of 12 months of active treatment for all patients completing the Main Study which will be extended to LT-OLE and to LT-OLE-PEN on a yearly basis until marketing approval

	in each country. The yearly extension notification will be submitted to local EC/IRB, where applicable
TEST DRUG:	MOD-4023 is a long-acting modified recombinant human growth hormone which utilizes the CTP technology. In the Main Study and OLE, MOD-4023 will be provided as a solution for subcutaneous (SC) injection containing [redacted] or [redacted] mg protein[1]/ml **In the LT-OLE-PEN period,** MOD-4023 will be provided as a solution for injection containing [redacted] or [redacted] mg/mL MOD-4023 in a single patient use, multi-dose, disposable pre-filled pen (PEN).
REFERENCE DRUG (main study):	Genotropin® 5.3 mg is dispensed in a two-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 Pen®) will be used for administration of the drug. Active comparator will only be administered in the Main Study.
STUDY DRUG ADMINISTRATION:	The investigational product will be administered preferably in the morning hours once a week and the comparator (Genotropin) will be administered in the evening hours once a day. Both drugs will be administered as a SC injection into the region of the upper arms, buttocks, thighs or abdomen. It is recommended that all 8 injection sites are used successively, using a different injection site at each subsequent injection.
STUDY DESIGN AND DOSE REGIMENS:	This is a phase 2, safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children. The study consists of a Screening, Active Treatment periods (Main Study), an OLE period, LT-OLE period and LT-OLE-PEN period: 1. Screening period will last up to 6 weeks 2. Main Study (12 months) Active treatment period: a. Period I: 6 month repeated dose period including PK/PD sampling b. Period II: additional 6 month continuous repeated dosing period 3. OLE (Period III, 12 months) – 12 months continuous repeated dosing of MOD-4023 4. LT-OLE (Period IV – from second year OLE) – long-term annual extension with repeated administration of MOD-4023 until transition to PEN device. During that period all patients will be switched to 0.66 mg/kg/week. 5. LT-OLE-PEN (Period V) - long-term, open-label extension using single patient use, multi-dose, disposable pre-filled pen. Upon regulatory clearance and Sponsor's written approval, study patients should be

[1] MOD-4023 concentration (mg protein/ml) refers to the protein backbone

switched to PEN device. Patient will continue with their current dose. Study duration will be until marketing approval; a yearly extension request will be submitted to local EC/IRB where it is required. An updated informed consent form (ICF) for the LT-OLE-PEN period treatment should be signed during the first PEN transition visit, prior to using the PEN or any other assessments related to the transition to PEN.

SCREENING

The Screening period will last up to 6 weeks.
The following key tests and assessments must be performed and data obtained:

1. Informed consent/assent signature.
2. Data on growth history and current anthropometric measurements (Auxology).
3. Body weight.
4. Medical history, including a description of pituitary deficiencies, concomitant and previous medications.
5. Overall health status assessments – complete physical examination, vital signs, and ECG.
6. Pubertal status (according to Tanner stages).
7. Bone age determination – with the method of Greulich-Pyle using a central bone age reader.
8. Assessment of biochemical markers and stimulation tests:
    - Two different GH stimulation (provocation) tests (insulin tolerance test, with cortisol response to hypoglycemia if insulin stimulation test is chosen/arginine test/clonidine test/glucagon test (with or without propranolol)/L-dopa plus propranolol. Sex-hormone priming will be performed prior to GH-stimulation tests for girls over the age of 8 and for boys over the age of 10. If the patient requires sex hormone priming (due to the age), and both stimulation tests must be performed during the Screening (no historical samples kept, or test was without priming), it is recommended to perform stimulation tests in consecutive setting in one day, or in two consecutive days, to avoid priming the patient twice. Local historical tests without sex-steroid priming will not be accepted for patients that require sex steroid priming according to the protocol
    - Standard Dose Short ACTH test (only if the patient was not previously assessed for the hypothalamus-pituitary-adrenal axis, or if there are clinical or laboratory signs of adrenal insufficiency)
    - Assessment of insulin-like growth factor-I (IGF-I) and IGFBP-3 levels
    - Assessment of anti-hGH antibody levels
    - Assessments of routine safety biochemistry and hematology parameters

- Assessment of hormones (TSH, Free T4, Free T3 and cortisol)
- Assessment of glucose metabolism (fasting insulin, glucose and HbA1C)

9. Head MRI.
10. Fundoscopy.
11. Assessment of karyotype in girls.
12. SHOX (short stature homeobox) gene evaluation in all patients.

Key data and all test results obtained during screening will be reviewed by the Sponsor Medical Monitor prior to randomization of each patient.

Eligible patients will be randomized (central randomization) to one of the three different MOD-4023 doses or to the standard daily r-hGH control group prior to the first injection. The following stratification factors will be considered when adding patients to one of the four treatment groups:

1. Provocation tests peak plasma GH level (patients with peak levels [redacted] ng/ml and patients with peak levels [redacted] ng/ml and [redacted] ng/ml).
2. Patients with peak plasma GH level [redacted] ng/ml will additionally be stratified by:
   a. Chronological age (3-7, above 7)
   b. Height SDS - target height SDS (≤ -3 and > -3)
   c. Peak GH levels [redacted] Patients with peak GH levels [redacted] can be enrolled in the study. However, these patients have a separate randomization list

PERIOD I: SIX MONTH REPEATED DOSE PERIOD

During this period, which will last 6 calendar months, eligible patients will receive weekly doses of MOD-4023 or daily doses of r-hGH, according to the table below. Safety will be assessed throughout this period, and individual growth assessments for each patient will be completed at the end of the period as described below.

TABLE 1: DOSE COHORTS

Cohort	MOD-4023/Genotropin Dose
1	0.25 mg MOD-4023 protein/kg/week equivalent to 0.18 mg hGH/kg weekly injection.
2	0.48 mg MOD-4023 protein/kg/week equivalent to 0.35 mg hGH/kg weekly injection.
3	0.66 mg MOD-4023 protein/kg/week equivalent to 0.48 mg hGH/kg weekly injection.
4	Genotropin: 0.034 mg/kg/day.

In order to introduce naïve patients to the allocated MOD-4023 dose in a gradual manner, a stepwise dose increase will be implemented (see Table 2). All patients

randomized to receive one of the three MOD-4023 doses will start treatment for 2 weeks with the low MOD-4023 dose (0.25 mg/kg). Based on the patient's dose allocation, this will be followed by a dose increase to the next dose level every two weeks until the final allocated dose is reached.

Subsequent to the second dose administration of the targeted dose, limited (population based) PK and PD sampling will be performed as described in Table 2.

TABLE 2: DOSE INCREASE SCHEME FOR MOD-4023 COHORTS

Cohort	Dosing Scheme					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cohort 1	**0.25 mg protein/kg/week** PK/PD sampling					
Cohort 2	0.25 mg protein/kg/week		**0.48 mg protein/kg/week** PK/PD sampling			
Cohort 3	0.25 mg protein/kg/week		0.48 mg protein/kg/week		**0.66 mg protein/kg/week** PK/PD sampling	

During the first 6 weeks of the study, the visit schedule will be as follows:

All Patients:

Visit 1 (Week 1): This visit will take place in the medical center for all patients on the day of the first dose. The following procedures will be performed: physical examination, vital signs, adverse events (AEs), local tolerability, concomitant medications, parameters of glucose metabolism (fasting glucose, insulin, and HbA1C), other hormonal levels (TSH, free T4, free T3, cortisol), antigenicity (anti-MOD-4023 antibodies for cohort 1-3 patients and anti-hGH antibodies for cohort 4 patients), routine safety biochemistry and hematology, patient's height and weight, parameters of lipid metabolism, pubertal status, IGF-I and IGFBP-3 serum levels, baseline MOD-4023 (cohorts 1-3) or hGH (cohort 4) levels, fundoscopy, and training for parents on drug administration. Patients allocated to the MOD-4023 cohorts will be administered the first dose by the study staff in the morning hours. Patients allocated to the Genotropin cohort will be administered the first dose at home in the evening hours.

MOD-4023 Dose Cohorts (Cohorts 1-3):

V2(a-h) – Week 2, V3(a-h) – Week 4 and V4(a-h) – Week 6: Patients allocated to a MOD-4023 dose cohort will be randomized within the cohort into one of three blocks and undergo limited PK/PD sampling (4 samples per patient over a period of one week), according to Table 3 below.

Patients allocated to Cohort 1 will undergo limited PK/PD sampling following the 2nd dose of MOD-4023 (V2a-g – week 2) and return to the medical centers for a single visit 4 days after dosing during week 6 (V4h).

Patients allocated to Cohort 2 will come to the medical centers for a single visit 4 days after dosing during week 2 (V2h), undergo limited PK/PD sampling following the 4th dose of MOD-4023 (week 4: the second dose at the allocated dose level; V3a-g) and return to the medical centers for a single visit, 4 days after dosing, during week 6 (V4h).

Patients allocated to Cohort 3 will come to the medical centers for a single visit 4 days after dosing during weeks 2 and 4 (V2h and V3h) and undergo limited sampling following the 6th dose of MOD-4023 (week 6: the second dose at the allocated dose level, V4a-g).

TABLE 3: MOD-4023 POPULATION PK AND PD SAMPLING SCHEME

Visit (V2, V3, V4)	A			b	c	d	e	F	g
Time after dosing(h)/ Block number	0h	6h	12h	24h	48h	72 h	96 h	120 h	168 h
Block 1									
Block 2									
Block 3									

The following procedures will be performed at visits 2a and 2h, 3a and 3h, and 4a and 4h:

Physical examination, vital signs, AEs, local tolerability, concomitant medications, parameters of glucose metabolism (fasting glucose and insulin; HbA1C only at V4), other hormonal levels (TSH, free T4, free T3, cortisol), routine safety biochemistry and hematology (visits 2a and 2h, 4a and 4h), patient's height and weight, parameters of lipid metabolism, IGF-I and IGFBP-3 serum levels.

Genotropin Cohort (Cohort 4):

Patients allocated to the Genotropin cohort (cohort 4) will return to the medical centers for visits 2 and 4, during the 2nd and 6th week of treatment. The following procedures will be performed:

Physical examination, vital signs, AEs, local tolerability, concomitant medications, parameters of glucose metabolism (fasting glucose and insulin; HbA1C only at V4), other hormonal levels (TSH, free T4, free T3, cortisol), routine safety biochemistry and hematology, patient's height and weight, parameters of lipid metabolism, IGF-I and IGFBP-3 serum levels.

In addition, after the 8th Genotropin dose (start of week 2 of dosing), the patients allocated to the Genotropin cohort will be randomized into one of three blocks and undergo limited PK/PD sampling (4 samples per patient over a period of 24 hours), according to Table 4 below.

TABLE 4: GENOTROPIN POPULATION PK AND PD SAMPLING SCHEME (VISIT 2)

Time after dosing(h)/ Block number	0h	1h	2h	4h	6h	12 h	16 h	20 h	24 h
Block 1	■		■	■			■		
Block 2		■		■	■			■	
Block 3			■		■	■			■

All patients:

Following the first 6 weeks of the study, all patients will visit the hospital on a monthly basis (weeks 10, 14, 18, 22 and 26). Patients allocated to the MOD-4023 dose cohorts (cohorts 1-3) will be asked to return 4 days after MOD-4023 dosing in order to obtain MOD-4023, IGF-I and IGFBP-3 levels and conduct routine safety assessments. In addition, after 5 months of dosing, patients allocated to MOD-4023 dosing will be asked to return to the medical center in the morning hours prior to dosing in order to obtain a trough level MOD-4023 and PD (IGF-I and IGFBP-3) samples. Patients allocated to the Genotropin dose cohort (cohort 4) will be asked to return on any day during the relevant dosing week.

The following assessments will be performed at indicated time-points (detailed scheduling in section 5.1 of the protocol):

Physical examination, vital signs, AEs, local tolerability, concomitant medications, parameters of glucose metabolism (fasting glucose, insulin and HbA1C), other hormonal levels (TSH, free T4, free T3, cortisol), antigenicity (anti MOD-4023 antibodies for cohort 1-3 patients and anti hGH antibodies for cohort 4 patients), routine safety biochemistry and hematology, patient's height and weight, parameters of lipid metabolism, pubertal status, IGF-I and IGFBP-3 serum levels, fundoscopy.

During Period I, the dose of MOD-4023 and r-hGH will be adjusted to the patient's body weight every three months. 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 elevated levels of IGF-I). For patients on MOD-4023, the dose may be decreased based on repeated day 4 levels of IGF-I above +2.0 SDS. For patients on Genotropin, the dose may be decreased based on repeated IGF-I levels above +2.0 SDS.

The study Medical Monitor shall review all AEs from entries in the e-CRF on a weekly basis and all SAE safety reports as received. The key safety data will be reviewed by an independent DSMB approximately every 6 months or on an ad-hoc basis if any safety concerns arise. After completion of Period I each patient will be assessed separately for the growth progress and overall safety. If the growth meets the pre-defined criteria[1] and there are no safety concerns, the

[1] Delta Height SDS at least 0.2

patient will continue with the same dose, otherwise dose modifications will be performed according to the pre-determined rules.

PERIOD II: SIX MONTH CONTINUOUS DOSING PERIOD

The purpose of Period II is to collect an additional 6 months of efficacy and safety data. During period II, patients will be kept whenever it is possible on the originally allocated dose levels; however, the dose may be adjusted for safety reasons throughout the study and/or for efficacy reasons after 6 months of dosing. Patients allocated to the r-hGH dose group will continue their doses as initiated earlier, up to the end of the 12-month treatment period.

Patients will visit the clinic twice during Period II, at months 9 and 12. Period II assessments will include the following at each visit: physical examination, vital signs, AEs, local tolerability, concomitant medications, parameters of glucose metabolism (fasting glucose, insulin, and HbA1C), other hormonal levels (TSH, free T4, free T3, cortisol), routine safety biochemistry and hematology, patient's height and weight, parameters of lipid metabolism (month 12 only), pubertal status (month 12 only), IGF-I and IGFBP-3 serum levels, fundoscopy (month 12 only or earlier if there are signs or symptoms indicative of benign intracranial hypertension), ECG (month 12 only), and bone age (month 12 only).

PERIOD III: 12 Months OPEN LABEL EXTENSION (OLE) PERIOD

All patients who completed 12 months of treatment in the Main Study will be eligible to continue to a 12-month Open Label Extension (OLE) period. After completion of Period II each patient will be assessed individually for the growth progress and overall safety. If the growth meets the pre-defined criteria[1] and there are no safety concerns, the patient will continue on the same dose, otherwise dose modifications will be performed according to the pre-determined rules. Patients who received MOD-4023 in the Main Study (initial 12 months of active treatment) will continue with the same dose (mg/kg) of MOD-4023 they received in the Main Study. Study visits will take place every 3 months (i.e. every 13±2 weeks, 4 days (or 3 days, when necessary) after dosing until the LT-OLE period. Patients who received active comparator, Genotropin, during the Main Study, will be switched to MOD-4023 (will be randomized to one of the three MOD-4023 cohorts). Their visit schedule during the first three months of the OLE will be as follows: Visit 1/OLE for first MOD-4023 injection (week 52 +1 day, which is on Month 12 visit of the Main Study) in which the patient will be trained on medication administration, Visit 2/OLE will be 28 days + 4 (-1) days after the first MOD-4023 injection and Visit 3/OLE will be 3 months after the first MOD-4023 injection (i.e. 13±2 weeks + 4 (-1) days after the first MOD-4023 injection). All subsequent visits will be every three months (i.e. every 13 weeks (±2 weeks), on day 4 or 3, when necessary post dosing) until the LT-OLE- period.

Patients who are off treatment for [redacted] days between the last MOD-4023/Genotropin dose in the Main Study and the first OLE dose (2nd year) will be allowed to continue into the OLE period after the following tests and assessments will be conducted:

- Parameters of glucose metabolism: fasting glucose, insulin, and HbA1c

[1] Delta Height SDS at least 0.2

	• Antigenicity: anti MOD-4023 antibodies (only Genotropin group – baseline for future tests) • Routine safety laboratory (biochemistry, hematology, and urinalysis) • PD: IGF-I and IGFBP-3 baseline serum levels • MOD-4023 baseline serum levels During the OLE period, the DSMB will review the data at month 12 or on an ad-hoc basis, if any safety concern arises. During the 12-month OLE period, the following assessments will be conducted at each visit: physical examination, auxology measurements (actual height measured on a calibrated stadiometer and body weight measurement); Adjustment of dose for weight; vital signs, AEs, local tolerability, concomitant medications, parameters of glucose metabolism (fasting glucose, insulin, and HbA1C), other hormonal levels (TSH, free T4, free T3, cortisol), , routine safety laboratory (biochemistry, hematology and urinalysis), MOD-4023 serum level and IGF-I and IGFBP-3 serum levels, antigenicity: anti MOD-4023 antibodies (every 6 months only) and drug dispensing. The following assessments will be done after patient completes the 12-month OLE (unless otherwise specified): parameters of lipid metabolism (Lp(a), pubertal status, ECG, bone age and fundoscopy (or earlier if there are signs or symptoms indicative of benign intracranial hypertension). The used study drug and filled patient diaries will be returned at the next visit. **PERIOD IV: LONG-TERM OPEN LABEL EXTENSION (LT-OLE) PERIOD** LT-OLE starts from the 2nd year of OLE (i.e. the 3rd year of treatment in the study) until transition to PEN (LT-OLE-PEN period). Patients in Cohorts 1 and 2 entering the LT-OLE will be switched to the highest MOD-4023 dose 0.66 mg/kg/week after signing a separate informed consent (unless a different medical decision was made). In case patients from Cohorts 1 and 2 have already entered the 2nd year of OLE, the switch to 0.66 mg/kg/week will be done at their next study visit after signing a separate informed consent. Patients in Cohort 3 will continue receiving 0.66 mg/kg/week. If the IGF-I value will be above +2.0 SDS, patients will be requested to return to the clinic within 4-6 weeks for another evaluation. If IGF-I level value will continue to be above +2.0 SDS, the dose will be reduced by 15% to 0.56 mg/kg/week. Patients with reduced dose will be required to return to the clinic within 4-6 weeks for another IGF-I evaluation. If IGF-I level value is still above 2.0 SDS, the dose will be reduced again by 15% to 0.48 mg/kg/week. Patients, who had their dose reduced twice and who still have IGF-I level above 2.0 SDS within 4-6 weeks of second dose reduction, will be required to have individual medical consultation with the Medical Monitor (with the assistance of the DSMB if necessary). Patients who are off treatment for [redacted] days between the last MOD-4023 in the OLE period and the first LT-OLE dose (3rd year) will be allowed to continue into the LT-OLE period after the following samples for testing will be collected • Parameters of glucose metabolism: fasting glucose, insulin, and HbA1c

- Antigenicity –anti MOD-4023 antibodies
- Routine safety laboratory (biochemistry, hematology, and urinalysis)
- PD: IGF-I and IGFBP-3 baseline serum levels
- MOD-4023 baseline serum levels

During LT-OLE, all patients will be assessed once every 3 months, as specified in the Schedule of Assessment, including: auxology measurements (actual height measured on a calibrated stadiometer and body weight measurement); adjustment of dose for weight; AEs; local tolerability; concomitant medication; and dispensing of drug.

In addition, IGF-I, IGFBP-3 and MOD-4023 serum levels will be assessed every 6 months on day 3 or 4 post dosing. Once a year, patients will be required to attend another visit on dosing day (in addition to the semi-annual visit on day 3 or 4 post dosing) where the following additional assessments will be conducted (on top of the three and six months assessments): antigenicity (anti MOD-4023 antibodies), MOD- 4023 serum levels, Physical examination, Vital signs, Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c), Routine safety laboratory (biochemistry, hematology and urinalysis), other hormonal levels (TSH, free T4, free T3 and cortisol), lipid metabolism parameters, pubertal status, ECG, bone age, fundoscopy (if required), and for males that are 13 years old and above: LH, FSH and testosterone. For females that are 12 years old and above: LH, FSH and estradiol.

All patients switching to 0.66 mg/kg/week (e.g. patients from cohort 1 &2 treatment arms) will be required to attend a site visit after 3 months (on day 3 or 4 post-dosing) for the process following evaluations: physical examination and vital signs, patient's height and weight, concomitant medications, glucose metabolism parameters (fasting glucose, insulin and HbA1c), antigenicity (anti MOD-4023 antibodies), routine safety laboratory (biochemistry, hematology and urinalysis) and IGF-I and IGFBP-3 serum levels.

In case the switch to the 0.66 mg/kg/week dose is on month 9 visit, the 3 months follow up visit will take place on dosing day. Additional visit will take place 3-4 days post dosing in which only IGF-I, IGFBP-3 and MOD-4023 serum levels will be measured.

Patients from cohort 3 should continue with their routine visit schedule.

Patients will sign a separate informed consent to be eligible to enter OLE and LT-OLE. Patients who have already entered OLE will be re-consented for LT-OLE. Patients from Cohorts 1 and 2 will be instructed by the investigator about the transition to the higher dose of MOD-4023 (0.66 mg/kg/week) and will also be re-consented.

Annual extension notification will be submitted to local EC/IRB.

Treatment Period V (LT-OLE-PEN) – until marketing approval

First year of LT-OLE-PEN period

Upon regulatory clearance of protocol amendment 9 and sponsor written approval, patients will be requested to come to the clinic for PEN Visit 1(PEN V1).

PEN V1 will occur on a planned dosing day (sites should make any effort to schedule this visit according to the current visit schedule and consider to combine visits in order to minimize the burden on the patients), patients should arrive at the clinic prior to dosing. This visit will serve as the 'baseline' for the LT-OLE-PEN Period in which the consent/assent form for the LT-OLE-PEN period will be signed. Patients should return used and un used vials that were dispensed during the study and kept at patient home. Site staff should remind the patients to bring all vials dispensed during the study (used and unused) before the visit.

During PEN V1, the patients will be trained on the use of the PEN, the PEN will be dispensed and the first PEN dose will be administered at the clinic by the parents/legal guardians. Patient will continue his/her treatment with the same dose level as before the switch to PEN. In addition to the PEN, the patients will be provided with updated patient diary, instructions for use and dosing instructions. If splitting the dose between 2 injections, the patient should complete new diary page for each injection.

Weekly dose	Number of patient Diary pages
1 injection	1
2 injections from the same pen	2
2 injections from 2 different pens	2

The following assessments will be conducted at PEN V1 (dosing day) pre-dose: auxology measurements (actual height measured on calibrated stadiometer); body weight measurement; adjustment of dose for weight; AEs; urine pregnancy test for female of child bearing potential (In case of positive result please refer to section 7.4); local tolerability; concomitant medication; dispensing of drug; patients should return completed diaries and will be provided with new diaries; IGF-I, IGFBP-3 and MOD-4023 serum levels; anti MOD-4023 antibodies; Physical examination; Vital signs; Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c); Routine safety laboratory (biochemistry, hematology and urinalysis); other hormonal levels (TSH, free T4 and cortisol); lipid metabolism parameters; pubertal status; fundoscopy (if required); return of used and unused vials; bone age assessment [1]; for males that are 13 years old and above: LH, FSH and testosterone, for females that are 12 years old and above: LH, FSH and estradiol; training on PEN.

[1] Bone age measurement will be performed in case the previous assessment was done more than 6 months prior to this visit.

	Four weeks (+1 week) after PEN visit 1, the patient will be required to come for PEN visit 2 (PEN V2). This visit should occur on Day 4 (-1) post dose. The following assessments will be conducted at PEN V2, Day 4(-1): • Completed patient diary and used PENs should be returned at this visit. If necessary, the patient will be re-trained on the PEN • Body weight measurements; adjustment of dose for weight; AEs; urine pregnancy test for females of child bearing potential (In case of positive result please refer to section 7.4); local tolerability; concomitant medication; dispensing of drug; IGF-I, IGFBP-3 and MOD-4023 serum levels; anti MOD-4023 antibodies; Physical examination; Vital signs; fundoscopy (if required); provide patient diary. For the following visits, patients will come to the clinic 4 days (-1) post dose every 3 months (±2 weeks), counting from PEN V1. In months 3 and 6 visits (counting from PEN V1) the patient will be assessed as specified in the schedule of assessment. The following assessments will be conducted on those visits: Auxology measurements (actual height measured by calibrated stadiometer); body weight measurement; adjustment of dose for weight; AEs; urine pregnancy test for females of child bearing potential (In case of positive result please refer to section 7.4); local tolerability; concomitant medication; dispensing and return of used drug; anti MOD-4023 antibodies; IGF-I, IGFBP3; MOD-4023 serum levels; fundoscopy (if required); physical examination and vital signs; Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c); other hormonal levels (TSH, free T4 and cortisol); lipid metabolism parameters; Routine safety laboratory (biochemistry, hematology and urinalysis); pubertal status; patients should return completed patient diaries and will be provided with new diaries. In month 9 (counting from PEN V1) visit the patient will be assessed as specified in the schedule of assessment. The following assessments will be conducted on this visit: Auxology measurements (actual height measure measured by calibrated stadiometer); Body weight measurement; adjustment of dose for weight; AEs; urine pregnancy test for females of child bearing potential (In case of positive result please refer to section 7.4); local tolerability; concomitant medication; Fundoscopy (if required); IGF-I and IGFBP-3; MOD-4023 serum levels; anti MOD-4023 antibodies; physical examination and vital signs; dispensing and return of used drug; pubertal status; patients should return completed patient diaries and will be provided with new diaries. On month 12 (±2 weeks) counting from PEN V1, two visits will be conducted, one on dosing day and one on day 4 (-1) post injection. On month 12 (±2 weeks) dosing day visit, the following procedures will take place (pre dose): Auxology measurements (actual height measure measured by calibrated stadiometer); body weight measurement; adjustment of dose for weight; AEs; local tolerability; concomitant medications; return and dispense of

	drug; anti MOD-4023 antibodies; MOD- 4023 serum levels; Physical examination; Vital signs; Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c); Routine safety laboratory (biochemistry, hematology and urinalysis); other hormonal levels (TSH, free T4 and cortisol); lipid metabolism parameters; pubertal status; bone age; fundoscopy (if required); urine pregnancy test for females of child bearing potential (In case of positive result please refer to section 7.4); patients should return completed diaries and will be provided with new diaries; for males that are 13 years old and above: LH, FSH and testosterone, for females that are 12 years old and above: LH, FSH and estradiol; ECG around Tmax (7-12 hours post dose). In case not possible to conduct the ECG around Tmax at this 12 month visit, it can be performed on month 12 ± 3 weeks (7-12 hours post dose). The second visit on month 12 (±2 weeks) will be conducted on day 4 (-1) post injection and IGF-I and IGFBP-3 will be assessed. **Second year of LT-OLE_PEN period until marketing approval** From the second year of the LT-OLE-PEN period and until marketing approval, visits will be conducted every 3 months (months 3, 6, 9 and 12), ±2 weeks, on day 4 (-1) post injection. The following assessments will be conducted on each visit: Auxology measurements (actual height measure measured by calibrated stadiometer); body weight measurement; adjustment of dose for weight; AEs; local tolerability; concomitant medications; return and dispensing of drug; fundoscopy (if required); IGF-I and IGFBP-3; physical examination and vital signs; urine pregnancy test for females of child bearing potential (In case of positive result please refer to section 7.4); pubertal status; patients should return completed patient diaries and will be provided with new diaries. In addition, the following assessments will be added every 6 months, on month 6 and month 12 visits: MOD-4023 serum levels; anti MOD-4023 antibodies; parameters of glucose metabolism (fasting glucose, fasting Insulin, HbA1c); Lipid parameters; routine safety laboratory (biochemistry, hematology and urinalysis); other hormonal levels (TSH, free T4 and cortisol. In addition, the following assessments will be conducted ones a year on month 12 visit: ECG; Bone age; for males that are 13 years old and above: LH, FSH and testosterone and for females that are 12 years old and above: LH, FSH and estradiol, The investigator may conduct unscheduled visits, for safety reasons, or any other reason per investigator medical judgment. Throughout the LT-OLE-PEN period, patients will continue to complete a patient diary at home to collect dosing and safety data.

INCLUSION CRITERIA:	1. Pre-pubertal child aged ≥ 3 years old and not above 10 years for girls or 11 years for boys with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency. 2. Confirmed diagnosis of GHD by two different GH provocation tests defined as a peak plasma GH level of [redacted] ng/ml[1], determined by central laboratory using a validated assay[2]. If the patient has already been tested locally and reserve samples that were taken at appropriate time-points are available, these will be reanalyzed by the central laboratory[3]. Historical tests missing the -30 minutes time point will be accepted. If no reserve samples are kept (only for tests performed prior to site initiation), then the details of the locally performed tests will be reviewed by the Coordinating Investigator: if the results cannot be accepted, the patient will undergo both stimulation tests during the screening period and the samples will be analyzed by the central laboratory. At least one of the two stimulation tests (and preferably both) will be analyzed by the central laboratory. If the patient requires sex hormone priming (due to the age), and both stimulation tests must be performed during the Screening (no historical samples kept, or test was without priming), it is recommended to perform stimulation tests in consecutive setting in one day, or in two consecutive days, to avoid priming the patient twice. Local historical tests without sex-steroid priming will not be accepted for patients that require sex steroid priming according to the protocol. 3. Bone age (BA) is not older than chronological age and should be no greater than 9 years for girls and 10 years for boys. 4. Without prior exposure to any r-hGH therapy. 5. Impaired height and height velocity defined as: a. Height (HT) of at least 2.0 standard deviations (SD) below the mean height for chronological age (CA) and gender according to the standards from Prader et al, 1989, (HT SDS ≤ -2.0). b. Annualized height velocity (HV) below the 25th percentile for CA (HV <-0.7 SDS) and gender according to the standards of Prader et al (1989). The interval between two height measurements should be at least 6 months, but should not exceed 18 months prior to inclusion. 6. BMI must be within ±2 SD of mean BMI for the chronological age and sex according to the 2000 CDC standards.

[1] Patients will be divided into two subgroups: Patients with peak serum GH levels after stimulation test [redacted] ng/ml and patients with peak serum GH levels after stimulation test [redacted] and [redacted] ng/ml.
[2] Insulin tolerance test, with cortisol response to hypoglycemia if insulin stimulation test is chosen / Arginine test / Clonidine test / Glucagon test (plus or without propranolol) / L-dopa plus propranolol.
[3] Central laboratory results will be used for eligibility confirmation.

	7. Baseline IGF-I level of at least 1 SD below the mean IGF-I level standardized for age and sex (IGF-I SDS ≤ -1.0) according to the central laboratory reference values. 8. Children with normal fundoscopy (ophthalmoscopy) at screening (without signs/symptoms of intracranial hypertension as assessed by fundoscopy). 9. Children with multiple hormonal deficiencies must be on stable replacement therapies for other hypothalamo-pituitary-organ axes for at least 3 months and 6 months for thyroid replacement therapy prior to the first study drug administration. 10. Normal 46 XX karyotype for girls. 11. Written informed consent of the parent or legal guardian of the patient and assent of the patient (if the patient can read) for the Main Study and for the OLE. <u>Specific Inclusion criteria for Period V (LT-OLE –PEN):</u> 12. Continuing participation in the LT-OLE-PEN Period. 13. Signed consent and assent (when applicable) form for the LT-OLE-PEN Period. 14. Investigator's assessment and confirmation of the patient anticipated compliance to the protocol procedures. 15. Agreement to refrain from sexual activity during the study i.e. observe complete sexual abstinence as the only acceptable contraceptive measure in this study.
EXCLUSION CRITERIA:	1. Children with past or present intracranial tumor growth as confirmed by an MRI scan (with contrast). 2. History of radiation therapy or chemotherapy. 3. Malnourished children defined as: a. Serum albumin below the lower limit of normal (LLN) according to the reference ranges of central laboratory; AND b. Serum iron below the lower limit of normal (LLN) according to the reference ranges of central laboratory; AND c. BMI < -2 SD for age and sex; 4. Children with psychosocial dwarfism. 5. Children born small for gestational age (SGA – birth weight and/or birth length < -2 SD 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. Patients with diabetes mellitus.

	9. Patients with impaired fasting sugar (based on WHO; fasting blood sugar >110 mg/dl or 6.1 mmol/l) after repeated blood analysis. 10. Chromosomal abnormalities and medical "syndromes" (Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi Syndrome, Russell-Silver Syndrome, SHOX mutations/deletions and skeletal dysplasias), with the exception of septo-optic dysplasia. 11. Closed epiphyses. 12. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids and methylphenidate for attention deficit hyperactivity disorder (ADHD), with the exception of hormone replacement therapies (thyroxin, hydrocortisone, desmopressin (DDAVP)). 13. Children requiring glucocorticoid therapy (e.g. asthma) that are taking a dose greater than 400 µg/d of inhaled budesonide or equivalents[1] for longer than 1 month during a calendar year. 14. Major medical conditions and/or presence of contraindication to r-hGH treatment. 15. Known or suspected HIV-positive patient, or patient with advanced diseases such as AIDS or tuberculosis. 16. Drug, substance, or alcohol abuse. 17. Known hypersensitivity to the components of study medication. 18. Other causes of short stature such as coeliac disease, hypothyroidism and rickets. 19. The patient and/or the parent/legal guardian are likely to be non-compliant in respect to study conduct. 20. Participation in any other trial of an investigational agent within 30 days prior to Screening. <u>Specific exclusion criteria for Treatment Period V (LT-OLE-PEN):</u> 21. Unresolved drug related SAE from previous treatment periods. 22. Diagnosis of cancer. 23. Patients who, based on the investigator's judgment, have a clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation. Conditions may include cardiovascular, peripheral vascular, pulmonary, hepatic, renal, neurological or metabolic disease. 24. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids or replacement of sex hormones, with the exception of ADHD drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin [DDAVP]).

[1] Approximately equivalent doses: Fluticasone: 264 µg/d; Beclomethasone: 504 µg/d; Flunisolide 1,000 µg/d; Triamcinolone: 1,000 µg/d.

	25. Unsatisfactory treatment response defined as improvement of height SDS of less than 0.2 SDS in a 6-month treatment interval if dose increase at this time point is not feasible.
EFFICACY ENDPOINTS **(Main and OLE) :**	**Primary endpoints (Main Study):** • Annual Height Velocity in cm/year at 12 months (Baseline Visit – Visit 1). **Secondary endpoints (Auxology/Clinical) (Main Study):** • Height velocity at 6 months (Baseline Visit – Visit 1). • Delta height SDS at 6 and 12 months (compared to Visit 1/Baseline value). **Secondary endpoints (Biochemical) (All study periods):** • Absolute IGF-I levels on day 4 after MOD-4023 dosing. • IGF-I SDS on day 4 after MOD-4023 dosing. [redacted] **OLE endpoints (including LT-OLE and LT-OLE-PEN)** • Annual Height Velocity in cm/year at each 12 months interval. • Delta height SDS every 12 months (compared to the previous value).
SAFETY ENDPOINTS: (Main and OLE)	• Incidence of adverse events; • Incidence of anti-MOD-4023 antibody formation (including characterization of the antibodies and neutralizing properties); • Local injection site assessment; • IGF-I levels; • Parameters of glucose metabolism: blood glucose, fasting insulin level, HbA1c; • Thyroid status; • Lipid parameters; • Cortisol levels; • All other hematology and biochemical parameters; • Physical examination; • Vital signs.
PK/PD ENDPOINTS:	Population based PK/PD profile of MOD-4023 after 2nd dose administration at final allocated dose (AUC, MRT, C_{max}, C_{trough}, T_{max}, $T_{1/2}$).

STATISTICAL ANALYSIS:	Details of applicable statistical methods will be provided in a Statistical Analysis Plan. Data from all clinical assessments will be listed and, where appropriate, summarized by cohorts using descriptive statistics. Endpoints will be summarized by cohorts and stratifying variables as well. Summary statistics (arithmetic mean, standard deviation, minimum value, maximum value, number of non-missing values) will be presented for continuous variables (absolute values at each time point and changes from baseline if applicable). Frequency statistics (counts and percentages) will be presented for categorical variables. Where appropriate, the presentation of results will include shift tables, plots, or confidence intervals. All statistical evaluations, including efficacy analysis, will be purely exploratory; no hypothesis tests will be conducted, hence this pilot study is not powered. The assessment of safety will be based mainly on the frequency of AEs, frequency of patients developed anti-MOD-4023 antibody, IGF-I serum levels and on the number of laboratory values that fall outside of pre-determined ranges. Data of all safety endpoints will be listed and tabulated. When all patients complete the Main Study a full statistical analysis will be performed for the Main Study based on the applicable approved SAP. The results will be presented and discussed in a full Clinical Study report. 2^{nd} year, 3^{rd} year and subsequent analysis will be conducted periodically for efficacy and safety updates. **PK/PD evaluations:** PK/PD parameters will be calculated utilizing a population PK modelling approach, based on limited sampling in each patient. The proposed analysis strategy will include the following steps: 1. Estimate the Population PK/PD means and variances using the Population PK/PD analysis. 2. Perform an Empirical Bayesian estimation to retrieve the individual PK/PD model Parameters. 3. Use these individual PK/PD estimates to generate individual concentration time profile using rich sampling to cover the entire desired time range for non-compartmental analysis calculation. 4. Perform Non compartmental Analysis for estimation of AUC and $C_{max.}$
PATIENT DISCONTINUATION RULES (all study periods) :	The patient's participation in this study may be discontinued due to the following reasons: 1. Request from regulatory agency, sponsor, primary care physician, or Investigator. 2. Patient (or parent/legal guardian) withdraws consent. 3. Adverse event (AE): o Occurrence of a malignancy during the course of study.

	○ Evidence of growth of an intracranial tumor during the course of the study. ○ Development of benign intracranial hypertension, if the symptoms return following resumption of drug (after a temporary stop). ○ Occurrence of AE's following which the Investigator or the patient wishes to discontinue treatment (such as, but not limited to, slipped capital femoral epiphysis, scoliosis, avascular necrosis and development of lipoatrophy, etc.). ○ Development of a serious inter-current critical illness. ○ Abnormal laboratory values that affect the patient's safety (if discontinuation is considered necessary by the Investigator or the Sponsor Medical Monitor). ○ A severe adverse drug reaction (if discontinuation of study medication is desired by the patient or considered necessary by the investigator or the Sponsor Medical Monitor). If the Investigator decision is made because of a SAE or clinically significant laboratory value, the Medical Monitor is to be alerted immediately 4. Intake of prohibited concomitant medication. 5. Unsatisfactory treatment response defined as improvement of height SDS of less than 0.2 SDS in a 6-month treatment interval if dose increase at this time point is not feasible (Applicable for periods I-IV) 6. Patient is unwilling or unable to continue the study or is lost-to-follow-up. 7. Patient is non-compliant with study procedures/ study protocol. 8. Investigator decides that withdrawal from the study is in the best interest of the patient: ○ Occurrence of neutralizing antibodies which, in the opinion of the Investigator, requires discontinuation of the patient. ○ Lack of patient compliance (if discontinuation is desired or considered necessary by the investigator or the Sponsor Medical Monitor). ○ A serious protocol deviation that affects the patient's safety or the accuracy and/or validity of data. 9. Patient meets one of the exclusion criteria during the study. 10. Any clinically significant change in the patient's medical condition. <u>Discontinuation rules specific to the LT-OLE-PEN period:</u> 11. Positive urine pregnancy test or confirmed pregnancy. In case of confirmed pregnancy, the study drug should be discontinued and the Medical Monitor be alerted immediately.

	12. When the patient reaches a growth rate of [redacted]cm/12 months (the interval between two height measurements should be at least 6 months).

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List of Abbreviations

Terms	Descriptions
ACTH	Adrenocorticotropic hormone (corticotrophin)
AE	Adverse event
ANOVA	Analysis of variance
BA	Bone age
BMI	Body mass index
CA	Chronological age
CRF	Case Report Form
CRO	Contract Research Organisation
CTP	Carboxyl-terminal peptide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GH	Growth hormone
GHD	Growth hormone deficiency
GMP	Good Manufacturing Practice
HDL	High density lipoprotein
hGH	Human growth hormone
HIV	Human immunodeficiency virus
HT	Height
HV	Height velocity
i.m.	Intramuscular
i.v.	Intravenous
ICF	Informed consent form
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IGF-I	Insulin-like growth factor- I
IRB	Institutional Review Board
ITT	Intention-to-treat
IU	International units
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLN	Lower limit of normal

LP	Lumbar puncture
LT-OLE	Long-term Open Label Extension
OLE	Open Label Extension
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
PD	Pharmacodynamics
PEN	Single patient use, multi-dose, disposable pre-filled pen containing 20 or 50 mg/mL
PK	Pharmacokinetics
PP	Per-protocol
SC	Subcutaneous
SAE	Serious adverse event
SD	Standard deviation
SDS	Standard deviation score
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SHOX	Short stature homeobox
T3	Triiodothyronine
T4	free thyroxin
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WHO	World Health Organisation
WHO-DRL	WHO-Drug Reference List

1. Background and Rationale

1.1 Introduction

Human growth hormone (hGH) deficiency is the consequence of low or absent secretion of growth hormone from the pituitary gland. hGH is a 191-amino-acid pituitary protein that stimulates the hepatic production and release of insulin-like growth factor-I (IGF-I) into the systemic circulation. IGF-I is instrumental in the promotion of linear growth in children, and in the control of metabolism and body-mass composition in adults. It is regulated through complex feedback mechanisms involving hGH, insulin-like growth factor-I binding protein 3 (IGF-BP3) and their complexes. The somatotroph cells of the anterior pituitary gland produce growth hormone. Secretion of hGH is under strict hormonal homeostatic control. Growth hormone-releasing hormone (GHRH) and ghrelin are the most significant stimulators of its production while somatostatin produces the strong inhibitory action. Both GHRH and somatostatin are released into the portal system from the hypothalamus. hGH has a pulsatile and mainly nocturnal pattern of secretion, occurring especially during REM (rapid eye movement) sleep. The frequency and amplitude of pulses increase during the growth spurt in adolescence and decline thereafter. Both acute stress and hypoglycemia stimulate hGH release, while hyperglycemia produces the opposite.

hGH is considered to be the most important endogenous factor responsible for body growth. It is also under the inhibitory control of IGF-I, its major protein effector, synthesized in the liver in response to hGH. The bone and connective tissue, in which hGH stimulates collagen synthesis and increases the activity of chondroblasts and chondrocytes, are the effector tissues of GH/IGF-I. GH is not only the hormone of growth; but it shows various effects on almost every tissue in the human organism. It is one of the most important anabolic agents enhancing whole body protein synthesis, increasing plasma glucose level and lipolysis via the direct effect on adipocytes as well as lipid oxidation by increasing substrate availability. New research continues to reveal other potential roles of hGH, including regulation of cardiac and immune function, mental agility and aging. The far reaching influence of these interactions is quite consistent with the very significant pleiotropic consequences for growth and metabolism when the system is imbalanced, as in the case of GHD.

In children, GHD results in inadequate circulating IGF-I levels and is manifested as abnormal linear growth.

In adults, GHD results in decreased lean body mass, increased fat mass, weakness, reductions in exercise capacity, muscle mass/strength, cardiac performance, and bone density, and in neuropsychological disturbances.

1.1.1 Aetiology

Childhood GHD can be congenital, acquired, or idiopathic. Underlying causes of two of these three types of GHD in children have been identified:

- Congenital
    - Defective pituitary development that leads to pituitary aplasia
    - Empty sella

  - Encephalocoele
  - Midline defects
  - Septo-optic dysplasia
  - Panhypopituitarism
  - Genetic abnormalities; autosomal-recessive, autosomal-dominant, or X-linked defects or a mutation or deletion in the growth hormone gene or in the GHRH.
- Acquired
  - Tumours of the hypothalamic-pituitary region - Craniopharyngioma is the most common tumor
  - Cranial irradiation, surgical intervention
  - Infiltrative diseases, including sarcoidosis, tuberculosis, histiocytosis X, haemochromatosis, and lymphocytic hypophysitis
  - Trauma (specifically traumatic brain injury)
  - Hypoxic insult
- Idiopathic

In most cases, no clear aetiology can be identified.

The idiopathic origin of GHD is poorly understood but it appears to be multifactorial. Retrospective analyses have considered familial traits (such as parental height) and perinatal risk factors (such as gestational age and birth size and weight) as possible predictors. Similarly, correlates of idiopathic GHD with untoward events during pregnancy and complications during birth have been examined. There are non-random effects evident in the frequency of GHD (and multiple pituitary hormone deficiency) dependent on some of these apparently extraneous influences, notably traumatic birth experience. The evidence suggests a model of causality in which there are ill-defined underlying familial and gender (males predominate 3-4:1) predispositions which are exacerbated by early life “adverse” events and result in deficiency, the degree of which (isolated GHD or multiple pituitary hormone deficiency) is determined by the severity of the “adverse” early life event.

Most morbidity in children with GHD relates to short stature. Average adult height for untreated patients with severe isolated growth hormone deficiency is 143 cm in men and 130 cm in women. The inability to achieve normal height leads to early onset of severe psychosocial problems directly related to short stature. This is compounded 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.

Human GH (*somatropin*) has been in clinical use for over 50 years primarily for treating GHD in children. In 1985, hGH from recombinant DNA origin replaced the cadaveric pituitary hGH, which was the only source available until then. hGH replacement therapy has been the standard of care for tens of thousands of adult and pediatric GHD patients and has proved to be safe and effective. The safety profile of daily dosing of hGH preparations in pediatric and adult populations is well established in clinical trials. Adverse events of injection site reactions do occur but are not deemed serious and resolve spontaneously. Safety is invariably concluded to be satisfactory in clinical trials.

The majority of currently available hGH products require daily or every other day subcutaneous or intramuscular injections in order to maintain hGH blood levels within the effective therapeutic window. Hence, compliance can be a problem, especially in self-administering patients. Daily administration and its concomitant side effects (e.g., injection site discomfort, transient oedema and arthralgia) can limit the therapeutic utility of existing formulations. A long-acting form of GH has the potential to reduce discomfort by requiring fewer injections and possibly by minimizing the adverse events associated with peaks and troughs in plasma concentration that occur with daily injection. With a baseline of non-compliance which has been shown to undermine the intended clinical effect of daily dosing, at least in the pediatric population, there is a strong imperative to enhance compliance in GH replacement therapy. In addition, in pediatric patients, psychological trauma related to years of regular injections is one of the major stressors reported by diabetic patients related to their medical treatment. The repeated injections required for daily r-hGH treatment may actually serve to enhance the negative self-image and stigmatization that already exist for many of these children. Patients receiving GH therapy less frequently may experience a benefit from such treatment, improving their quality of life.

At the present time there are no commercially available sustained-release or long-acting GH preparations. However, their proof of principle and effectiveness has been extensively demonstrated both in clinical trials and in routine clinical use in childhood and adult GHD populations.

CTP technology has enabled the production of a long-acting hGH (MOD-4023), which may obviate the need for the numerous injections now required for the treatment of GHD. This technology is based on a natural peptide, the C-terminal peptide (CTP) of the beta chain of hCG, which provides hCG with the required longevity to maintain pregnancy (initial T1/2 ~10 hours, terminal T1/2 ~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 T1/2 ~1 hour, terminal T1/2 ~10 hours). MOD-4023 is an hGH molecule fused to 3 copies of CTP; one at the N-terminus and two at the C-terminus. Therefore, adding CTP to protein other than hCG will enable to increase their longevity.

As demonstrated in animal models, healthy subject (Phase I) and GHD adult patients (Phase 2), MOD-4023 may have the potential to be injected once per week to once every two weeks, resulting in similar clinical efficacy to daily injections of r-hGH.

1.2 THE INVESTIGATIONAL PRODUCT

MOD-4023 is a long acting hGH under development which utilizes the CTP technology.

MOD-4023 consists of hGH fused to three copies of the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin (hCG); one copy at the N-terminus and two copies (in tandem) at the C-terminus. Each CTP peptide contains up to four O-glycosylation sites, and has a theoretical molecular weight of 30,469 Daltons (Da) for the protein backbone and ~38,500 Da for the entire molecule including the O-glycans. MOD-4023 is expressed in CHO cells grown in protein-free, serum-free medium. The protein is purified using a series of

chromatographic separation steps. The final material is formulated in [redacted]

Unlike other investigational long-acting/sustained-release hGH products, the liquid formulation of the MOD-4023 drug product is non-viscous (viscosity at 20 mg protein/ml is similar to saline). Therefore the material can be administered using thin needles of 30-33 G.

1.3 Risk-Benefit Analysis

Each of the study patients requires GH replacement, and may potentially be advantaged by approval of a safe and effective long acting growth hormone.

Adverse events (AEs) in children seem to be mostly mild in nature (reported for up to a maximum of 10% of the patients participating in clinical trials). Side effects which have to be primarily considered when using hGH preparations include: symptoms of fluid retention (edema), arthralgia/myalgia, symptoms of carpal tunnel syndrome and transient local skin reactions at the injection site. In addition, symptoms of hypothyroidism, insulin resistance, nausea, increase of leukocytes and plasma free fatty acids, disturbance of blood lipids, benign intracranial hypertension, headache, muscle and joint pain, weakness, tiredness, hyperglycemia, glucosuria, and lipoatrophy (at the injection site) might occur.

As with any other protein, treatment with a growth hormone preparation may induce immune responses, including the formation of anti- hGH antibodies. While growth response in children or change of body composition in adults may or may not considerably be affected by formation of such antibodies, it has been a concern with respect to the safety as well as the efficacy of such products. Although this concern historically arose following the use of human pituitary-derived hGH, earlier impure recombinant hGH preparations, and of methionylated-r-hGH, assessment of the potential antigenicity of current r-hGH products is still justified.

On the basis of the preclinical studies and clinical studies conducted in adult GHD patients (see Investigator's Brochure), serious toxicological reactions are not to be expected in patients upon the injection of the study substance at the envisaged dose and route of administration.

1.4 Dose Selection Rationale

The Phase 2 pediatric study will evaluate three dose levels of MOD-4023, intended to be equimolar to the dose level for cumulative weekly r-hGH treatment, or a multiple thereof. All dose levels tested are supported by a significant safety margin derived from the “no observed adverse effect level” (NOAEL) established in nonclinical toxicology studies. The low dose administered to Cohort 1 (0.25 mg MOD-4023 protein/kg/week) is a weekly molar equivalent to a standard daily dose of r-hGH of 0.025 mg/kg/day or 0.18 mg/kg/week (after adjusting for the 1.38-fold difference in mass between the two proteins). Cohort 2 will be administered the weekly molar equivalent of the maximal recommended dose for GHD treatment (0.05 mg/kg/day, based on the Growth Hormone Society Consensus Guideline on the Diagnosis and Treatment of GHD in Childhood and Adolescence published in 2000) and Cohort 3 will be administered the weekly molar equivalent of the maximal approved dose for other pediatric indications (equivalent to 0.068 mg/kg/day).

During the 12-month Open-Label Extension (OLE), patients will continue with the same dose (mg/kg) as in the Main Study.

Patients who received active comparator, Genotropin®, during the Main Study, will be switched to MOD-4023; they will be randomized to one of the three MOD-4023 cohorts.

In the Long-term OLE (LT-OLE) period, patients in the lower dose cohorts (cohorts 1 and 2) will be switched to 0.66 mg/kg/week as specified in this protocol.

In the LT-OLE-PEN period, patients should continue with the same dose.

1.4.1 Justification for Switching All Patients to MOD-4023 Dose of 0.66 mg/kg/week in OLE 2nd year

Based on favorable outcome of the 12-month data of this phase 2 pediatric dose range study (Main Study CP-4-004), it was decided to switch all patients from Cohorts 1 and 2 entering the LT-OLE (2nd year of the OLE) to MOD-4023 0.66 mg/kg/week. At 12-months (end of Main Study), patients on MOD-4023 at a dose of 0.66 mg/kg/week had comparable efficacy and safety outcome to patients on daily hGH (Genotropin) at a dose of 34 µg/kg/day (equivalent to 0.24 mg/kg/week). Specifically, MOD-4023 at 0.66 mg/kg/week elicited comparable auxology outcome (HV SDS and Ht SDS) and IGF-I and IGFBP-3 profiles to daily hGH while maintaining optimal IGF-I serum levels, with values that were in the middle part of the gender and age-adjusted normal range (~0 SDS). The 0.66 mg/kg/week dose of MOD-4023 was also associated with a satisfactory safety and tolerability profile which is consistent with known properties of r-hGH products. No patients withdrew from the study due to an AE associated with MOD-4023.

Based on these results, the Sponsor proposes that the dose of 0.66 mg/kg/week of MOD-4023 has the highest probability to successfully demonstrate non-inferior efficacy to Genotropin in a subsequent Phase 3 pediatric GHD study with a comparable safety profile, and is the preferable therapeutic dose considering benefit/risk to the pediatric GHD patients.

2. Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives are to compare the safety, efficacy and tolerability of three MOD-4023 doses to that of a commercially available standard daily r-hGH formulation, in pre-pubertal children with growth failure due to insufficient secretion of endogenous growth hormone.

2.1.2 Secondary Objectives

The secondary objectives are:

1. To evaluate the PK and PD profiles of 3 different doses of MOD-4023 in pre-pubertal GHD children.
2. To select the optimal dose of MOD-4023 for the subsequent phase 3 study on the basis of safety, efficacy.

2.2 STUDY ENDPOINTS

EFFICACY ENDPOINTS:

Primary endpoints (Main study):

- Annual Height Velocity in cm/year at 12 months (Baseline Visit – Visit 1).

Secondary endpoints (Auxology/Clinical) (Main study):

- Height velocity at 6 months (Baseline Visit – Visit 1);
- Delta height SDS at 6 and 12 months (compared to Visit 1/Baseline value).

Secondary endpoints (Biochemical) (all study periods):

- Absolute IGF-I levels on day 4 after MOD-4023 dosing.
- IGF-I SDS on day 4 after MOD-4023 dosing.

[redacted]

OLE endpoints (including LT-OLE and LT-OLE-PEN)

- Annual Height Velocity in cm/year at each 12 months interval.
- Delta height SDS every 12 months (compared to the previous value).

SAFETY ENDPOINTS: (all study periods)

- Incidence of adverse events;
- Incidence of anti-MOD-4023 antibody formation (including characterization of the antibodies and neutralizing properties);
- Local injection site assessment;
- IGF-I levels;
- Parameters of glucose metabolism: blood glucose, fasting insulin level, HbA1c;
- Thyroid status;
- Lipid parameters;
- Cortisol levels;
- All other hematology and biochemical parameters;
- Physical examination;
- Vital signs.

PK/PD ENDPOINTS:

Population based PK/PD profile of MOD-4023 after 2nd dose administration at final allocated dose (AUC, MRT, C_{max}, C_{trough}, T_{max}, $T_{1/2}$).

3. Overall Study Design

This is a phase 2, safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children.
Eligible patients will undergo the following treatment schedule consisting of a Screening period, 2 Active Treatment Periods (Main Study), an Open Label Extension (OLE) period, a Long-term OLE (LT-OLE) period and a long-term LT-OLE-PEN period:

1. Screening period will last up to 6 weeks.
2. Active treatment period – Main Study:
    a. Period I: 6-month repeated dosing including PK/PD sampling (see Section 5.1.2 for schedule).
    b. Period II: an additional 6-month continuous repeated dosing period (see Section 5.1.2 for schedule).
3. OLE period (Period III, 12 months) – 12 months continuous repeated dosing of MOD-4023.
4. LT-OLE period (Period IV, from the second year OLE – long-term annual extension with repeated administration MOD-4023 at 0.66 mg/kg/week until transition to PEN.
5. LT-OLE-PEN (Period V) - long-term, open-label extension using single patient use, multi-dose, disposable pre-filled pen. Upon regulatory clearance and Sponsor's written approval, study patients should be switched to PEN. Patient will continue with their current dose. Study duration will be until marketing approval; a yearly extension request will be submitted to local EC/IRB where it is required. An updated ICF for the LT-OLE-PEN period treatment should be signed during the first PEN transition visit, prior to using the PEN or any other assessments related to the transition to PEN.

PERIOD I: SIX MONTH REPEATED DOSE (Main Study)

Following screening, eligible patients will receive their weekly doses of MOD-4023 or daily dose of r-hGH for 6 months repeated dosing including PK/PD sampling. Safety will be assessed throughout this period.

In order to introduce naïve patients to the allocated MOD-4023 dose in a gradual manner, a stepwise dose increase will be implemented. All patients randomized to receive one of the three MOD-4023 doses will start treatment for 2 weeks with the low MOD-4023 dose (0.25 mg protein/kg). Based on the patient's dose allocation, this will be followed by a dose increase to the next dose level every two weeks until the final allocated dose is reached.

TABLE 5: DOSE INCREASE SCHEME FOR MOD-4023 COHORTS

Cohort	Dosing Scheme					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cohort I	0.25 mg protein/kg/week PK/PD sampling					
Cohort II	0.25 mg protein/kg/week		0.48 mg protein/kg/week PK/PD sampling			
Cohort III	0.25 mg protein/kg/week		0.48 mg protein/kg/week		0.66 mg protein/kg/week PK/PD sampling	

Subsequent to the second dose administration of the targeted dose, limited (population-based) PK and PD sampling will be performed as described in visit schedules in Section 5. The proposed sampling plan is based on the following:
Selection of time points that will cover both the PK and PD absorption phase to the peak which was about 20 hours for PK and 40-60 hours for IGF-I (in the phase 2 study conducted in GHD adult patients) and having in addition time points to cover the PK elimination phase and PD return to baseline (remaining time points).

This proposed sampling schedule was tested by simulating multiple data sets under these design conditions and all other conditions as the one of the upcoming and then fit those back using the same optimization procedures we will use after the trial. The results of that fitting procedure showed an average of only 15% in the percent error of the true simulating average PK/PD model parameters.

Patients allocated to Genotropin cohort will undergo limited PK/PD sampling after the 8th Genotropin dose (start of week 2 of dosing), as described in visit schedules (section 5).

Following the first 6 weeks of the study, all the patients will visit the hospital on a monthly basis. Patients allocated to the MOD-4023 dose cohorts (cohorts 1-3) will be monitored monthly for MOD-4023 serum levels, IGF-I and IGFBP-3 serum levels and routine safety assessments on day 4 after MOD-4023 dosing. In addition, after 5 months of dosing, patients allocated to MOD-4023 dosing will be asked to return to the medical center on the day of dosing in the morning hours prior to dosing in order to obtain a trough level MOD-4023 and PD (IGF-I and IGFBP-3) sample. Patients allocated to the Genotropin dose cohort (cohort 4) will be asked to return on any day during the relevant dosing week.

During Period I, the dose of MOD-4023 and r-hGH will be adjusted to the patient's body weight every three months. 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 on repeated consecutive elevated IGF-I levels, see section 5.8). For patients on MOD-4023, the dose may be decreased based on repeated consecutive day 4 levels of IGF-I above +2.0 SDS. For patients on Genotropin, the dose may be decreased based on repeated consecutive IGF-I levels above +2.0 SDS.

The study Medical Monitor will review all Adverse Events (AEs) from the entries on the e-CRF on a weekly basis and all SAE safety reports as received. The key safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) every 6 months approximately. After completion of this period each patient will be assessed separately, for the growth progress and overall safety. If the growth meets the pre-defined criteria (delta height SDS at least 0.2) and there are no safety concerns the patient will continue with the same dose, otherwise dose modifications will be performed, according to the pre-determined rules.

PERIOD II: SIX MONTH CONTINUOUS DOSING (Main Study)

During this six-month-continuous dosing period additional efficacy and safety data will be collected. During period II, patients will be kept on the originally allocated dose levels/dose regimens whenever possible. However, the dose may be adjusted due to safety reasons throughout the study and/or due to efficacy reasons after 6 months of dosing. Patients allocated to the r-hGH dose group will continue their doses as initiated earlier up to the end of the 12-month treatment period. Patients will visit the clinic every three months at which time safety and efficacy data will be collected.

Derived height and growth parameters (HTSDS and HVSDS) will be calculated centrally, and the bone age will be determined by a central bone age reader from the provided copies of X-ray films blinded for patient's identity and chronological age. All laboratory samples, including samples collected during growth hormone stimulation tests, will be analyzed centrally.

PERIOD III –12-Month OPEN LABEL EXTENSION (OLE) PERIOD

Patients who completed 12 months of treatment in the Main Study will be eligible to continue to a 12-month OLE period. After completion of Period II each patient will be assessed individually for the growth progress and overall safety. If the growth meets the pre-defined criteria[1], and there are no safety concerns, the patient will continue on the same dose, otherwise dose modifications will be performed according to the pre-determined rules. Patients who received MOD-4023 in the Main Study (initial 12 months of active treatment) will continue with the same dose (mg/kg) of MOD-4023 they received in the Main Study. For these patients, study visits will take place every 3 months (i.e. every 13±2 weeks, 4 days (or 3 days, when necessary) after dosing).

Patients who received active comparator, Genotropin, during the Main Study, will be switched to MOD-4023 (will be randomized to one of the three MOD-4023 cohorts). Their visit schedule during the first three months of the OLE will be as follows: Visit 1/OLE for first MOD-4023 injection (week 52 +1 day, which is on Month 12 visit of the Main Study), Visit 2/OLE will be 28 days + 4 (-1) days after the first MOD-4023 injection and Visit 3/OLE will be 3 months after first MOD-4023 injection (i.e. 13±2 weeks, on day 4 or 3 post dose, when necessary after the first MOD-4023 injection). All subsequent visits will be every three months, as for patients who were on MOD treatment in main study.

Patients who are off treatment for over [redacted] between the last MOD-4023/Genotropin dose in the Main Study and the first OLE dose (2nd year) will be allowed to continue into the OLE period after informing the sponsor and attending an interim visit.

[1] Delta Height SDS at least 0.2

During the OLE period, the DSMB will review the data at month 12 - or on an ad-hoc basis, if any safety concern arises.

PERIOD IV – LT-OLE PERIOD

LT-OLE starts from the 2nd year of OLE (i.e. the 3rd year of treatment in the study). Patients in Cohorts 1 and 2 who are entering the 2nd year of OLE (i.e. the 3rd year of treatment) will be switched to the highest dose 0.66 mg/kg/week after signing a separate informed consent. In selected group of patients from Cohorts 1 and 2 who have already entered the LT-OLE period, the switch to 0.66 mg/kg/week will be done at their next study visit after signing a separate informed consent. Patients in Cohort 3 will continue receiving 0.66 mg/kg/week.

All patients switching to 0.66 mg/kg/week will be required to attend a site visit after 3 months. Patients on cohort 3 will continue with their routine visit schedule.

Patients who are off treatment for over [redacted] between the last MOD-4023 in the OLE period and the first LT-OLE dose (3rd year) will be allowed to continue into the LT-OLE period after informing the sponsor and attending an interim visit.

Patients will sign a separate informed consent to be eligible to enter OLE and LT-OLE. Patients who have already entered OLE will be re-consented for LT-OLE. Patients from Cohorts 1 and 2 will be instructed by the investigator about the transition to the higher dose (0.66 mg/kg/week) and will also be re-consented.

Annual extension notification will be submitted to local EC/IRB.

Treatment Period V (LT-OLE-PEN) – until marketing approval

First year of LT-OLE-PEN period

Upon regulatory clearance of protocol amendment 9 and after sponsor written approval, patients will be requested to come to the clinic for PEN visit 1 (PEN V1). PEN V1 will occur on a planned dosing day, sites should make any effort to schedule this visit according to the current visit schedule and consider to combine visits in order to minimize the burden on the patients. Patients should arrive to the clinic prior to dosing. This visit will serve as the 'baseline' for the LT-OLE-PEN in which the consent/assent form for the LT-OLE-PEN period will be signed. Patients should return used and unused vials that were dispensed during the study and kept at patient home. Site staff should remind the patients to bring all vials dispensed during the study (used and unused) before the visit.

During PEN V1, the patients will be trained on the use of the PEN, the PEN will be dispensed and the first PEN dose will be administered at the clinic by the parents/legal guardians. Patient will continue his/her treatment with the same dose level as before the switch to PEN. In addition to the PEN, the patients will be provided with updated patient diary, instructions for use and dosing instructions.

Four weeks (+1 week) after PEN Visit 1, the patients will be required to come for PEN Visit 2 (PEN V2). This visit should occur on Day 4 (-1) post dose. Completed patient diary and used PENs should be returned at this visit. If necessary, the patient will be re-trained on the PEN.

For the following visits, patients will come to the clinic 4 days (-1) post dose every 3 months (±2 weeks), counting from PEN V1.

On month 12, in addition to 4 (-1) post dose visit, one more visit will be conducted on dosing day.

All first year visits assessments are detailed in section 5.4.1.

Second year of LT-OLE_PEN period until marketing approval

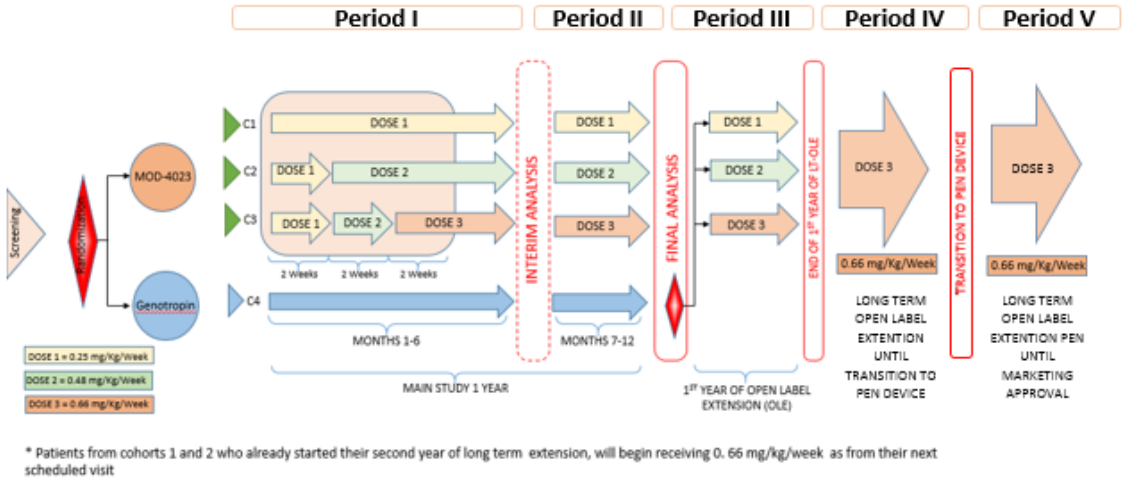
From the second year of the LT-OLE-PEN period and until marketing approval visits will be conducted every 3 months (months 3, 6, 9 and 12) ±2 weeks, on day 4 (-1) post injection.

All visits assessments are detailed in section 5.4.2.

The investigator may conduct unscheduled visits, for safety reasons, or any other reason per investigator medical judgment.

Throughout the LT-OLE-PEN period, patients will continue to complete a patient diary at home to collect dosing and safety data.

Figure 1: Overall Study Design



* Patients from cohorts 1 and 2 who already started their second year of long term extension, will begin receiving 0. 66 mg/kg/week as from their next scheduled visit

4. Study Population

In order to enroll up to 56 patients (allocated to 4 cohorts) into the Main Study, a sufficient number of pre-pubertal males aged 3 – 11 and females aged 3 – 10, with either isolated growth hormone deficiency (GHD) or GH insufficiency as a part of multiple pituitary hormone deficiency, will be recruited from 10 to 12 countries and 20 to 40 different centers. All centers will be specialized in the treatment and management of pediatric GHD.

The study population will consist of 2 subgroups:

1. Patients with peak GH level of [redacted] ng/ml (up to 40 patients).
2. Patients with peak GH level of [redacted] ng/ml and [redacted] ng/ml (up to 16 patients).

Patients must meet all of the inclusion and none of the exclusion criteria to be eligible. Patient eligibility will be verified by the study Medical Monitor before randomization.

Patients who complete 12 months of treatment in the Main Study will be eligible to continue the treatment with MOD-4023 in a 12-month OLE period, and subsequent LT-OLE period and LT-OLE-PEN period until marketing approval in their country. The LT-OLE-PEN period will be extended on an annual basis until marketing approval in each country, subject to submission of an annual extension notification to the local EC/IRB.

4.1 INCLUSION CRITERIA

1. Pre-pubertal child aged ≥ 3 years old and not above 10 years for girls or 11 years for boys, with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency.
2. Confirmed diagnosis of GHD by two different GH provocation tests defined as a peak plasma GH level of [redacted]ng/ml[1], determined by central laboratory using a validated assay[2]. If the patient has already been tested locally and reserve samples that were taken at appropriate time-points are available, these will be reanalyzed by the central laboratory[3]. Historical tests missing the -30 minutes time point will be accepted. If no reserve samples are kept (only for tests performed prior to site initiation), then the details of the locally performed tests will be reviewed by the Coordinating Investigator: if the results cannot be accepted, the patient will undergo both stimulation tests during the screening period and the samples will be analyzed by the central laboratory. At least one of the two stimulation tests (and preferably both) will be analyzed by the central laboratory. If the patient requires sex hormone priming (due to the age), and both stimulation tests must be performed during the Screening (no historical samples kept, or test was without priming), it is recommended to perform stimulation tests in consecutive setting in one day, or in two consecutive days, to avoid priming the patient twice. Local historical tests without sex-steroid priming will not be accepted for patients that require sex steroid priming according to the protocol.
3. Bone age (BA) must be not older than chronological age, and should be no greater than 9 years for girls and 10 years for boys.
4. Without prior exposure to any r-hGH therapy.
5. Impaired height and height velocity defined as:
    a. Height (HT) of at least 2.0 standard deviations (SD) below the mean height for chronological age (CA) and gender according to the standards of Prader et al. (1989) (HT SDS ≤ -2.0);
    b. Annualized height velocity (HV) below the 25th percentile for CA (HV <-0.7 SDS) and gender according to the standards of Prader et al. (1989). The interval

[1] Patients will be divided into two subgroups: Patients with peak serum GH levels after stimulation test [redacted] ng/ml and patients with peak serum GH levels after stimulation test [redacted] and [redacted] ng/ml.
[2] Insulin tolerance test, with cortisol response to hypoglycemia if insulin stimulation test is chosen / Arginine test / Clonidine test / Glucagon test (plus or without propranolol) / L-dopa plus propranolol.
[3] Central laboratory results will be used for eligibility confirmation.

between two height measurements should be at least 6 months, but should not exceed 18 months prior to inclusion.

6. BMI must be within ±2 SD of mean BMI for the chronological age and sex according to the 2000 CDC standards (www.cdc.gov/growthcharts).
7. Baseline IGF-I level of at least 1 SD below the mean IGF-I level standardized for age and sex (IGF-I SDS ≤ -1.0) according to the central laboratory reference values.
8. Children with normal fundoscopy (ophthalmoscopy) at screening (without signs/symptoms of intracranial hypertension as assessed by fundoscopy).
9. Children with multiple hormonal deficiencies must be on stable replacement therapies for other hypothalamo-pituitary-organ axes for at least 3 months and 6 months for thyroid replacement therapy prior to the first study drug administration.
10. Normal 46 XX karyotype for girls.
11. Written informed consent of the parent or legal guardian of the patient and assent of the patient for the Main Study and for the OLE.

    Patients who completed the first year of treatment in the Main Study are allowed to enter the OLE. Patients who were off treatment for over [redacted] after completing the main study (or during the OLE) are allowed to participate/continue in the OLE after completing additional testing.

Specific inclusion criteria for Period V (LT-OLE –PEN):

12. Continuing participation in the LT-OLE-PEN period.
13. Signed consent and assent (when applicable) form for the LT-OLE-PEN period.
14. Investigator's assessment and confirmation of the patient anticipated compliance to the protocol procedures.
15. Agreement to refrain from sexual activity during the study i.e. observe complete sexual abstinence as the only acceptable contraceptive measure in this study.

4.2 Exclusion Criteria

1. Children with past or present intracranial tumor growth as confirmed by an MRI scan (with contrast).
2. History of radiation therapy or chemotherapy.
3. Malnourished children defined as:
    a. Serum albumin below the lower limit of normal (LLN) according to the reference ranges of central laboratory, AND
    b. Serum iron below the lower limit of normal (LLN) according to the reference ranges of central laboratory, AND
    c. BMI < -2 SD for age and sex.
4. Children with psychosocial dwarfism.

5. Children born small for gestational age (SGA = birth weight and/or birth length < -2 SD 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. Patients with diabetes mellitus.
9. Patients with impaired fasting sugar (based on WHO; fasting blood sugar >110 mg/dl or 6.1 mmol/l after repeated blood analysis).
10. Chromosomal abnormalities and medical "syndromes" (Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi Syndrome, Russell-Silver Syndrome, SHOX mutations/deletions and skeletal dysplasias), with the exception of septo-optic dysplasia.
11. Closed epiphyses.
12. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids and methylphenidate for attention deficit hyperactivity disorder (ADHD), with the exception of hormone replacement therapies (thyroxin, hydrocortisone, desmopressin (DDAVP)).
13. Children requiring glucocorticoid therapy (e.g. asthma) that are taking a dose of greater than 400 µg/d of inhaled budesonide or equivalents[1] for longer than 1 month during a calendar year.
14. Major medical conditions and/or presence of contraindication to r-hGH treatment.
15. Known or suspected HIV-positive patient, or patient with advanced diseases such as AIDS or tuberculosis.
16. Drug, substance, or alcohol abuse.
17. Known hypersensitivity to the components of study medication.
18. Other causes of short stature such as coeliac disease, hypothyroidism and rickets.
19. The patient and/or the parent/legal guardian are likely to be non-compliant in respect to study conduct.
20. Participation in any other trial of an investigational agent within 30 days prior to Screening.

[1] Approximately equivalent doses: Fluticasone: 264 µg/d; Beclomethasone: 504 µg/d; Flunisolide 1,000 µg/d; Triamcinolone: 1,000 µg/d.

Specific exclusion criteria for Treatment Period V (LT-OLE-PEN):

21. Unresolved drug related SAE from previous treatment periods.
22. Diagnosis of cancer.
23. Patients who, based on the investigator's judgment, have a clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation. Conditions may include cardiovascular, peripheral vascular, pulmonary, hepatic, renal, neurological and metabolic disease.
24. Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids or replacement of sex hormones, with the exception of ADHD drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin [DDAVP]).
25. Unsatisfactory treatment response defined as improvement of height SDS of less than 0.2 SDS in a 6-month treatment interval if dose increase at this time point is not feasible.

4.3 Patient Identification

Parents or legal guardians (as well as patients when relevant) will sign an informed consent/assent form prior to any study activities. Upon signature of informed consent, the patient will be allocated a study number comprised of two digits to identify the site and three digits to identify the patient. This number will identify the patient throughout the study. In the case of re-screening, a new unique number will be allocated.

Additional informed consent/assent forms will be signed by parents or legal guardians before the patient continues to the OLE, LT-OLE and LT-OLE-PEN periods.

4.4 Screening Failures

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

Screen failure patients will be withdrawn from the study and receive common practice performed at the site. Screen failures will be replaced to achieve enrolment of up to 56 patients.

If a patient is not eligible, the Investigator will record the reason for screening failure in the screening eCRF. Patients who have completed the Screening visit and are assessed as not eligible (screening failures) may be considered for re-screening at a later time, subject to the Principal Investigator's approval.

4.5 Randomization

In the Main Study, patients will be randomized in a 1:1:1:1 ratio to one of 3 different MOD-4023 weekly dose cohorts, or the Genotropin cohort.

The randomization will ensure that the study population will consist of: up to 40 patients with peak GH level of [redacted] ng/ml (up to 10 patients per cohort) and up to 16 patients with peak GH level of [redacted] ng/ml and [redacted] ng/ml (up to 4 per cohort);

Randomization will be stratified by:

1. Stimulation tests peak plasma GH level: patients with peak GH level [redacted] ng/ml and patients with peak GH level [redacted] ng/ml and [redacted] ng/ml.
2. Patients with peak plasma GH level [redacted] ng/ml will additionally be stratified by age (patients ≤7 years and patients > 7 years), height SDS minus target height SDS (distance from target height SDS ≤ -3 and > -3) and by peak GH levels [redacted] Patients with peak GH levels [redacted] can be enrolled in the study. However, these patients have a separate randomization list.

The randomization will be performed via a web-based electronic data capture (EDC) system once all screening data is available and reviewed by the Medical Monitor.

In the OLE period all patients will receive MOD-4023. Patients who received MOD-4023 in the Main Study will continue on the same dose. Patients treated with Genotropin will be switched to MOD-4023 and will be randomized to one of the three MOD-4023 cohorts.

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

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

Patients withdrawn from the study after starting treatment with MOD-4023 will not be replaced.

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

1. Request from regulatory agency, sponsor, primary care physician, or Investigator.
2. Patient (or parent/legal guardian) withdraws consent.
3. Adverse event (AE):
    - Occurrence of a malignancy during the course of study.
    - Evidence of growth of an intracranial tumor during the course of the study.
    - Development of benign intracranial hypertension, if the symptoms return following resumption of drug (after a temporary stop).
    - Occurrence of AE's following which the Investigator or the patient wishes to discontinue treatment (such as, but not limited to, slipped capital femoral epiphysis, scoliosis, avascular necrosis and development of lipoatrophy, etc.).
    - Development of a serious inter-current critical illness.
    - Abnormal laboratory values that affect the patient's safety (if discontinuation is considered necessary by the Investigator or the Sponsor Medical Monitor).

4. A severe adverse drug reaction (if discontinuation of study medication is desired by the patient or considered necessary by the investigator or the Sponsor Medical Monitor). If the Investigator decision is made because of a SAE or clinically significant laboratory value, the Medical Monitor is to be alerted immediately.
5. Intake of prohibited concomitant medication.
6. Unsatisfactory treatment response defined as improvement of height SDS of less than 0.2 SDS in a 6-month treatment interval if dose increase at this time point is not feasible (Applicable for periods I-IV)
7. Patient is unwilling or unable to continue the study or is lost-to-follow-up.
8. Patient is non-compliant with study procedures/ study protocol.
9. Investigator decides that withdrawal from the study is in the best interest of the patient:
    - Occurrence of neutralizing antibodies which, in the opinion of the Investigator, requires discontinuation of the patient.
    - Lack of patient compliance (if discontinuation is desired or considered necessary by the investigator or the Sponsor Medical Monitor).
    - A serious protocol deviation that affects the patient's safety or the accuracy and/or validity of data.
10. Patient meets one of the exclusion criteria during the study.
11. Any clinically significant change in the patient's medical condition.

<u>Discontinuation rules specific to the LT-OLE-PEN period:</u>

12. Positive urine pregnancy test or confirmed pregnancy. In case of confirmed pregnancy, the study drug should be discontinued and the Medical Monitor be alerted immediately.
13. When the patient reaches a growth rate of [redacted]12 months (the interval between two height measurements should be at least 6 months).

4.6.1 Handling of Withdrawals

If a patient is withdrawn from the study either at his or her request (or parent/legal guardian request) or at the Investigator's discretion or fails to return, every effort should be made to determine the reason. This information will be recorded on the patient's case report form (eCRF). All patients who withdraw from the study prematurely, regardless of cause, should undergo all early termination assessments (see Section 5.5.2). It is vital to obtain follow-up data for any patient withdrawn because of an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

If withdrawal is caused by an AE that the Investigator considers possibly related to the study drug, it will be reported to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the Sponsor.

Any serious adverse event must be reported to the Sponsor by telephone and in writing within 24 working hours, and to the IRB/IEC according to site's regulations (see Section 7.2). The study may also be terminated by the Principal Investigator (PI) following consultation with the Sponsor.

All follow-up information will be recorded in the patient's eCRF until full patient recovery is achieved, and the PI has stated that the patient is dismissed from the medical care. Subsequent follow-up will be documented in the patient's personal file.

5. Study Procedures and Assessments

No protocol related procedures, including the cessation of prohibited concomitant medications, should be performed before the parent or legal guardian provides a written informed consent and the patients provide an assent (a signed assent for children who can read). 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.

All visit windows will be on scheduled days or -1 day (except visit 9 main study) for MOD-4023 dose cohorts unless it's specified otherwise. The study flow chart provides the summary of assessments scheduled for each visit during the Main Study (Appendix 1), 12 months OLE study (Appendix 2), Long Term OLE (LT-OLE) period (Appendix 3) and Long Term OLE PEN (LT-OLE-PEN) period (Appendix 4 and Appendix 5). At each visit after start of treatment, patients will be given enough Investigational or Comparator Product for treatment until the next visit, as well as patient diary cards to record injection pain or other adverse events and other comments.

5.1 Main Study

5.1.1 Screening

Patients' eligibility will be determined during the screening period lasting for up to 6 weeks and the following key tests and assessments must be performed and data obtained:

1. Informed consent of parent/legal guardian and patient assent.
2. Data on growth history and current anthropometric measurements (auxology).
3. Body weight.
4. Medical history, including a description of pituitary deficiencies, concomitant and previous medications.
5. Overall health status assessments – complete physical examination, vital signs, and ECG.
6. Pubertal status (according to Tanner stages).
7. Bone age determination – with the method of Greulich-Pyle using a central bone age reader.
8. Assessment of biochemical markers and stimulation tests:

- Two different GH stimulation (provocation) tests:

  Insulin tolerance test (with cortisol response to hypoglycemia if insulin stimulation test is chosen) / arginine test / clonidine test / glucagon test (with or without propranolol) / L-dopa plus propranolol. Sex hormone priming will be performed prior to GH-stimulation tests for girls over the age of 8 and for boys over the age of 10 (for a description of the GH stimulation tests and sex hormone priming, refer to Appendix 7). If the patient has already been tested locally and reserve samples that were taken at appropriate time-points are available, these will be reanalyzed by the central laboratory[1]. Historical tests missing the -30 minutes time point will be accepted. If no reserve samples are kept (only for tests performed prior to site initiation), then the details of the locally performed tests will be reviewed by the Coordinating Investigator: if the results cannot be accepted, the patient will undergo both stimulation tests during the screening period and the samples will be analyzed by the central laboratory. At least one of the two stimulation tests (and preferably both) will be analyzed by the central laboratory.

- Standard Dose Short ACTH test (only if the patient was not assessed previously for the hypothalamus-pituitary-adrenal axis, or if there are clinical or laboratory signs of adrenal insufficiency).
- Assessment of insulin-like growth factor (IGF-I) and IGFBP-3 levels.
- Assessment of anti-hGH antibody levels.
- Assessments of routine safety biochemistry and hematology parameters.
- Assessment of hormones (TSH, free T4, free T3 and cortisol).
- Assessment of glucose metabolism (fasting insulin, glucose, and HbA1C).
- Parameters of lipid metabolism (with Lp(a) lipoprotein).

9. Head MRI performed in the 6 months prior to the trial.
10. Fundoscopy.
11. Assessment of karyotype in girls.
12. SHOX evaluation in all patients.

Key data and all test results obtained during the screening will be reviewed by the Sponsor Medical Monitor to verify eligibility prior to randomization of each patient. Following confirmation of eligibility by the Principal Investigator, the patients will be randomized to one of the dose groups.

5.1.2 Visit 1 – All Patients

This visit will take place in the medical center for all patients on the day of the first dose. The following procedures will be performed (prior to dosing for MOD-4023 cohorts):

1. Physical examination including height and weight;

[1] Central laboratory results will be used for eligibility confirmation.

2. Vital signs (within one hour prior to dosing);
3. AEs, local tolerability;
4. Concomitant medications;
5. Parameters of glucose metabolism (fasting glucose, insulin, and HbA1C);
6. Other hormonal levels (TSH, free T4, free T3, cortisol);
7. Baseline antigenicity (anti MOD-4023 antibodies for cohort 1-3 patients) and anti hGH for Genotropin patients
8. Routine safety biochemistry and hematology;
9. Parameters of lipid metabolism (with Lp(a) lipoprotein);
10. IGF-I and IGFBP-3 serum levels, baseline MOD-4023 (cohorts 1-3) and Genotropin (cohort 4) levels;
11. Training for parents or legal guardians on drug administration.

Patients allocated to the MOD-4023 cohorts will be administered the first dose by the study staff in the morning hours, after completion of all of the above.

The following procedures will be performed after dosing (for MOD-4023 cohorts):

1. Vital signs: 30 min, 2 hours (±20 min) and 4 hours (±20 min) post dose;
2. Injection site reaction: 30 min and 4h (±20 min) after injection.

Patients allocated to the Genotropin cohort will be administered the first dose at home in the evening hours.

5.1.3 PK/PD Visits (V2 - Week 2; V3 - Week 4; V4 -Week 6)

All patients randomized to receive one of the three MOD-4023 doses will start treatment for 2 weeks with the low MOD-4023 dose (0.25 mg protein/kg). Based on the patient's dose allocation, this will be followed by a dose increase to the next dose level every two weeks until the final allocated dose is reached (see Table 5).

Subsequent to the second dose administration of the targeted dose, limited (population based) PK and PD sampling will be taken (according to Table 6 and Table 7).

Patients allocated to a MOD-4023 dose cohort (cohorts 1-3) will be randomized within the cohort into one of three blocks and undergo limited PK/PD sampling (4 samples per patient over a period of one week), according to Table 6 below.

TABLE 6: MOD-4023 POPULATION PK AND PD SAMPLING SCHEME

Visit (V2, V3, V4)	a			b	c	d	e	f	g
Time after dosing(h)/ Block number	0h	6h	12h	24h	48h	72h	96h	120h	168h
Block 1									
Block 2									
Block 3									

Patients allocated to the Genotropin dose cohort (cohort 4) will be randomized within the cohort into one of three blocks and undergo limited PK/PD sampling (4 samples per patient over a period of 24 hours), according to Table 7 below.

TABLE 7: GENOTROPIN POPULATION PK AND PD SAMPLING SCHEME (VISIT 2)

Time after dosing(h)/ Block number	0h	1h	2h	4h	6h	12h	16h	20h	24h
Block 1									
Block 2									
Block 3									

This blood sampling schedule may require hospitalization for some of the patients due to convenience reasons.

During the first 6 weeks of the study, the visit schedule will be as follows (see scheme in Appendix 1: Schedule of Assessments – Main Study):

5.1.3.1 Week 2: V2 (a-h) – MOD-4023 Dose Cohorts

a. **Dose Cohort 1:** Patients allocated to dose cohort 1 will perform Visit 2 (PK/PD following the 2nd dose of MOD-4023 at target dose level) as follows:

Visit	a			b	c	d	e	f	g
Time after dosing(h)/ Block number	0h	6h	12h	24h	48h	72h	96h	120h	168h
Block 1									
Block 2									
Block 3									

On day of dosing (V2a), all patients allocated to dose cohort 1 will arrive at the medical center in the morning hours (irrespective of the allocation to blood sampling blocks).

The following procedures will be performed prior to dosing:

1. Physical examination;
2. Vital signs (within one hour prior to dosing);
3. AEs, local tolerability;

4. Concomitant medications;
5. Parameters of glucose metabolism (fasting glucose, insulin);
6. IGF-I and IGFBP-3 serum levels (for patients in block 1);
7. MOD-4023 serum levels (for patients in block 1).

The following procedures will be performed **after dosing**:

1. IGF-I and IGFBP-3 serum levels: (6h post-dose for patients in block 2 and 12h post-dose for patients in block 3);
2. MOD-4023 serum levels: (6h post-dose for patients in block 2 and 12h post-dose for patients in block 3);
3. Vital signs: 30 min, 2 hours (±20 min), and 4 hours (±20 min) post-dose;
4. Injection site reaction: 30 min and 4h (±20 min) after injection.

In addition, the following procedures will be performed upon subsequent blood withdrawals throughout the week:

1. Vital signs (prior to blood sampling);
2. AEs and local tolerability (prior to blood sampling);
3. Concomitant medications (prior to blood sampling);
4. IGF-I and IGFBP-3 serum levels;
5. MOD-4023 serum levels.

b. **Dose Cohorts 2+3:** Patients allocated to dose cohorts 2 and 3 will perform visit 2h (4 days after dosing). The following procedures will be performed:

1. Physical examination;
2. Vital signs;
3. AEs and local tolerability;
4. Concomitant medications;
5. Parameters of glucose metabolism (fasting glucose, insulin);
6. IGF-I and IGFBP-3 serum levels;
7. MOD-4023 serum levels.

5.1.3.2 Week 4: V3 (a-h) – MOD-4023 Dose Cohorts

a. **Dose Cohort 2:** Patients allocated to dose cohort 2 will perform Visit 3 - PK/PD following the 4th dose of MOD-4023 (2nd dose at target dose level) as follows:

Visit	a			b	c	d	E	f	g
Time after dosing(h)/ Block number	0h	6h	12h	24h	48h	72h	96h	120h	168h
Block 1									
Block 2									
Block 3									

On the day of dosing (V3a), all patients allocated to dose cohort 2 will arrive at the medical center in the morning hours (irrespective of the allocation to blood sampling blocks).

The following procedures will be performed prior to dosing:

1. Physical examination;
2. Vital signs (within one hour prior to dosing);
3. AEs, local tolerability;
4. Concomitant medications;
5. Parameters of glucose metabolism (fasting glucose, insulin);
6. IGF-I and IGFBP-3 serum levels (for patients in block 1);
7. MOD-4023 Serum levels (for patients in block 1).

The following procedures will be performed **after dosing**:

1. IGF-I and IGFBP-3 serum levels: (6h post-dose for patients in block 2 and 12h post-dose for patients in block 3);
2. MOD-4023 serum levels: (6h post-dose for patients in block 2 and 12h after dose for patients in block 3);
3. Vital signs: 30 min, 2 hours (±20 min), and 4 hours (±20 min) post-dose;
4. Injection site reaction: 30 min and 4h (±20 min) after injection.

In addition, the following procedures will be performed upon subsequent blood withdrawals throughout the week:

1. Vital signs (prior to blood sampling);
2. AEs and local tolerability (prior to blood sampling);
3. Concomitant medications (prior to blood sampling);
4. IGF-I and IGFBP-3 serum levels;
5. MOD-4023 serum levels.

b. **Dose Cohort 1 and Dose Cohort 3 (V3h):** Patients allocated to dose cohort 1 will skip Visit 3 and patients allocated to dose cohort 3 will perform visit 3h (4 days after dosing).
The following procedures will be performed:
1. Physical examination;
2. Vital signs;

3. AEs and local tolerability;
4. Concomitant medications;
5. Parameters of glucose metabolism (fasting glucose, insulin);
6. IGF-I and IGFBP-3 serum levels;
7. MOD-4023 serum levels.

5.1.3.3 Week 6: V4 (a-h) - MOD-4023 Dose Cohorts

a. **Dose Cohort 3:** Patients allocated to dose cohort 3 will perform Visit 4 - PK/PD following the 6th dose of MOD-4023 (2nd dose at target dose level) as follows:

Visit	a			b	c	d	e	f	g
Time after dosing(h)/ Block number	0h	6h	12h	24h	48h	72h	96h	120h	168h
Block 1									
Block 2									
Block 3									

On the day of dosing (V4a), all patients allocated to dose cohort 3 will arrive at the medical center in the morning hours (irrespective of the allocation to blood sampling blocks).

The following procedures will be performed prior to dosing:

1. Physical examination;
2. Vital signs (within one hour prior to dosing);
3. AEs, local tolerability;
4. Concomitant medications;
5. Parameters of glucose metabolism (fasting glucose, insulin, and HbA1C);
6. Routine safety biochemistry, hematology, and urinalysis parameters;
7. IGF-I and IGFBP-3 serum levels (for patients in block 1);
8. MOD-4023 Serum levels (for patients in block 1).

The following procedures will be performed **after dosing**:

1. IGF-I and IGFBP-3 serum levels: (6h post-dose for patients in block 2 and 12h post-dose for patients in block 3);
2. MOD-4023 serum levels: (6h post-dose for patients in block 2 and 12h post-dose for patients in block 3);
3. Vital signs: 30 min, 2 hours (±20 min), and 4 hours (±20 min) post-dose;
4. Injection site reaction: 30 min and 4h (±20 min) after injection.

In addition, the following procedures will be performed upon subsequent blood withdrawals throughout the week:

1. Vital signs (prior to blood sampling);
2. AEs and local tolerability (prior to blood sampling);
3. Concomitant medications (prior to blood sampling);
4. IGF-I and IGFBP-3 serum levels;
5. MOD-4023 serum levels.

b. **Dose Cohorts 1 and 2:** Patients allocated to dose cohort 1 and 2 will perform visit 4h (4 days after dosing)
The following procedures will be performed:

1. Physical examination;
2. Vital signs;
3. AEs and local tolerability;
4. Concomitant medications;
5. Parameters of glucose metabolism (fasting glucose, insulin, and HbA1C);
6. Routine safety biochemistry, hematology, and urinalysis parameters;
7. IGF-I and IGFBP-3 serum levels;
8. MOD-4023 serum levels.

5.1.3.4 Week 2 and 6: Visits 2 and 4 for Genotropin Cohort (Cohort 4)

Patients allocated to Cohort 4 will perform Visits 2 and 4. Cohort 4 patients will skip Visit 3 (week 4).

Patients allocated to the Genotropin cohort (cohort 4) will return to the medical center for visits 2 and 4 during the 2nd and 6th week of treatment. The following procedures will be performed (prior to dosing if dosing is done at the medical center):

1. Physical examination;
2. Vital signs;
3. AEs, local tolerability;
4. Concomitant medications;
5. Parameters of glucose metabolism - fasting glucose, insulin, and HbA1C (V4 only);
6. Routine safety biochemistry, hematology, and urinalysis parameters (week 6 only – visit 4);
7. IGF-I and IGFBP-3 serum levels;
8. Genotropin serum levels.

In addition, after the 8th Genotropin dose (at the beginning of week 2 of dosing) the patients allocated to the Genotropin cohort will undergo limited PK/PD sampling according to Table 7 above. Patients allocated to the Genotropin dose cohort (cohort 4) will be randomized within the cohort into one of three blocks and undergo limited PK/PD sampling (4 samples per patient over a period of 24 hours), according to following scheme:

Time after dosing(h)/ Block number	0h	1h	2h	4h	6h	12h	16h	20h	24h
Block 1									
Block 2									
Block 3									

5.1.4 Monthly Follow Up Visits: Visit 5 (wk10), Visit 6 (wk14), Visit 7 (wk18), Visit 8 (wk22) - All Patients

These visits will be performed on a monthly basis for all patients. For patients allocated to MOD-4023 dose cohorts, the visit will take place 4(-1) days after dosing. For patients allocated to Genotropin cohort, the visit will take place on any day during the dosing week.

The following assessments will be performed:

1. Physical examination and vital signs;
2. AEs, local tolerability, and concomitant medications;
3. Parameters of glucose metabolism: fasting glucose, insulin (every visit), HbA1c (only visit 6);
4. Other hormonal levels: TSH, free T4, free T3, cortisol (only visit 6);
5. Routine safety biochemistry, hematology, and urinalysis parameters;
6. Patient's height;
7. Patient's weight;
8. Parameters of lipid metabolism (with Lp(a) lipoprotein at visit 6);
9. PD: IGF-I and IGFBP-3 serum levels;
10. MOD-4023 (cohort 1-3) and Genotropin (cohort 4) serum levels;
11. Adjustment of dose to patient's weight (only visit 6).

5.1.5 Visit 9 (wk23) – Only MOD-4023 Dose Cohorts

This visit will take place **exactly** one week (7 days) after MOD-4023 dosing, prior to administration of the next dose. If patient is unable to attend the visit, the entire visit can be postponed by one week in order to obtain pre-dose levels of MOD-4023 and IGF-I+IGFBP-3.

The following assessments will be performed prior to MOD-4023 dosing:

1. Physical examination and vital signs (prior to blood sampling);
2. AEs, local tolerability, and concomitant medications (prior to blood sampling);

3. PD: IGF-I and IGFBP-3 serum levels (prior to dosing);
4. MOD-4023 (cohort 1-3) serum levels (prior to dosing);
5. MOD-4023 dosing.

The following procedures will be performed **after MOD-4023 dosing**:

1. Vital signs: 30 min, 2 hours (±20 min), and 4 hours (±20 min) post dose.
2. Injection site reaction: 30 min and 4h (±20 min) after injection.

5.1.6 Visit 10 (wk26) – All Cohorts

The following assessments will be performed:

1. Physical examination and vital signs;
2. AEs, local tolerability, and concomitant medications;
3. Parameters of glucose metabolism: fasting glucose, insulin, HbA1c;
4. Other hormonal levels: TSH, free T4, free T3, cortisol;
5. Antigenicity: anti MOD-4023 antibodies/anti-hGH antibodies;
6. Routine safety biochemistry, hematology and urinalysis parameters;
7. Patient's height;
8. Patient's weight;
9. Fundoscopy;
10. Parameters of lipid metabolism (with Lp(a) lipoprotein);
11. Pubertal status;
12. PD: IGF-I and IGFBP-3 serum levels;
13. MOD-4023 (cohort 1-3) and Genotropin (cohort 4) levels;
14. Adjustment of dose to patient's weight.

After completion of visit 10, each patient will be assessed separately, for the growth progress and overall safety. If the growth meets pre-determined criteria[1], and there are no safety concerns, the patient will continue with the same dose.

5.1.7 V11 (month 9), V12 (month 12) – All Cohorts – PERIOD II

This period will consist of 2 visits at Months 9 and 12. Month 9 visit will be conducted on day 4(-1) after MOD-4023 dosing for MOD-4023 dose cohorts, and any day during the week for

[1] Delta height SDS at least 0.2

Genotropin cohorts. Month 12 visit (final visit of the Main Study) will be conducted 4 days (-1) after the last MOD-4023 dose for MOD-4023 cohorts and the day after the last Genotropin dose for Genotropin cohorts. Period II assessments will include the following at each visit:

1. Physical examination and vital signs;
2. AEs, local tolerability, and concomitant medications;
3. Parameters of glucose metabolism: fasting glucose, insulin, and HbA1c;
4. Other hormonal levels: TSH, free T4, free T3, cortisol;
5. Antigenicity: anti MOD-4023 antibodies/anti-hGH antibodies (only month 12 visit);
6. Routine safety biochemistry, hematology, and urinalysis parameters;
7. Patient's height;
8. Patient's weight;
9. Parameters of lipid metabolism at both visits (with Lp(a) lipoprotein at month 12 only);
10. Pubertal status (only month 12 visit);
11. PD: IGF-I and IGFBP-3 serum levels;
12. MOD-4023 (cohort 1-3) and Genotropin (cohort 4) serum levels;
13. Fundoscopy (Month 12 only or earlier if there are signs or symptoms indicative of benign intracranial hypertension);
14. ECG (Month 12 only);
15. Bone age (Month 12 only).

At the end of Period II, a formal data analysis of all endpoints will be performed.

5.2 12-Month Open Label Extension (OLE) Period III

Visits (Visit 1 OLE/Day 1, Visit 2 OLE/Month 1, Visit 3 OLE/Month 3, Visit 4 OLE/Month 6, Visit 5 OLE/Month 9 and Visit 6 OLE/Month 12)

Patients who completed 12 months of treatment in the Main Study will be eligible to continue to a 12-month OLE period. Patients who received MOD-4023 in the Main Study (initial 12 months of active treatment) will continue to receive MOD-4023; dose will be same as in the Main Study. For these patients, study visits will take place every 3 months, starting at visit 3 OLE.

For these patients, V12 of the Main study will be considered as the first visit of the OLE phase in which the patient will receive the study drug for the next 3 months of the OLE.

Patients who received active comparator, Genotropin, during the Main Study, will be switched to MOD-4023 (will be randomized to one of the three MOD-4023 cohorts). Their visit schedule during the first three months of the OLE will be as follows: Visit 1 OLE for the first MOD-4023 injection and training of MOD-4023 administration (week 52 +1 day, which is

on Month 12 visit of the Main Study), Visit 2 OLE will be 28 days + 4 (-1) days after the first MOD-4023 injection and Visit 3 OLE will be 3 months after first MOD-4023 injection (i.e. 13±2 weeks + 4 (-1) days after the first MOD-4023 injection). All subsequent visits will be every three months (i.e. every 13±2 weeks, 4 days (or 3 days, when necessary) after dosing).
Patients who are off treatment for over [redacted] between the last MOD-4023/Genotropin dose in the Main Study and the first OLE dose (2nd year) will be allowed to continue into the OLE period after the following tests will be conducted:

- Parameters of glucose metabolism: fasting glucose, insulin, and HbA1c
- Antigenicity: anti MOD-4023 antibodies (only Genotropin group – baseline for future tests)
- Routine safety laboratory (biochemistry, hematology, and urinalysis)
- PD: IGF-I and IGFBP-3 baseline serum levels
- MOD-4023 baseline serum levels

In the 12-month OLE visit (the second year of treatment) the following assessments will be included at each visit (unless otherwise specified):

- Adjustment of dose for weight
- local tolerability
- Physical examination and vital signs;
- AEs, and concomitant medications;
- Parameters of glucose metabolism: fasting glucose, insulin, and HbA1c;
- Other hormonal levels: TSH, free T4, free T3, cortisol;
- Antigenicity: anti MOD-4023 antibodies (only once every 6 months);
- Routine safety laboratory (biochemistry, hematology, and urinalysis);
- Patient's height;
- Patient's weight;
- Parameters of lipid metabolism;
- Lp(a) lipoprotein (only once at Month 12 OLE);
- Pubertal status (only once at Month 12 OLE);
- PD: IGF-I and IGFBP-3 serum levels;
- MOD-4023 serum levels;
- Fundoscopy (once at Month 12 OLE, or earlier if there are signs or symptoms indicative of benign intracranial hypertension);
- ECG (only once at Month 12 OLE)

- Bone age (only once at Month 12 OLE);
- Dispensing of drug and return of used drug
- Patient diary dispensing and return of completed patient diaries

5.3 LONG-TERM OPEN LABEL EXTENSION (LT-OLE) PERIOD IV

LT-OLE starts from the 2nd year of OLE (i.e. the 3rd year of treatment in the study) and until transition to PEN (LT-OLE-PEN period).

Patients in Cohorts 1 and 2 entering the LT-OLE will be switched to the highest MOD-4023 dose 0.66 mg/kg/week after signing a separate informed consent (unless a different medical decision was made). In case patients from Cohorts 1 and 2 who have already entered the 2nd year of OLE, the switch to 0.66 mg/kg/week will be done at their next study visit after signing a separate informed consent. Patients in Cohort 3 will continue receiving 0.66 mg/kg/week.
All patients switching to 0.66 mg/kg/week will be required to attend a site visit after 3 months (on day 3 or 4 post-dosing) for the following evaluations: physical examination and vital signs, patient's height and weight, concomitant medications, glucose metabolism parameters (fasting glucose, insulin and HbA1c), antigenicity (anti MOD-4023 antibodies), routine safety laboratory (biochemistry, hematology and urinalysis), IGF-I and IGFBP-3 serum levels.
In case the switch to the 0.66 mg/kg/week dose is on month 9 visit, the 3 months follow up visit will take place on dosing day. Additional visit will take place 3-4 post dosing in which only IGF-I, IGFBP-3 and MOD-4023 serum levels will be measured.

In general, if the IGF-I value will be above +2.0 SDS, please refer to section 5.8.3.
Patients who are off treatment for over [redacted] between the last MOD-4023 in the OLE period and the first LT-OLE dose (3rd year) will be allowed to continue into the LT-OLE period after the following tests and assessments will be conducted:

- Parameters of glucose metabolism: fasting glucose, insulin, and HbA1c
- Antigenicity: anti MOD-4023 antibodies
- Routine safety laboratory (biochemistry, hematology, and urinalysis)
- PD: IGF-I and IGFBP-3 baseline serum levels
- MOD-4023 baseline serum levels

The following assessments will be conducted once every 3 months (13 ±2 weeks) during LT-OLE (on day 4 (-1) post dose):

- Auxology measurements: Actual height measured on a calibrated stadiometer and body weight measurement;
- Adjustment of dose for weight;
- AEs;
- Local tolerability;
- Concomitant medication;
- Dispensing of drug and return of used drug
- Patient diary dispensing and return of completed diaries

The following assessments will be conducted every 6 months (±2 weeks) on day 4 (-1) post dose on top of the 3 month assessments:

- IGF-I, IGFBP-3 and MOD-4023 serum levels.
- Once a year, patients will be required to attend another visit **on dosing day** (in addition to the semi-annual visit on day 3 or 4 post dosing) where the following additional assessments will be conducted (on top of the three and six months assessments):Anti-MOD-4023 antibodies;
- MOD- 4023 serum levels
- Physical examination;
- Vital signs;
- Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c);
- Other hormonal levels (TSH, free T4, free T3, cortisol);
- Parameters of lipid metabolism;
- Routine safety laboratory (biochemistry, hematology and urinalysis);
- Pubertal status;
- ECG;
- Bone age;
- For males above the age of 13 - LH, FSH and testosterone. For females above the age of 12 - LH, FSH and estradiol;
- Fundoscopy (if indicated).

5.4 LONG-TERM OPEN LABEL EXTENSION PEN (LT-OLE-PEN) PERIOD V- UNTIL MARKETING APPROVAL

5.4.1 First year of LT-OLE-PEN period

5.4.1.1 PEN Visit 1 (PEN V1) – Dosing Day

Upon regulatory clearance of protocol Amendment 9 and sponsor's written approval, patients will be requested to come to the clinic for a visit named PEN Visit 1 (PEN V1). PEN V1 will occur on a planned dosing day, sites should make any effort to schedule this visit according to the current visit schedule and consider to combine visits in order to minimize the burden on the patients. Patients should arrive at the clinic prior to dosing. The visit will serve as 'baseline' to the LT-OLE-PEN period, in which the consent/assent form for the LT-OLE-PEN period will be signed. Patients should return used and unused vials that were dispensed during the study and kept at patient home. Site staff should remind the patients to bring all vials dispensed during the study (used and unused) before the visit.

Prior to rolling over into the LT-OLE-PEN period, specific period inclusion/exclusion criteria should be assessed (as specified in section 4.1). In addition changes in status of ongoing AEs or concomitant medications since completion of the LT-OLE period IV.

During PEN V1, the patients will be trained on the use of the PEN, the PEN will be dispensed, and the first PEN dose will be administered at the clinic by the parents/legal guardians. Patient will continue his/her treatment with the same dose level as before the switch to PEN. Patients will be provided with updated patient diary, instructions for use and dosing instructions.

The following will be done during PEN V1, pre dose:

- Auxology measurements (actual height measured on calibrated stadiometer);
- Body weight measurement;
- Adjustment of dose for weight;
- AEs;
- Urine pregnancy test for females of child bearing potential (In case of positive result please refer to section 7.4);
- Local tolerability;
- Concomitant medication;
- Dispensing of drug;
- Return of all used and unused vials;
- IGF-I, IGFBP-3 and MOD-4023 serum levels (PK);
- Anti MOD-4023 antibodies (ADA);
- Physical examination;
- Vital signs;
- Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c);
- Routine safety laboratory (biochemistry, hematology and urinalysis);
- Other hormonal levels (TSH, free T4 and cortisol);
- Lipid metabolism parameters;
- Pubertal status;
- For males above the age of 13 - LH, FSH and testosterone. For females above the age of 12 - LH, FSH and estradiol;
- Training on PEN;
- Fundoscopy- if required;
- Bone age assessment - Will be performed in case the previous assessment was done more than 6 months prior to this visit.

- Provide patient diary and return of completed diaries;

5.4.1.2 PEN Visit 2 (PEN V2) - Week 4 (+1 weeks) counting from PEN V1

Patients will come for PEN Visit 2 (PEN V2) 4 weeks (+1 week) following PEN V1, day 4 (-1) post dose. Patients will bring back the used PEN and the completed patient diary at this visit. In addition, if necessary, the patient will be re-trained on the PEN until the site and the patient are confident.

During PEN V2 the following will be conducted:

- Body weight measurement;
- Adjustment of dose for weight;
- AEs;
- Urine pregnancy test for females of child bearing potential (In case of positive result please refer to section 7.4);
- Local tolerability;
- Concomitant medication;
- Dispensing and return of drug;
- IGF-I, IGFBP-3 and MOD-4023 serum levels (PK);
- Anti MOD-4023 antibodies (ADA);
- Physical examination;
- Vital signs;
- Fundoscopy (if required);
- Provide patient diary and return of completed diaries;
- Training on PEN (if required).

Following routine visits schedule per patient is described in Appendix 4 and Appendix 5. The patients should follow the study specific visit assessments.

Following the completion of PEN V1 and PEN V2 patients will come to the clinic 4 days (-1 day) post dose every 3 months, (±2 weeks), counting from PEN V1.

5.4.1.3 Months 3 and 6 (±2 week) visits counting from PEN V1

The following will be conducted on these visits:

- Auxology measurements (actual height measured on calibrated stadiometer);
- Body weight measurement;
- Adjustment of dose for weight;

- AEs;
- Urine pregnancy test for females of child bearing potential (in case of positive result please refer to section 7.4);
- Local tolerability;
- Concomitant medication;
- Dispensing of drug and return of used drug
- IGF-I and IGFBP-3;
- MOD-4023 serum levels;Anti-MOD-4023 antibodies;
- Fundoscopy (if required);
- Physical examination and vital signs;
- Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c);
- Routine safety laboratory (biochemistry, hematology and urinalysis);
- Other hormonal levels (TSH, free T4 and cortisol);
- Lipid metabolism parameters;
- Pubertal status;
- Provide patient diary and return of completed diaries;

5.4.1.4 Month 9 (±2 week) visit counting from PEN V1

The following will be conducted at this visit:

- Auxology measurements (actual height measured on calibrated stadiometer);
- Body weight measurement;
- Adjustment of dose for weight;
- AEs;
- Urine pregnancy test for females of child bearing potential (in case of positive result please refer to section 7.4);
- Local tolerability;
- Concomitant medication;
- Dispensing of drug and return of used drug;
- Provide patient diary and return of completed diaries;
- IGF-I and IGFBP-3;
- MOD-4023 serum levels;
- Anti-MOD-4023 antibodies;
- Fundoscopy (if required);
- Physical examination and vital signs;
- Pubertal status;

5.4.1.5 Months 12 (±2 week) visit counting from PEN V1

On month 12 (±2 weeks) post PEN V1 two visit will be conducted, one on day 4 (-1) post injection and one on dosing day.

On month 12 (±2 weeks) on day 4 (-1) post injection IGF-I and IGFBP-3 will be assessed.
On month 12 (±2 weeks) on dosing day, the following will take place (pre dose):

- Auxology measurements (actual height measured on calibrated stadiometer);
- Body weight measurement;
- Adjustment of dose for weight;
- AEs;
- Urine pregnancy test for females of child bearing potential (in case of positive result please refer to section 7.4);
- Local tolerability;
- Dispensing of drug and return of used drug;
- Concomitant medication;
- Anti-MOD-4023 antibodies;
- MOD- 4023 serum levels;
- Physical examination;
- Vital signs;
- Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c);
- Other hormonal levels (TSH, free T4, cortisol);
- Parameters of lipid metabolism;
- Routine safety laboratory (biochemistry, hematology and urinalysis);
- Pubertal status;
- ECG around Tmax (7-12 hours post dosing). In case not possible to conduct the ECG around Tmax at this 12 month visit, it can be performed on month 12 ± 3 weeks (7-12 hours post dose)
- Bone age;
- For males above the age of 13 - LH, FSH and testosterone. For females above the age of 12 - LH, FSH and estradiol;
- Fundoscopy (if required);
- Provide patient diary and return of completed diaries

5.4.2 Second year of LT-OLE-PEN until marketing approval

From the second year of the LT-OLE-PEN period and until marketing approval, visits will be conducted every 3 months, ±2 weeks (months 3, 6, 9 and 12) on day 4 (-1) post injection.
The following will be conducted at each visit:

- Auxology measurement (actual height measured on calibrated stadiometer);
- Body weight measurement;
- Adjustment of dose for weight;
- AEs;
- Local tolerability;
- Concomitant medications;
- Dispensing of drug and return of used drug;
- Fundoscopy (if required);
- IGF-I and IGFBP-3;
- Physical examination and vital signs;
- Urine pregnancy test for females of child bearing potential (in case of positive result please refer to section 7.4);
- Pubertal status;
- Provide patient diary and return of completed diaries;

In addition, the following will be conducted every 6 months, on month 6 and month 12 visits:

- MOD-4023 serum levels;
- Anti MOD-4023 antibodies;
- Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c);
- other hormonal levels (TSH, free T4, cortisol);
- Parameters of lipid metabolism;
- Routine safety laboratory (biochemistry, hematology and urinalysis);

In addition, the following will be conducted once a year, on 12 month visit:

- ECG;
- Bone age;
- For males above the age of 13 - LH, FSH and testosterone. For females above the age of 12 - LH, FSH and estradiol

Throughout the LT-OLE-PEN period, patients will continue to complete a patient diary at home to collect dosing and safety data.

If splitting the dose between 2 different injections, the Patient should complete new diary page for each PEN or injection:

Weekly dose	Number of patient Diary pages
1 injection	1
2 injections from the same pen	2
2 injections from 2 different pens	2

The investigator may conduct unscheduled visits, for safety reasons, or any other reason per investigator medical judgment.

5.5 Unscheduled and Early Termination Visits

5.5.1 Unscheduled Visits

Unscheduled visits are those visits that will occur between regularly scheduled visits and will be performed in order to assess a previously noted adverse event, abnormal/alarming laboratory values, and or clinical findings. In such cases, the patient's parent or legal guardian will be contacted via telephone to arrange an unscheduled visit to assess the noticed abnormalities. Only focused assessments are foreseen for these visits and there will be no need to collect very extensive additional laboratory or other safety and efficacy data. If blood collection is required, this should in principle not exceed the volume foreseen for the assessment of questionable/targeted parameter(s) and/or should not be over 50% of volume foreseen for the routine safety panel at regularly scheduled visits. If urgent or more convenient for the patient, a local laboratory can be used.

According to point 4.5.4 of GCP-ICH, the investigator may implement a deviation form, or a change in the protocol, to eliminate an immediate hazard to a trial patient without prior IRB/IEC approval/favorable opinion. In this case the IRB/IEC will be notified retrospectively.

5.5.2 Early Termination and End of Study Visits – Main Study, OLE, LT-OLE and LT-OLE-PEN Periods

Early termination visits are appointed for the early termination/withdrawal of a patient from this clinical study. These visits may be performed on the same day as originally scheduled visits, or appointed separately. Data collection from these visits should primarily be guided according to GCP principles, protecting patient's safety and wellbeing. The schedule of assessments for early termination and end of study visits (both for patients in the Main Study and for those in other study periods) should follow those **requested for the last Study visit**

(i.e. month 12) of each period. The structure of early termination visit should be as much as possible similar to the last study visit.

5.6 Efficacy Assessments

Efficacy assessments will be done according to the schedule provided in Appendix 1: Schedule of Assessments – Main Study.

Height measurements must be performed according to Appendix 9. with a calibrated wall-mounted (e.g. Harpenden or similar) stadiometer and should ideally be conducted at the same time of the day for each visit, preferably in the morning. To ensure consistency of results, ideally the same auxologist will perform these measurements for each patient at each visit to minimize the variability of measurements. The time of measurement and the observer's name is to be recorded in the CRF. The arithmetic mean of three independent readings will be recorded for each visit in the CRF.

The means and the standard deviations (SD) of height for age and gender for normal children will be derived from the standards of Prader et al (Prader A, 1989).

The HV standardized for chronological age (CA) and gender (HVSDS) will be determined according to the standards of Prader et al (Prader A, 1989).

Predicted adult height (PAHT) will be calculated for children above 7 years of chronological age using Bayley-Pinneau tables for children with bone age greater than 6 years and a modified Bayley-Pinneau table for children with a bone age of 4-6 years (Bayley N, 1952). SD scores for PAHT will be based on normative data for adults.

Bone age (BA) will be determined by X-ray according to the method of Greulich and Pyle (Greulich & Pyle, 1959) at the Screening visit and 12 months and every 12 months in the OLE periods. X-ray films of the left hand and wrist will be taken as outlined in Appendix 10 and will be sent to a **qualified central reader**. The central reader will be blinded to the CA (chronological age), drug allocation, and name of the patients. X-ray films will hold only an identification number and gender. Details of the central bone age reader and the procedure for blinding and shipping of X-rays will be provided to the Investigator.

5.7 Safety Assessments

Safety assessments will consist of: monitoring and recording of all adverse events including serious adverse events, monitoring of glucose and lipid metabolism, thyroid status, cortisol levels, local injection site reactions, antibody formation, regular monitoring of hematology and blood biochemistry and urinalysis, regular monitoring of vital signs and physical condition.

5.7.1 Laboratory Safety Assessments

Analyses of routine hematology, serum biochemistry parameters and urinalysis, glucose and lipid parameters, antibody evaluation, IGF-I, as well as hormonal (thyroid and adrenal) status will be performed at a central laboratory.

Additional information regarding the collection, shipment of samples, reporting of results and alerting of extreme values will be provided in the Laboratory Manual.

Special attention will be paid to the monitoring of the following laboratory parameters:

- Indicators of glucose metabolism;
- Indicators of lipid metabolism;
- Assessment of IGF-I levels as safety parameters;
- Hormonal status with special attention to the thyroid and adrenal status;
- Assessment of liver enzymes;
- Assessment of MOD-4023 and r-hGH antigenicity.

5.7.1.1 IGF-I

IGF-I will be measured using the IDS-iSYS assay. The assay is based on chemiluminescence technology. Samples are incubated with an acidic solution to dissociate IGF-I from the binding proteins. A portion of this, along with neutralisation buffer, a biotinylated anti-IGF-I monoclonal antibody and an acridinium labelled anti-IGF-I monoclonal antibody is incubated for a further period of time. Streptavidin labelled magnetic particles are then added and following a further incubation step, the magnetic particles are "captured" using a magnet. After a washing step and addition of trigger reagents, the light emitted by the acridinium label is directly proportional to the concentration of IGF-I in the original sample.

IGF-I will be assessed according to the schedule provided in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

5.7.1.2 Assessment of glucose metabolism

Impaired glucose metabolism may lead to the discontinuation of study treatment. Glucose metabolism will be assessed through fasting insulin, fasting glucose levels and HbA1C levels.

Fasting glucose, insulin, and HbA1C will be assessed according to the schedule provided in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

Safety monitoring of potentially impaired glucose metabolism will also include parameters that have been associated with insulin resistance (e.g., fasting lipid profiles, changes in blood pressure, weight and BMI).

5.7.1.3 Indicators of lipid metabolism

In GHD patients, administration of GH has resulted in lipid mobilization, reduction in body fat stores, and increase in plasma fatty acids. However there still exists a slight controversy about potential atherogenic effects of chronic GH replacement therapy. Parameters that will be assessed in this protocol are: total cholesterol, HDL-cholesterol, LDL-cholesterol triglycerides and Lp(a) lipoprotein (Lp(a) lipoprotein will not be measured in the LT-OLE-PEN period). Monitoring of changes in lipid metabolism may be meaningful from two aspects, as an indicator of atherogenesis and as an indicator of insulin resistance. Lp(a) lipoprotein has been selected as a potentially challenging parameter. Previously there were reports indicating that Lp(a) lipoprotein, as well as the risk of atherogenesis increase under the treatment of r-hGH (Mooser V, 1997) (Olivecrona H, 1993), however there were several publications confirming that Lp(a) doesn't change during the GH treatment (Hassan HMS, 1995) (Hassan HMS, 1996).

One explanation for these contradictory findings could be the high variability of the assays used (Wieringa G, 2000), however the effects of sustained release and long-acting growth hormones have not been sufficiently investigated.

Indicators of lipid metabolism will be assessed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

5.7.1.4 Hormonal status with special attention on thyroid and adrenal status

Cortisol: Blood cortisol should be monitored throughout the study since GH treatment may unmask previously undiagnosed or sub-clinical central hypoadrenalism.
Supra-physiological glucocorticoid treatment may attenuate the growth promoting effect of somatropin (as for asthma). Therefore, children requiring a glucocorticoid dose of greater than 400 µg/d of inhaled budesonide or equivalents (approximately equivalent doses: Fluticasone: 264 µg/d; Beclomethasone: 504 µg/d; Flunisolide 1,000 µg/d; Triamcinolone: 1,000 µg/d) for longer than 1 month during a calendar year will not be included in the study or may be discontinued if additional dosing is required.

Thyroid hormones: Blood TSH and T4 should be monitored throughout the study since GH treatment may unmask previously undiagnosed or sub-clinical central hypothyroidism. Undiagnosed/untreated hypothyroidism attenuates growth and metabolism. Upon diagnosis of hypothyroidism, thyroid hormone replacement therapy should be initiated following approval by Coordinating Investigator. Thyroid dose should be adjusted throughout the study so that T4 levels will be close to the median range.

Gonadotrophic hormones - (applicable only for the LT-OLE and LT-OLE-PEN periods) - FSH, LH and Estradiol for females that are 12 years old and above and LH, FSH and testosterone for males that are 13 years old and above.

5.7.1.5 Assessment of antigenicity

Immunogenicity of MOD-4023 and of r-hGH will be assessed.

Baseline data for anti-hGH will be collected at Screening, and no patients with positive anti-hGH antibodies will be included in the study. Baseline anti-MOD levels will be measured at Visit 1. During the treatment period, samples will be taken according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

5.7.1.6 MOD-4023 hGH Concentrations

Samples for MOD-4023 concentrations will be collected according the schedule specified in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

Full blood (and blood smears) will be collected for hematology assessments.

The following parameters will be evaluated: hemoglobin, erythrocyte count, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), leukocytes, differential blood count of leukocytes, platelet count.

Hematology will be assessed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

5.7.1.7 Blood biochemistry

The following parameters will be evaluated: sodium, potassium, calcium, phosphate, chloride, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), gamma-glutamyl transferase (GGT), albumin, total proteins, creatinine, urea-nitrogen, uric acid, serum iron and transferrin, albumin.

Blood chemistry will be assessed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

5.7.2 Vital signs and Physical Examination

Body temperature, sitting blood pressure, respiratory rate and pulse rate (after at least 5 min rest) will be assessed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5, as per standard practice at each investigational site.

Physical examination, that includes assessment of head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system and, where appropriate, other body systems will be performed.

Physical examinations will be performed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

5.7.3 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 a visit) and on the basis of anamnestic data and records in the patient diary.

The abnormal injection site reaction is defined as:

- Injection site reaction which is observed at the time of visit and moderate to severe in intensity.
- Injection site reaction between the last and present visit, or remaining at the time of visit which require medical attention, or injection site reaction resulting from a previous injection, other than the last injection.
- Any other injection site reaction deemed abnormal to the investigator's judgment, other than those ordinarily observed in subcutaneous injections.

Observations will be recorded on appropriate eCRF pages. If an injection site reaction meets the criteria defined for an "abnormal result'" it will be considered an AE.

- Pain and Tenderness: For patients in all Cohorts, 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 [redacted] Pain Rating Scale (Appendix 8). In addition,

each patient and parent/guardian will be queried during study visits regarding possible injection site pain.

- Site status: For patients in all Cohorts, injection site status will be evaluated by the Investigator, or designated using the Injection Site Assessment Visual Analogue Scale (Appendix 8) at each of the PK/PD sampling time points. In addition, each patient and parent/guardian will be queried during study visits regarding possible site reactions.

The Investigator's Local Assessment of Tolerability eCRF page will be designed to capture the following information.

- Description of the reaction;
- Location: left arm/right arm/left thigh/right thigh/left buttock/right buttock/left part of abdomen/right part of abdomen;
- Duration: Onset, end date;
- Intensity: grading according to the scales provided in appendices;
- Action taken: action(s) taken by patients, medical intervention or concomitant medication;
- Comments.

Patient-reported local site reactions and diary records will be captured on the "Local Tolerability assessment" CRF page. Only data about reaction type (e.g. pain, erythema, etc.), frequency, and intensity will be captured.

5.7.4 Fundoscopy and MRI

Fundoscopy (opthalmoscopy) will be performed by the Investigator or an ophthalmologist consultant in order to assess signs of increased intracranial pressure prior to initiating or as a result of GH replacement. At screening (or within 6 months prior to screening), to confirm the diagnosis of GH deficiency and to confirm that there is no evidence of pituitary adenoma or any other intracranial tumor, a magnetic resonance imaging scan (MRI) with contrast will be done. It will be performed by the relevant department of the hospital according to the routine practice. During the study, MRIs may be performed per the investigator's discretion, (i.e. when there is suspicion of either growth of pituitary adenoma or any other intracranial tumor).

Fundoscopy will be performed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

5.7.5 ECG

ECG will be performed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5.

In the first year of the LT-OLE-PEN period ECG will be performed once a year on 12 months visit around Tmax (7 to 12 hours post injection). In case not possible to conduct the ECG around Tmax at this 12 month visit, it can be performed on month 12 ± 3 weeks (7-12 hours post dose). Adverse Events

Adverse events (AEs) will be assessed immediately following the written informed consent and assent (if applicable) and at all study visits throughout the study. Any AEs that occur throughout the study will be recorded. Any new systemic AE that occurs between scheduled visits should be brought to the attention of the Investigator and recorded in the patient's medical file and on the appropriate eCRF page.

For a list of common AEs associated with human GH, please refer to the Investigator's brochure.

5.8 Dose Modification and Discontinuation

The following symptoms and laboratory abnormalities measured at a single occasion or repeatedly, are considered to be the main guide for the decision about dose modification or treatment interruption:

- Growth factors plasma levels:
  - **Repeated consecutive** IGF-I > +2.0 SDS
- Glucose tolerance
  - HbA1c level > 6.2 %
  - Fasting glucose level is > 5.5 mmol/L
- Increase of liver enzymes (≥ 2x of ULN)
- Immune response
  - Development of high anti-growth hormone antibody titre with strong neutralizing effect
- Any other CTC grade 3 or 4 laboratory abnormality
- Development of intracranial hypertension or pseudotumor cerebri - If a patient has persistent severe headaches for more than 1 day not relieved by aspirin or other analgesics or visual disturbances, then examine the patient for papilledema (to be confirmed by an ophthalmologist). If there is papilledema, perform an MRI of the head with contrast; if there are signs of intracranial hypertension, perform a lumbar puncture (LP) and record the opening pressure. Only positive MRI findings and increased opening pressure on LP confirm the diagnosis of pseudotumor.

In the Main Study, dose efficacy will be analysed first after 6 months of treatment on an individual patient level. Patients who do not achieve the minimally satisfactory growth rate (i.e. delta height SDS of at least 0.2) at this time point will be moved to the next highest dose group for the remaining 6 months of treatment. Dose efficacy will be analysed again after 12 months of treatment on an individual patient level. Patients who do not achieve the minimally satisfactory growth rate at this time point will be moved to the next highest dose group. If the patient is in the highest dose group, the Coordinating Investigator of the study will be informed.

Cohort 1-3 patients transitioning to the OLE will continue with the same dose (mg/kg) in which they completed the main study.

In the OLE period, the patients who were in cohort 4, in the main study (e.g. treated with Genotropin) will be randomized to one of the MOD-4023 treatment groups.

In the LT-OLE period, all patients will be switched to the highest MOD-4023 dose 0.66 mg/kg/week.

In the LT-OLE-PEN period, patients should continue with the same dose.

The dose modifications will be performed according to the same rules as in the main study, including adjustment for weight every 3 months.

5.8.1 Dose Modifications Based on Adverse Effects (main study)

If a patient develops a **severe GH-related adverse event** at any time during the course of the study (Main and OLE), the Sponsor, the Coordinating Investigator, the investigator or the Data Safety Monitoring Board (DSMB) may propose one of three options:

1. **If the patient is allocated to Cohort 1 (0.25 mg protein/kg/week)** the following dose will not be given. If the symptoms disappear, the patient will continue on the same dose level as initially allocated. In case the symptoms reoccur, the patient may be withdrawn from the study.
2. **If the patient is allocated to Cohort 2 (0.48 mg protein/kg/week)** the dose will be lowered to the lower dose level (0.25 mg/kg/week) for a 2-4 week period. The patient may be re-challenged, once the symptoms disappear, with the same dose level as initially allocated. In case symptoms reoccur, the patient may be kept on the reduced dose level.
3. **If the patient is allocated to Cohort 3 dose (0.66 mg protein/kg/week)** the dose will be reduced by 15% to 0.56 mg/kg/week. If the symptoms are resolved, the patient will continue on the same dose level.

   In case the AE is persist or the symptoms reoccur the dose will be reduced again by 15% to 0.48 mg/kg/week. Patients, who had their dose reduced twice and who still have symptoms or they reoccur will be required to have individual medical consultation, depends on AE and /or symptoms assessment.

   It is recommended to consult with study Medical Monitor prior to dose changes (the Medical Monitor must be informed of such a change after the event if prior consultation is not possible).
4. **Patient will be withdrawn from the study either:**

- Without attempt of dose reduction if such a severe AE(s) develops that may affect patient safety and wellbeing.
- If symptoms do not disappear after the transient dose interruptions or dose reductions (Please see case 1-3 above).

5.8.2 Overdose with the Study Medication

An accidental overdose is not an AE if there are no signs or symptoms. Any undesirable medical occurrence resulting from an accidental overdose is an AE, and should be recorded and reported on the appropriate AE case report form. Since accidental overdoses with the study drug could have serious clinical consequences and/or represent a compliance issue, they should be reported immediately to [redacted] Safety Team [redacted] and evaluated by the Sponsor. The investigator should document any case of overdose and monitor the patient. Parent, or legal guardian training on adverse event reporting will be conducted at the screening visit and re-reviewed prior to patient randomization and additional retraining will be done before entering the OLE.

5.8.3 Dose adjustment paradigm

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-I SDS).

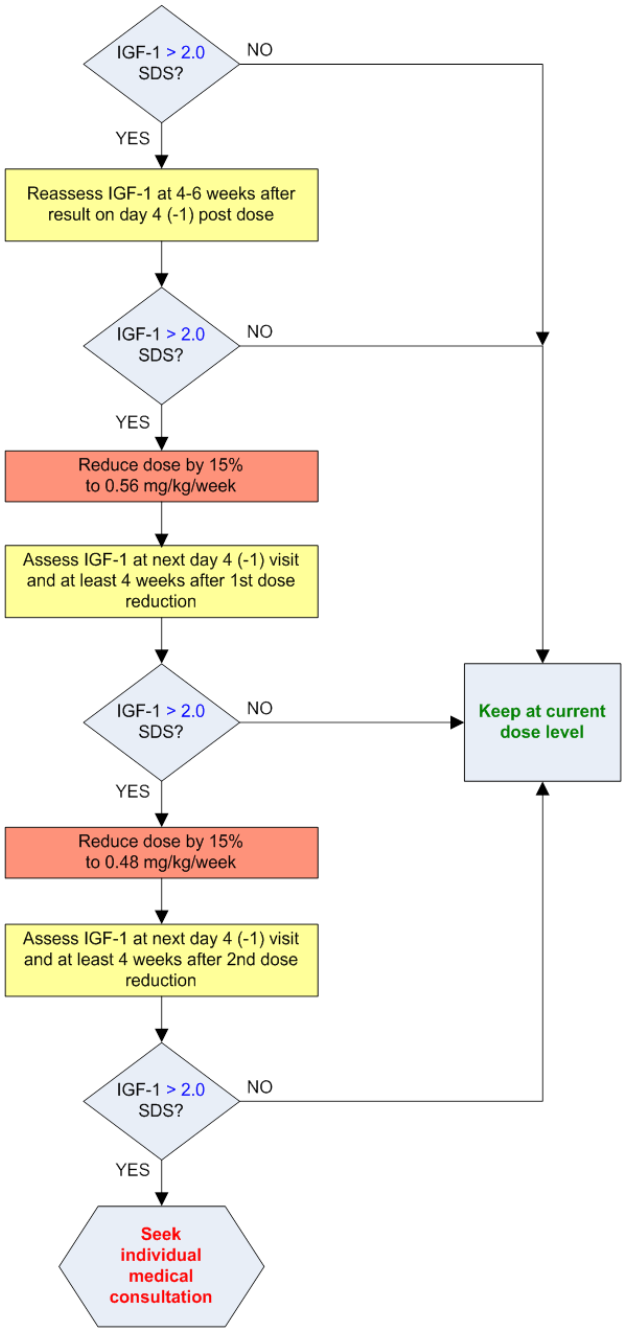
The dose will be decreased based on two repeated day 4(-1) levels of IGF-I > +2.0 Standard Deviation Score (SDS).

If a patient has an IGF-I 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. If their IGF-I level is still above +2.0 SDS, the most recent dose will be reduced by 15% (i.e. in case the starting dose is 0.66 mg/kg/week, reduction to 0.56 mg/kg/week). The patient will be treated with the new dose for at least 4 weeks before a subsequent IGF-I 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-I 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-I will be resampled. If the IGF-I is still above +2.0 SDS, the dose will be reduced an additional 15% (i.e. in case the starting dose is 0.66 mg/kg/week, reduction to 0.48 mg/kg/week). If the IGF-I is still above +2.0 SDS following 2 dose reductions (at least 4 weeks after second dose reduction), the sponsor Medical Monitor (with the assistance of the DSMB if necessary) will decide on course of treatment on an individual basis.

If AEs are defined as “severe” and drug-related, dose reduction will be introduced upon discussion with Sponsor Medical Monitor and DSMB - dose should be reduced at a similar manner as above in two step approach.

Figure 2: Overall Dose Adjustment Scheme

This figure is an example for a dose of 0.66 mg/kg/week. The rules also applies for patients who receive lower doses.



6. Investigational Product

6.1 Investigational Therapy and Reference Therapy

6.1.1 MOD-4023

The active component of MOD-4023 is a recombinant human growth hormone modified by adding carboxyl terminal peptides (CTP) to the protein molecule, thereby extending its life span in the human body.

MOD-4023 will be provided in single use vials as a solution for injection containing [redacted] or [redacted] mg protein[1]/ml (having a net r-hGH content of [redacted]%) in [redacted]

In the LT-OLE-PEN period, MOD-4023 will be provided as a solution for injection containing [redacted] or [redacted] mg/mL MOD-4023 for a single patient use, multi-dose disposable pre-filled PEN. The formulation will include [redacted]

6.1.2 MOD-4023 Administration (all study periods)

In the main study, patients will be administered a weekly dose of one of the three different dose strengths of MOD-4023 based on equal molar conversion of the weekly cumulative r-hGH dose. The weekly dose regimens will be as follows.

TABLE 8: MAIN STUDY WEEKLY DOSE REGIMENS

COHORT	Weeks 1-2	Weeks 3-4	Subsequent doses
1: MOD-4023	**0.25 mg protein/kg/week***	0.25 mg protein/kg/week	0.25 mg protein/kg/week
2: MOD-4023	0.25 mg protein/kg/week	**0.48 mg protein/kg/week****	0.48 mg protein/kg/week
3: MOD-4023	0.25 mg protein/kg/week	0.48 mg protein/kg/week	**0.66 mg protein/kg/week*****

* Equivalent to 0.18 mg hGH/kg weekly injection
** Equivalent to 0.35 mg hGH/kg weekly injection
*** Equivalent to 0.48 mg hGH/kg weekly injection

In the 12 months-OLE the patients will continue with the same dose (mg/kg) of MOD-4023 they received in the Main Study.

Patients who received active comparator, Genotropin, during the Main Study, will be switched to MOD-4023 (will be randomized to one of the three MOD-4023 cohorts).

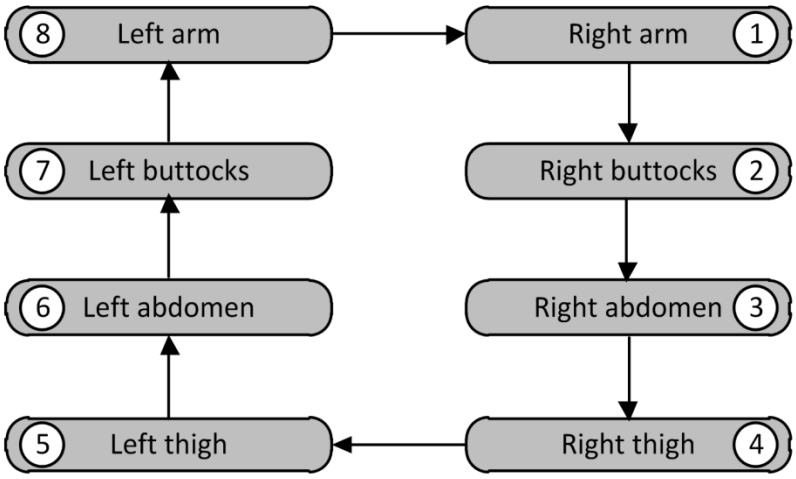
In the LT-OLE all patients will receive 0.66 protein mg/kg/week.

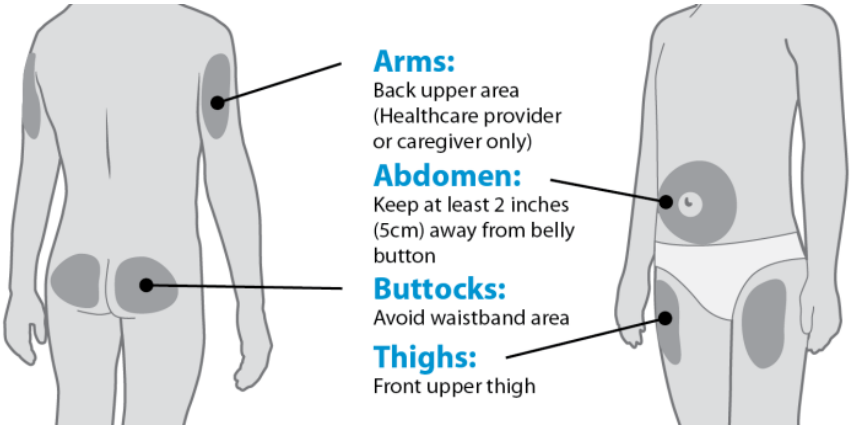
In LT-OLE-PEN patients will continue his/her treatment with the same dose.

[1] MOD-4023 concentration (mg protein/ml) refers to the protein backbone

In all study periods, MOD-4023 will be administered as a SC injection preferably in the morning hours once weekly, using the PEN into the upper arms, buttocks, thighs, or abdomen (8 locations). It is recommended that all 8 injection sites are used successively, using a different injection site at each subsequent injection. The same injection site should be used only after all other injection sites have been rotated (see recommended rotation scheme in Figure 3 below).

Figure 3: Injection Sites and Recommended Rotation for MOD-4023





Sterile, disposable syringes and needles (provided by OPKO Biologics) will be used for the administration of the MOD-4023 for the first four administration periods (excluding the LT-OLE-PEN period). In the LT-OLE-PEN period the patients will use single patient use, multi-dose disposable pre-filled PEN containing 20 or 50 mg/mL 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.

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: 3-4 days post dosing, in case IGF-I 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, the patient should be instructed how to split the dose into two injections. The partial dosing can occur in two cases:

1. Two injections using one PEN. In case the prescribed dose is higher than the maximum dose which can be delivered by a single injection according to the PEN concentration, the patient should be instructed to subtract the dose already received from the prescribed dose and set the PEN accordingly.

   For example, in the [redacted]mg/ml pen, if the full prescribed dose is 13.6 mg and the PEN allows only to set the dose selector to 12.0mg, the patient should inject another 1.6 mg using the same PEN.

2. Split dose between two PENs, the current PEN and a new PEN. This may happen when the complete dose cannot be fully administered from the used PEN, the patient should be instructed to subtract the dose already received from the prescribed dose and set the new PEN accordingly.

   For example, in the [redacted]mg/ml pen, if the full prescribed dose is 25.0 mg and the volume left in the current PEN allows only to set the dose selector to 20.5 mg, the patient should inject another 4.5 mg from the new PEN.

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

Patient should be reminded that the injection site should be rotated for each injection. That is, for the second injection, whether from the same PEN or a new PEN, the patient should rotate the injection site and complete the patient diary page for each of the two injections administered.

Further details are provided in the Patient Dosing Instructions document.

Patients and parents/legal guardians will be instructed to call the investigator in the event a dose was missed and record this information in the patient diary. During the PK/PD period (first 2, 4 or 6 weeks of treatment depending on the dose cohort), any deviations from weekly dosing will be considered a protocol deviation.

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

6.1.3 Reference Non-Investigational Medicinal Product (Non-IMP): Genotropin (Period I)

Genotropin (used only in the main study) lyophilized powder contains somatropin [rDNA origin], which is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatotropin).

Genotropin is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone. Genotropin is a sterile white lyophilized powder intended for subcutaneous injection.

Genotropin 5.3 mg is dispensed in a two-chamber cartridge. The front compartment contains recombinant [redacted] The rear compartment contains m-Cresol and mannitol in water for injection.

6.1.4 Genotropin Administration (Period I)

Genotropin (used only in the main study) will be administered to patients in Cohort 4 during the Main Study only at a dose of 0.24 mg/kg/week (0.034 mg/kg/day), divided and administered as a daily subcutaneous dose (7 times a week) at bedtime.

Genotropin will be administered with a delivery device (Genotropin Pen) for subcutaneous injection into the region of the upper arms, buttocks, thighs, or abdomen. It is recommended that all injection sites (left upper arm, right upper arm, left buttock, right buttock, left thigh, right thigh, left abdomen, and right abdomen) 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.

6.2 Packaging and Labeling of Study Medication

6.2.1 MOD-4023 vials (Periods I to IV)

The study drug will be provided as glass vials for use until the LT-OLE-PEN period. The bottles will be packed and labeled in compliance with the GMP, Annex 13 of drugs used in clinical trials.

Patients will be provided with dosing and storage instructions, and study drug vials in special cool bags.

Medication labels will comply with the legal requirements of each country and will be printed in the local language. The storage conditions for the study drug will be described on the medication label.

MOD-4023 will be labelled with:

- Product name;
- Patient's code;
- Protein concentration;
- Lot number;

- Expiry date;
- Protocol number;
- Sponsor's name;
- Storage instructions.

6.2.2 MOD-4023 PEN (Period V)

During the LT-OLE-PEN period, study drug will be provided as single patient use, multi-dose disposable pre-filled PEN and will be supplied to the site in cartons of 1 PEN/box.

Storage and dosing instruction are provided in the patient dosing instruction document. Patients will be provided with study drug Pens in special cool bags.

6.2.3 The PENs will be packed and labelled in compliance with the FDA, EU and ICH guidelines. Genotropin (Periods I)

Genotropin will be supplied from a central source packed in cartons with 1 cartridge each. In addition to the manufacture's label, Genotropin will be labelled according to GMP, ANNEX 13 requirements.

6.3 Distribution and Shipment of Study Medication

The study investigational drug will be packed and shipped in appropriate boxes. If upon arrival at the clinical investigation site, the study drug supplies appear to be damaged, the study monitor should be contacted immediately.

Each shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment, product certificate of analysis, acknowledgement of receipt and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records. The study staff will confirm the receipt of clinical supply and will return signed drug accountability logs to the study monitor.

All study supplies should arrive at the Pharmacy/Investigational site in sufficient quantity and in time to enable dosing as scheduled. The Sponsor or its representative must notify the PI prior to dispatch of drug supplies, with the anticipated date of their arrival.

If upon arrival at the clinical investigational site, the study drug supplies appear to be damaged, site staff should follow pharmacy manual instructions.

6.4 Storage, Dispensing and Return of the Investigational Product

Records should be kept by the Investigator or pharmacist as to how much study drug was used by each patient. The study monitors must periodically check the study drug supplies to ensure expiry date and sufficient quantity of study drug.

All investigational products must be kept 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 the local pharmacist are authorized to dispense study drug.

During storage at the pharmacy, the temperature of the refrigerators and freezers will be monitored continuously and recorded by a pharmacist on a temperature log. The Sponsor will be notified of any deviation from the storage conditions.

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

In the LT-OLE-PEN period, drug dispensing and clinical supplies inventory will be managed through 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. 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.**

6.4.1 MOD-4023 (all study periods)

MOD-4023 vials (main, OLE and LT-OLE periods) will be shipped on dry ice, after which it should be stored in a freezer (-20^{o}C). Patients will receive the frozen vials and will keep them refrigerated until used. Before administration it should be kept at ambient room temperature for 30 min to 1h. If injection is performed at the site, the frozen vial should be thawed in a refrigerator (+2 to +8^{o}C) for 24 h.

In the LT-OLE-PEN period, the investigational drug (PEN) will be shipped in +2^{o}C to +8^{o}C in appropriate shippers with temperature loggers. At the sites and patients home the PEN should be stored in +2^{o}C to +8^{o}C (refrigerator temperature).The Investigator or study pharmacist will acknowledge receipt of all shipments of study drug to the clinical investigational site through the IRT system.

The assigned study team member(s) will hand-out the study medication and instruct the patient and parent, or legal guardian on its usage. The amount needed for the period between two visits will be handed out at each visit.

The packaging and storage instructions and further details are described in the Instructions for Use and IP labels.

6.4.2 Genotropin (Period I)

Genotropin cartridges must be stored at 4°C (2°-8°C/36°-46°F); do not freeze. Protect from light. The cartridges of Genotropin contain a diluent with a preservative. Thus, after reconstitution, they may be stored under refrigeration for up to 28 days.

The assigned study team member(s) will dispense Genotropin cartridges to the patients according to their weight and dosing schedule and instruct the patients and parents or legal guardians on its usage. The amount needed for the period between two visits will be handed out at every visit. The study site pharmacist will be responsible for the dispensation. The cartridges, as well as the boxes, will be re-labeled according to GMP, ANNEX 13 requirements.

6.5 Accountability and Compliance of Investigational Product

Each delivery must be acknowledged by the hospital pharmacist (or authorized study team member responsible for the investigational medicinal product) by filling in the receipt record form. The study staff will confirm the receipt of clinical supply and will return signed drug accountability logs to the study monitor.

The medical center pharmacist (or authorized study team member responsible for the investigational medicinal product) is responsible for ensuring the supervision of the storage and allocation of these supplies, which will be forwarded to the Investigator at the appropriate time before administration. The Investigator may dispense investigational drug only to patients enrolled in the study.

Compliance to protocol procedures will be assessed according to the schedule in Appendix 1: Schedule of Assessments – Main Study to Appendix 5, and will be based on drug accountability and patient's diary review. Patients and parents, or legal guardians will be instructed to bring their diaries to each visit. Study drug compliance may be enhanced with regular telephone reminders.

Drug accountability records must be maintained by the clinical investigational site at all times. At the last study periods visits, all used and unused investigational drug will be assessed for accountability by the study monitor, as detailed in the study monitoring plan. Interim accountability and destruction may also be performed during the study, following Sponsor's written approval.

The patient number, the date, batch number/pack number, and quantity of study drug used by the patient will be checked for correctness and recorded on the appropriate accountability forms. Unused drug supplies will be returned to the Sponsor or destroyed at the site **only after approval of drug accountability forms by Sponsor QA**. At the end of the study, all the clinical supply and the corresponding accountability forms must be returned by the study monitor for reconciliation and destruction. A photocopy of these records must be kept at the clinical investigation site.

The inventory will be made available to the study monitor who will verify accountability and dose during the course of the study.

Study drug orders, records of study drug receipts, dispensing records, and inventory forms located at the site will be examined and reconciled by the study monitor periodically during and at the end of the study. Detailed instructions will be provided in the Pharmacy Manual.

All medication supplies are to be used only for this protocol and not for any other purpose.

The investigator must not destroy any medication labels, or any partly-used or unused medication supply. At the conclusion of the study and, as appropriate, during the course of the study, the investigator will return all used and unused medication containers, medication labels and a copy of the completed medication disposition form to CRO monitor or to the Sponsor address provided in the investigator folder at each site.

6.6 BLINDING

This is an open-label study. Due to different dose frequencies and dosing techniques, it is not practical to employ any blinding methods. A double-blind double-dummy design in this particular indication is deemed to be unethical.

6.7 PRIOR AND CONCOMITANT THERAPY

6.7.1 General Guidelines

All prior treatments received by the patient within 30 days before the initial Screening visit will be recorded on the patient's eCRF including the treatment's name, indication and the start and stop dates.

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

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

If the administration of a non-permitted concomitant medication becomes necessary, participation in the study may be discontinued.

Prior medications will be defined as any medication with start of administration from 30 days prior to screening up to the first dose of study drug, regardless of continuation status.

Concomitant medications will be defined as any medication administered during the period starting at or after the first dose of study drug (MOD-4023 or Genotropin) until discontinuation of study drug (in all study periods), regardless of the start date for the concomitant medication.

6.7.2 Allowed Medications

The following medications are allowed:

1. Dose replacement therapy for pituitary insufficiencies of other axes is permitted, but doses of all agents must be stable for at least 3 months prior to study entry; however, thyroid replacement should be stable for 6 months prior to randomization. As growth hormone may enhance the transformation of hydrocortisone to cortisone, the investigator may increase the dose of hydrocortisone replacement therapy, as needed. Also in case of development of hypothyroidism after the start of GH replacement treatment, the investigator may prescribe and adjust a dose of thyroid replacement therapy, as needed (after consultation with the Sponsor Medical Monitor).
2. Excessive glucocorticoid therapy may prevent optimal response to somatropin. If Glucocorticoid replacement therapy is required, patients may receive hydrocortisone in replacement doses. These doses of glucocorticoids (<12 mg/m^2/d) will not interfere with the growth promoting effects of somatropin and are permitted in this protocol. If required, the glucocorticoids may be increased periodically for stress coverage.

3. Glucocorticoid therapy for indications other than adrenal replacement (e.g. asthma) may be administered in a dose equivalent to inhaled budesonide of not more than 400 µg/d for no longer than 1 month during any one calendar year (approximately equivalent doses: Fluticasone: 264 µg/d; Beclomethasone: 504 µg/d; Flunisolide 1,000 µg/d; Triamcinolone: 1,000 µg/d).
4. Over-the-counter vitamins, mineral preparations, calcium supplements or corresponding dietary supplements may only be taken if their use and dose is agreed by the study Investigator beforehand.

All medications must be documented appropriately in the CRF.

6.7.3 Prohibited Concomitant Medication

The following medications are prohibited:

1. Estrogen is not permitted as concomitant therapy.
2. Weight-reducing drugs or appetite suppressants, anabolic steroids, gonadal steroid replacement therapy and systemic corticosteroids other than in replacement doses are not permitted as concomitant therapy in the main study, OLE and LT-OLE periods
3. In LT-OLE-PEN period, Psychiatric medications typically associated with weight changes and/or diabetes are not allowed, with the exception of ADHD drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin [DDAVP]).
4. The use of any drugs for recreational use (e.g., barbiturates, marijuana, ecstasy, etc.) is forbidden.

During all study periods , the coordinating investigator should be informed as soon as possible about any new medications (including prescription, over-the-counter, herbal supplements and health store products) taken by the patient.

7. Safety and Pharmacovigilance

7.1 Adverse Events

Information about all adverse events, whether volunteered by the patient, recorded in the patient's diary, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed-up as appropriate. An adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation.

Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). The period for collecting adverse events begins after signing the informed consent form and continues until 4 weeks after the patient has received the last dose of study treatment.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy. Such adverse events are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

Any AE that occurs in the course of a clinical study must be monitored and followed-up until:

- It has receded
- Pathological laboratory findings have returned to normal
- Steady state has been achieved

It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

Whenever possible, the Investigator(s) should always group signs and symptoms into a single term that constitutes a single unifying diagnosis. The Investigator's opinion of the association of each AE to study drug, the duration, frequency, intensity, countermeasures and the outcome of each AE will be documented.

The event's **relationship to the study drug** should be indicated according to the following **definitions:**

Relationship to study drug definitions:

1. Not related	• This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
2. Unlikely to be related (at least two conditions fulfilled)	In general, this category can be considered applicable to those adverse events which, after careful medical consideration at the time of evaluation, are judged to be unrelated to the test drug. An adverse event may be considered unlikely related if or when: 1) It does not follow a reasonable temporal sequence from administration of the study drug 2) It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient 3) It does not follow a known pattern of response to the study drug 4) It does not reappear or worsen when the drug is re-administered
3. Possibly related (at least two conditions fulfilled)	This category applies to those adverse events for which, after careful medical consideration at the time of evaluation, a connection with the study drug administration appears unlikely, but cannot be ruled out with certainty. An adverse event may be considered possibly related if or when:

	1) It follows a reasonable temporal sequence from administration of the drug 2) It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient 3) It follows a known pattern of response to the study drug
4. Probably related (at least three conditions fulfilled)	This category applies to those adverse events which, after careful medical consideration at the time of evaluation, are felt with a high degree of certainty to be related to the study drug. An adverse experience may be considered related if or when: 1) It follows a reasonable temporal sequence from administration of the drug 2) It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other models of therapy administered to the patient 3) It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia) 4) It follows a known pattern of response to the test drug
5. Definitely related (all four conditions fulfilled)	This category applies to those adverse events which the investigator feels are inconvertibly related to the study drug. An adverse event may be assigned as definitely related if or when: 1) It follows a reasonable temporal sequence from administration of the drug 2) It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient 3) It disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug 4) It follows a known pattern of response to the study drug

The **intensity** and **frequency** of the AE will be classified using the definitions below.

The following **intensity** grades should be used:

Mild	The event is easily tolerated by the patient and does not affect the patient's usual daily activities. (Grade I)
Moderate	The event causes the patient more discomfort and interrupts the patient's usual daily activities. (Grade II)
Severe	The event is incapacitating and causes considerable interference with the patient's usual daily activities. (Grade III)
Life Threatening	The event is incapacitating, and results in the inability to perform daily activities; events which are unacceptable, intolerable, or which are irreversible or life threatening. (Grade IV)

The **frequency** of the event should be indicated according to the following definitions:

Single Episode	This is the first and only experience/episode of the event in the patient.
Recurrent	The patient has experienced the event more than once.
Continuous	The event is continuing.

Action Taken with Study Drug should be indicated according to the following definitions (all applicable options should be checked):

None	No treatment was required and no changes were made to study drug administration and dose.
Study drug permanently discontinued	Study drug was discontinued.
Study drug dose reduced	Due to the adverse event, the study drug dose was reduced.
Study drug delayed	Due to the adverse event, the study drug dosing was delayed.

Treatment Given for AEs should be indicated according to the following options:

Concomitant medications	Medications given to specifically treat the AE.
Concomitant procedures	Procedures performed specifically to treat the AE.

Other	The patient was provided other treatment.
None	No treatment or medication was required for the AE.

AE Outcome should be indicated according to the following definitions:

Ongoing	AE continues at the end of the patient's participation in the study (or at the time of reporting of a SAE).
Resolved	Patient has returned to baseline state of health, or in the Investigator's opinion no further improvement or worsening of the adverse event is expected.
Resolved with sequelae	Patient has recovered from the AE with residual incapacity.
Death	AE was the primary cause of death
Patient lost to follow-up	Outcome is unknown

In the event of any abnormalities considered to be clinically significant by the investigating physician, patients will be followed up with appropriate medical management until the outcome is determined or stabilized, according to the Investigator's clinical judgment.

7.2 Serious Adverse Events

Information about all serious adverse events (SAEs) will be collected and recorded on the Serious Adverse Event Report Form. To ensure patients' safety each SAE must also be reported to [redacted] within 24 hours of learning of its occurrence.

An SAE is an undesirable sign, symptom or medical condition which:

1. Is fatal or life-threatening.
2. Requires or prolongs hospitalization.
3. Results in persistent or significant disability/incapacity.
4. Constitutes a congenital anomaly or a birth defect.
5. Is medically significant, in that it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, like training for the study drug administration, hospitalization for the period of pharmacokinetic sampling.
- Treatment, which was elective or pre-planned for a pre-existing condition that is unrelated to the indication under study and did not worsen.

- Admission to a hospital or other institution for general care not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the aforementioned definitions of “serious” and not resulting in hospital admission.

The period for collecting and reporting SAEs for this study starts after the patient has provided assent (where applicable) and the parent(s)/guardian(s) has provided written informed consent, and continues until the formal end of study-notification**.**

7.2.1 Notification of Serious Adverse Events

7.2.1.1 Reporting responsibility

Each serious adverse event (SAE) must be reported by the investigator to the [redacted] Safety group within **24 hours of learning of its occurrence**, even if it is not felt to be treatment-related. Follow-up information about a previously reported SAE must also be reported within 24 hours of the investigator receiving it. If the SAE is unexpected and is thought to be possibly related to the study drug, a Clinical Safety Associate shall urgently request further information from the investigator. This is essential for collecting information to report to the competent regulatory authority (RA). All safety information obtained will be provided to the DSMB for review and assessment. The DSMB in collaboration with the sponsor will assess any suspected unexpected serious adverse reaction (SUSAR) occurring during the study to determine whether additional risks are imposed on patients and make a decision as to suspending further enrollment until a final decision has been made. The Sponsor may need to issue an investigator notification, to inform all investigators involved in any study with the same drug (or therapy) that this SUSAR has occurred.

7.2.1.2 Reporting procedures

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment, and submit it electronically via eCRF within 24 hours to [redacted] CRO.

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

7.2.1.3 Contact persons and numbers

All SAE forms should be notified to the following address:

[redacted]

7.2.1.4 Information to include on SAE form

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

1. Investigator name and site address.
2. Patient study identification number.
3. Patient's initials.
4. Patient demographics (gender, date of birth or age, weight, height).
5. Clinical Event:
    - Description
    - Date and time of onset, stop date, or duration
    - Severity
    - Treatment (including hospitalization)
    - Relationship to study drug (causality)
    - Action taken regarding study drug
    - Information on recovery and any sequelae
    - If the SAE resulted in death

- Cause of death (whether or not the death was related to study drug)
- Autopsy findings (if available)

- Medical History case report form (copy)
- Concomitant Medication case report form (copy)
- Any relevant reports (laboratory, discharge, etc.)

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

Reporting of SAEs and other relevant safety information to the Health Authorities, Ethics Committees, Principal and Coordinating Investigators and Trial Investigators required by the above-mentioned functionaries and institutions will be fulfilled according to the current local laws and guidance. The detailed reporting duties and division of responsibilities between the sponsor and [redacted] CRO will be detailed in a separate document (Medical Management Manual). Once an event has been assessed as a SUSAR, then information must meet the expedited reporting requirements to the local regulatory authorities. The investigator is obliged to familiarize herself/himself with the reporting requirements for investigators in her/his country. The monitor can help with this.

7.3 Anticipated Adverse Events

Frequent AE in children are related to viral infections and bacterial infections:

Upper respiratory infection, lower respiratory infection, tonsillitis, ear infection, gastroenteritis, skin infection, allergic disease, asthma, arthritis, trauma secondary to physical activity, fracture, scoliosis.

Frequent symptoms in children are: weakness, fever, headache, hoarseness, cough, headache, dizziness, earache, abdominal pain, diarrhea, constipation, leg pains, musculo-skeletal pain, arthralgia, pruritus, skin rash, injection site pain, injection site swelling.

Frequent operations in children are: Tonsillectomy, adenoidectomy, acute appendicitis

7.4 Pregnancy Reporting and Follow-Up

For female child, 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 study physician is obligated to discuss this issue ahead of time with the patient and her parents. Study participants 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.

Furthermore, pubertal female child should undergo urine pregnancy test at each upcoming visit including EOS visit.

If a patient were to become pregnant or thinks she may have become pregnant during the study, study physician 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 2 weeks to confirm or exclude the pregnancy. In case of negative test results the patient will be offered to remain in the study and complete the remaining study procedures as scheduled. The pregnancy will be reported to the Medical Monitor, pharmacovigilance and sponsor and follow up period on mother and child will be defined based on individual basis and per discussion with DSMB.

For male participant, the study physician is obligated to discuss this issue of possible conception ahead of time with the male patients and his parents. Study participants 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, study physician should be informed immediately. The patient mustn't stop taking the study medication. The pregnancy will be reported to the Medical Monitor, pharmacovigilance and sponsor and follow up period on mother and child will be defined based on individual basis and per discussion with DSMB.

7.5 PEN Device Complaint Reporting Requirements

Any devices which are perceived to malfunction (either before or during use) will be returned through a formal complaint system and evaluated to understand the root cause of the failure. All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on a complaint form either at the site or using the 24/7 Helpline. 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. Sponsor is to be notified immediately of all medical device complaints of the investigator's awareness of the event.

8. Statistical Analysis

8.1 Statistical Methods

Details of applicable statistical methods will be provided in a Statistical Analysis Plan.

Data from all clinical assessments will be listed and, where appropriate, summarized by cohort using descriptive statistics. Endpoints will be summarized by cohorts and stratifying variables as well.

Summary statistics (arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values) will be presented for continuous variables (absolute values at each time point and changes from baseline if applicable). Frequency statistics (counts and percentages) will be presented for categorical

variables. Where appropriate, the presentation of results will include shift tables, plots or confidence intervals.

All statistical evaluations, including efficacy analysis, will be purely exploratory; no hypothesis tests will be conducted, hence this pilot study is not powered.

The assessment of safety will be based mainly on the frequency of AEs, frequency of patients developed anti-MOD-4023 antibody and on the number of laboratory values that fall outside of pre-determined ranges. Data of all safety endpoints will be listed and tabulated.

When all patients complete the Main Study a full analysis (CSR) will be performed based on the SAP.

When all patients will complete the second year of treatment an additional analysis will be performed.

8.2 SAMPLE SIZE

There are no previous pediatric GHD patients for MOD-4023 available to support a formal sample size calculation.

A sample size of 12 patients per cohort has been chosen in this pilot investigation (14 patients will be enrolled to get 12 per protocol evaluable patient in each cohort). Each cohort is stratified according to peak GH levels with up to 10 patients having peak stimulation test GH levels ≤7 ng/ml and up to 4 patients with peak GH levels [redacted] and [redacted] ng/ml. The justifications for this sample size are based on rationale about feasibility; precision about the mean and variance; and regulatory considerations as described by (Julious, 2005).

The selected sample size is large enough that there is about a 50% chance of identifying at least 1 patient in the cohort who experiences a treatment emergent adverse event where the nature of the event is such that the true chance that a patient has this type of an event during the treatment period is 5%.

If the true chance that a patient has event during the treatment period is:	then the chance of identifying at least 1 patient who experiences the event during the treatment period is:
5 %	50%
10 %	78%
15 %	90%
20 %	96%

When combining all MOD-4023 patients (n=42) there is about a 94 percent chance of identifying at least 1 patient in the entire group of patients treated with MOD-4023 who experiences a treatment emergent event where the nature of the event is such that the true chance that a patient has this type of an event during the treatment period is 5%.
In fact,

If the true chance that a patient has event during the treatment period is	then the chance of identifying at least 1 patient who experiences the event during the treatment period in a sample of size 42 is
5 %	94%
10 %	99.7%
15 %	100%

8.3 Population Analysis

The data from randomized patients who did not receive any study medication will be excluded from the statistical analysis and will only be listed individually in the Appendix of the final study report.

The following data subsets will be analyzed:

Safety analysis subset (SAS)

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

Full analysis subset (FAS)

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

The full analysis set will comprise all randomized patients who have received at least one dose of active treatment and who provide any follow-up data for the primary target variables.

Per protocol subset (PP)

The basis of PP subset is the full analysis set.

Handling of drop-outs and missing values will be performed as for the full analysis dataset. Protocol deviations excluding patients from the Per Protocol analysis set will be defined in the statistical analysis plan and will include failure to satisfy inclusion or exclusion criteria, taking any not permitted concomitant medication during the study, serious non-compliance.

8.3.1 Background and Demographic Characteristics

Assessments made at the screening and baseline visits will be summarized by treatment group. These assessments will include demographic characteristics and other relevant parameters and prognostic factors. By-treatment summaries will serve to identify any imbalances between the treatment groups at baseline. Summary tables will be provided for the full analysis set, for the per-protocol analysis set and for the safety analysis set by means of descriptive statistics and frequency tables, where appropriate. In accordance with Altman, no significance tests will be performed to assess baseline comparability.

8.3.2 Study Medication

For each patient, the individual extent of exposure will be calculated in terms of:

- Total duration of treatment

- Total dose

These variables will be listed by patient, sorted by treatment group and patient number. Summary statistics per treatment group will be tabulated.

Study drug compliance will be calculated as specified in the Statistical Analysis Plan. It will be listed by patient and presented for the FAS and the PP set by means of summary statistics by treatment group.

8.3.3 Concomitant Therapy

Previous and current medication will be summarized by counts and percentages, overall (any pervious or current medication) and per WHO-DRL category. This table will include those medications reported on the "Previous and current medication (all visits)" CRF, which have a stop date prior to the date of first administration of study medication. All other medication entered on these CRF pages will be considered as concomitant medication.

Previous and current non-medicinal therapy will be handled and tabulated in the same way as specified above for previous and current medication.

8.4 EFFICACY EVALUATION

The secondary and [redacted] efficacy endpoints related to IGF-I and IGFBP-3 assessments will be subsumed under biochemical endpoints and may serve as pharmacodynamic endpoints.

EFFICACY ENDPOINTS:

Primary endpoints (Main study):

- Annual Height Velocity in cm/year at 12 months (Baseline Visit – Visit 1).

Secondary endpoints (Auxology/Clinical) (Main study):

- Height velocity at 6 months (Baseline Visit – Visit 1);
- Delta height SDS at 6 and 12 months (compared to visit 1/Baseline value).

Secondary endpoints (Biochemical) (All study periods):

- Absolute IGF-I levels on day 4 after MOD-4023 dosing;
- IGF-I SDS on day 4 after MOD-4023 dosing.

[redacted]

OLE endpoints (including LT-OLE and LT-OLE-PEN)

- Annual Height Velocity in cm/year at each 12 months interval;
- Delta height SDS every 12 months (compared to the previous value);

8.4.1 Methods of Efficacy Analysis

The efficacy analysis will be exploratory, and based upon descriptive summary statistics, confidence intervals, exploratory nature statistical tests and graphical data presentations. For those parameters (IGF-I or other pharmacodynamic parameters subsumed under secondary biochemical endpoints) in which the analysis reveals that a consideration of extent of availability – similar to PK parameters – seems to be a meaningful supplement to the usual descriptive statistics, additionally, appropriate areas under the time-concentration curves may be defined and determined.

The effect of dose or dose group on the primary and secondary efficacy criteria subsumed under biochemical endpoints may be analyzed using ANOVA (analysis of variance) methods.

Primary and secondary clinical endpoints will be calculated using SAS or other validated software and these endpoints may be analyzed using ANOVA methods in order to compare the treatment arms.

The efficacy analysis will be performed based upon the FAS and PP subsets and subgroups based on peak hGH level following stimulation tests.

SAFETY ENDPOINTS: (All study periods)

- Incidence of adverse events;
- Incidence of anti-MOD-4023 antibody formation (including characterization of the antibodies and neutralizing properties);
- Local injection site assessment;
- IGF-I levels;
- Parameters of glucose metabolism: blood glucose, fasting insulin level, HbA1c;
- Thyroid status;
- Lipid parameters;
- Cortisol levels;
- All other hematology and biochemical parameters;
- Physical examination;
- Vital signs.

8.5 SAFETY EVALUATION

The assessment of safety will be based mainly on the frequency of AEs, frequency of anti-MOD-4023 antibody development and on the number of laboratory values that fall outside of laboratory normal ranges. Other safety data (e.g. vital signs, special tests, etc.) will be considered as appropriate.

AEs will be listed by treatment group and patient for the treatment phase. AEs will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each body system and having each individual AE. Any other

information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Summaries and analyses will be based on treatment-emergent adverse events (TEAE), which are defined as AEs occurring after the first administration of study medication (as recorded on the study discontinuation / end of study CRF) or AEs present before the first dose and ongoing after administration with increased severity. Other AEs (pre-treatment AEs) will only be listed.

If appropriate, laboratory and/or ECG data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data (means, medians, standard deviations, ranges) and change from baseline values and by the flagging of notable values in data listings.

Blood glucose, HbA1c, cortisol, thyroid panel tests and lipid panel tests (with special attention on LpA) will be evaluated using standard descriptive statistics, the number of patients who had values outside normal values, and by listing values considered clinically relevant by the investigator.

Data from other tests (e.g. blood pressure or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Summary statistics will be given where appropriate.

In addition the number and percentage of patients developing antibodies, including neutralizing antibodies, will be summarized by cohort.

Local tolerability will be summarized based on the investigator's assessments of pain, tenderness, erythema, warmth and swelling which will be done by a scale and predetermined schedule during intensive PK/PD sampling.

The safety analysis will be performed based upon the safety analysis subset.

8.6 PK/PD Evaluation

PK/PD parameters will be calculated utilizing a population PK modeling approach, based on limited sampling in each patient.

The proposed analysis strategy will include the following steps:

1. Estimate the Population PK/PD means and variances using the Population PK/PD analysis.
2. Perform an Empirical Bayesian estimation to retrieve the individual PK/PD model Parameters.
3. Use these individual PK/PD estimates to generate individual concentration time profile using rich sampling to cover the entire desired time range for Non compartmental Analysis calculation.
4. Perform Non compartmental Analysis for estimation of AUC and Cmax.

9. Ethics

9.1 Ethics and Good Clinical Practice (GCP)

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Sponsor/CRO standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).

The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of ICH-Good Clinical Practice that it conforms to.

9.2 Institutional Review Board (IRB) /Independent Ethics Committee (IEC)

Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol/amendment(s), written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients and parents, or legal guardians. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to the Sponsor before the study initiation. The name and occupation of the chairman and the members of the IRB/IEC must be supplied to the Sponsor. Any amendments to the protocol, other than administrative ones, produced during the course of the study must be approved by these committees.

9.3 Informed Consent

Informed consent for the patient to participate in the clinical study must be given in writing prior to participation in the study.

It must be signed and personally dated by the parent and/or legal guardian and by the investigator and/or the study team member designated by the investigator to conduct the informed consent procedure. Children who can read well are expected to sign an assent form prior to the commencement of any study-related procedures. Children who cannot read well will be assessed for maturity by the investigator to determine whether an assent can be obtained.

The investigator must explain to each patient and parent (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The informed consent (for parents/legal guardian) and assent form (for patients) should be given by means of a standard written statement, written in non-technical language. The parent/legal guardian (and where appropriate, the patient) should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the patient cannot read or sign the documents, oral presentation may be made or signature given by the patient's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

Additional informed consent form should be signed (re-consent process) by the patient or by parents/legal guardian before entering OLE, LT-OLE and LT-OLE-PEN study.

The informed consent form and assent form is considered to be the part of the protocol, and must be submitted by the investigator with it for IRB/IEC approval. The Sponsor will supply a proposed informed consent form and assent form, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/IEC and a copy of the approved version must be provided to the Sponsor monitor after IRB/IEC approval.

9.4 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/b3.htm

9.5 Insurance

The Sponsor will obtain liability insurance, which covers health impairments resulting from the medications and/or substances/investigational products administered in the course of the study for which the patient has given his/her written informed consent to participate. The liability insurance also covers health impairments resulting from measures carried out on the body of the person in connection with this study of a medication and/or substance/investigational product carried out in accordance with the study protocol procedures.

9.6 Data Safety Monitoring Board (DSMB)

An independent DSMB will be convened for this study. Its duty is to regularly review the progress of the study and assess the accumulating safety data from the study. It will, after each meeting, advise the Sponsor on the continuing safety of current participants in the study and on the continuing validity and scientific merit of the study. All decisions about the conduct of the study will rest solely with the Sponsor.

Membership of the DSMB will comprise at least one adult endocrinologist, two pediatric endocrinologists, and one biostatistician. All of them will have expertise in their field, extensive experience in clinical studies and experience of serving on other drug safety monitoring committees.

DSMB procedures will be described in the DSMB Charter, which will be approved by the Sponsor and by each Board member.

9.7 Protocol Amendments, Other Changes in Study Conduct

9.7.1 Protocol Exceptions and Deviations

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

9.7.2 Protocol Amendments

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

9.7.3 Other Changes in Study Conduct

Changes in study conduct are not permitted. Any unforeseen changes in study conduct will be recorded in the clinical study report.

All clinical work conducted under this protocol is subject to GCP requirements. This includes an inspection by the sponsor and/or health authority representatives at any time. The investigator will agree to the inspection of study-related records by health authority representatives and/or the sponsor or its delegates.

10. Quality Control and Quality Assurance

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

10.1 Audits and Inspections

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

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor quality assurance or its

designees or to regulatory authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

10.2 Study Monitoring

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

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

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

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

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

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

10.3 Quality Laboratory Standards

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

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

methods employed for each assay should be available on request. Any change in the laboratory, procedures, references, values, etc. during the study must be notified promptly to the Sponsor. The laboratories may also be audited by the Sponsor or by Regulatory Authorities.

10.4 Study Documentation

Study documents will include the following:

- Signed ICFs (for Main and OLE, LT-OLE and LT-OLE-PEN periods);
- Source documents (e.g. patient files, medical notes);
- Investigator copies of the CRFs and SAE reports;
- Investigator site file + contents;
- Study manual (Including laboratory manual);
- Study Pharmacy manual;
- Investigator meeting binder and or other training materials.

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

10.5 Source Documents

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, and completed scales for each study participant. Source documents should be kept in a secure area with limited access. 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 the date the ICF was signed, clinical protocol number and title, treatment number, and evidence that inclusion/exclusion criteria have been met.

10.6 Recording of Data on Electronic Case Report Forms (eCRFs)

The eCRF is an integral part of the study and subsequent reports. The eCRF provided by OPKO Biologics must be used to capture all study data recorded in the patient's medical record. The eCRF must be kept current to reflect patient status during the course of the study. Only a patient identification number and patient initials will be used to identify the patient. The investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers).

The study will use an Internet-Based Remote Data Entry System, primarily to collect clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 Good Clinical Practice. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The system used for this study is Target e*CRF™ (Target Health, Inc., New York, NY, USA). The system was configured based on requirements from the Sponsor. Paper source documents are to be retained to enable a reconstruction and evaluation of the trial. No original observations will be entered directly into the computerized system. Source documents include the hospital patient files and study worksheets provided by the Sponsor. Data will be recorded in the study worksheets as appropriate in order to complete and/or clarify source data.

The design of the computerized system complies with all applicable regulatory requirements for record keeping and record retention in clinical trials (21 CFR Part 11 and ICH E6 Good Clinical Practice) to the same degree of confidence as is provided with paper systems. Clinical investigators must retain either the original or a certified copy of all source documents sent to a sponsor or contract research organization, including query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly provides a means to locate and read the prior information. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

No data will be directly entered into the e-CRF without source documentation. Corrections are made in source documents by crossing out the error with a single line, making the correct entry in close proximity to the data field, then initialing and dating the strike-through and the new entry.

10.7 Investigator Site File

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

10.8 Clinical Trial Supplies

The Sponsor will be responsible for the supplying, administrating, inventory, and accountability of all clinical trial supplies, 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, not limited to: lab supplies and study drugs.

10.9 Data Management

Data items are entered indirectly from source data documents by designated Accelsiors-trained investigator staff using single data entry with electronic verification. [redacted] staff reviews the data for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are generally sent to the investigational site using an electronic data query system which provides an automatic audit trail of the corrections made by designated investigator staff. Laboratory data will be recorded by Data Management to Clinical Data Management system based on the received source documentation.

After the data have been entered and saved, various edit checks will be performed for the purpose of ensuring the accuracy, integrity, and validity of the collected data. These should include:

- Missing value checks;
- Range checks;
- Consistency checks;
- Sequence checks;
- Probabilistic checks; and
- Protocol adherence checks.

It is the responsibility of the study site and investigator to resolve all data queries that arise during data validation in a timely manner.

When all study data is collected, and the database is complete and accurate, a database quality control (QC) check is performed on 100% of key safety and efficacy (critical) variables and portion of randomly selected non-critical variables. If all critical and selected non-critical data is quality checked and the error rate is acceptable the database can be locked. Any changes to the database after that time can only be made by joint written agreement between the Sponsor, the Statistician and the Clinical Data Manager.

Ongoing QC can additionally be performed at any time-point during the conduct of a clinical study.

10.9.1 Coding Dictionaries

Concomitant medications entered into the database will be coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 10.0 or higher).

11. Study Administration

11.1 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 local health authority documentation properly signed and dated by the required Investigator (i.e. the submission package);
- Signed copy (original) of the approved protocol;
- Completed and signed statement of Investigator;
- A signed Clinical Trial Agreement;
- Curriculum vitae for the Investigator and sub-Investigator (can be collected at site initiation visit);
- IRB/IEC name and address; and membership list (can be collected at site initiation visit);
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number) and ICF (identified by protocol title and number);
- Copy of the Sponsor and IRB/IEC-approved written ICF to be used in the study;
- Provisions for direct access to source/data documents if necessary for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

Upon satisfactory receipt of all required regulatory documents, the Sponsor will arrange that study drugs be delivered to the study site. Supply of all other study materials will be the responsibility of OPKO Biologics 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 which will include review of study protocol, instructions for CRF completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee (study monitor) will prepare an Investigator's File. This file which will 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.

11.2 Study Completion

The Main study is expected to end when all required patients have been enrolled and the last patient has completed the Main study (first 12 months of treatment) and the query resolution has been completed and clinical study report (CSR) has been compiled

The LT-OLE-PEN is expected to end when marketing approval is received in countries where the study was conducted.

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;
- CRF (including correction forms) properly completed by appropriate study personnel and signed by the Investigator;
- Completed Drug Accountability Records;
- Statement of outcome for each SAE reported;

Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable).

11.3 Sponsor's Termination of Study

OPKO Biologics reserves the right to discontinue the study at any time for medical or administrative reasons.

Such reasons may be any of, but not limited to, the following:

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

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

11.4 Clinical Study Report

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

11.5 Retention of Documents

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc., and keep a copy of the signed informed consent form. All information on eCRFs must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the case report forms, which will be documented as being the source data.

The Investigator will retain copies of the approved protocol, completed CRF, ICFs, relevant source documents, and all other supporting documentation related to the project for 15 years in a secure and safe facility with limited access. If the Investigator is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed of the individual who will be assuming this responsibility.

Further retention, if required, will be negotiated at the end of this 15-year period. In that case, OPKO Biologics will notify, in writing, the Investigator when the clinical study data may be discarded. The Investigator will take measures to prevent accidental or premature destruction of these documents.

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

11.6 Publication of Results

The results of this study will not be published or communicated to any scientific meeting without the express agreement of the Sponsor. When permission is given, the Sponsor reserves the opportunity to discuss the content and conclusions of any abstract, presentation or paper before the material is submitted for publication. Any formal presentation or

publication of data from this trial will be considered as a joint publication by the investigator(s) and the appropriate Sponsor personnel. Authorship will be determined by the mutual agreement. For multicenter studies it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol by the Sponsor statisticians, and not by the investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to by all other investigators and the Sponsor.

The Sponsor must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). The Sponsor will review the communications for accuracy (in order to avoid potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

The principal investigator will be required to sign the final integrated study report.

11.7 Disclosure and Confidentiality

By signing the protocol, the investigator agrees to keep all information provided by the Sponsor in strict confidence and to require similar confidentiality from his/her staff and the IRB/IEC. Confidential Information includes, without limitation, the protocol or the protocol synopsis, and all other study-related information; any trade secrets, inventions or research and development information; information related to technology, know-how, engineering or other data, processes or techniques; manufacturing, planning or marketing information. Study documents provided by the Sponsor (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure confidentiality. The information provided by the Sponsor to the investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain the informed consent from patients who wish to participate in the trial.

12. Investigator's Statement of Responsibility

By my signature, I confirm that my staff and I have carefully read and understood this protocol and agree to comply with the conduct and terms of the study specified therein. In particular, I/we have agreed to:

1. Abide by all obligations stated on Form FDA 1572;
2. Conduct the study according to the protocol, its amendments, and study guides;
3. Obtain Ethics Committee approval of the study, any amendments to the study, and periodic re-approval, as required;
4. Obtain witnessed, written informed consent from each study participant or their legal representative;
5. Report all serious adverse events to the Sponsor or its agents and to the Ethics Committee, as required by the protocol and Ethics Committee regulations;
6. Assure access by study monitors to original source documents;
7. Cooperate fully with any study-related GCP audit as performed by the Sponsor and/or Regulatory Agencies;
8. Maintain confidentiality and assure security of confidential documents such as the protocol, consent form, case report form, investigator's brochure, final study reports, manuscript, and/or unpublished data and correspondence.

Name and address of the site

Principal Investigator of the site

Printed Name_____

Signature_____ Date_____

Appendix 1: Schedule of Assessments – Main Study

Main Study		**Treatment Period**													
X – Done in all Cohorts *M – Done in (MOD-4023) Cohorts 1-3* *G – Done in (Genotropin) Cohort 4*	**Screening**	**Period I**												**Period II**	
		Months 1-6												**Months 7-12**	
	≤6 weeks	W1 (V1)	**W2* (V2)**	W3	**W4* (V3)/ [M]**	W5	**W6* (V4)**	W10 (V5)	W14 (V6)	W 18 (V7)	W22 (V8)	W23 (V9)/ **[M]**	W26 (V10)	Month 9 (V11)	Month 12 (V12)
Informed consent/Assent	X														
Medical history	X														
Previous and concomitant medication	X	Throughout the study													
Demography	X			Dose escalation for Cohorts 2 and 3		Dose escalation for Cohort 3									
Growth history	X														
Actual height	X	X						X	X	X	X		X	X	X
Body weight	X	X						X	X[1]	X	X		X[1]	X	X
Physical examination	X	X	X		M		X	X	X	X	X	M	X	X	X
Vital signs[2]	X	X[5]	X[5]		M[5]		X[5]	X	X	X	X	M[5]	X	X	X
Injection Site Reaction (local tolerability)		M[6]	X[6]		M[6]		X[6]	X	X	X	X	X[6]	X	X	X
ECG	X														X
Pubertal status (Tanner)	X												X		X
Bone age (Greulich-Pyle)	X														X
Karyotype in girls	X														
SHOX evaluation	X														
GH stimulation tests[7]	X														
Routine safety biochemistry/hematology and urinalysis	X	X					X	X	X	X	X		X	X	X
IGF-I and IGFBP-3	X	X	According to sampling tables at the end of this appendix					X	X	X	X	M	X	X	X
MOD-4023 levels		M	According to sampling tables at the end of this appendix					M	M	M	M	M	M	M	M

Main Study		**Treatment Period**												
X – Done in all Cohorts *M – Done in (MOD-4023) Cohorts 1-3* *G – Done in (Genotropin) Cohort 4*	**Screening**	**Period I**												**Period II**
		Months 1-6												**Months 7-12**
	≤6 weeks	W1 (V1)	**W2* (V2)**	W3	**W4* (V3)/ [M]**	W5	**W6* (V4)**	W10 (V5)	W14 (V6)	W 18 (V7)	W22 (V8)	W23 (V9)/ **[M]**	W26 (V10)	Month 9 (V11)	Month 12 (V12)
Genotropin levels		G	According to sampling tables at the end of this appendix					G	G	G	G		G	G	G
Anti-MOD- 4023 antibodies		M											M		M
Anti-hGH antibodies	X	G											G		G
Thyroid status (free T4, free T3, TSH)	X	X							X				X	X	X
Cortisol levels	X	X							X				X	X	X
Standard dose short ACTH test[3]	X														
Fasting glucose, fasting insulin	X	X	X		M		X	X	X	X	X		X	X	X
HbA1C	X	X					X		X				X	X	X
Lipid panel	X[8]	X[8]						X	X[8]	X	X		X[8]	X	X[8]
AE assessment		Throughout the study													
Fundoscopy	X												X[4]		X[4]
MRI	X														
MOD-4023 administration		M	M		M		M					M			M[9]
Genotropin administration			G												G[10]
Training for study medication administration	X	X													
Hand-out of study medication		X	X		M		X	X	X	X	X		X	X	
Hand-out of patient diary		X	X		M		X	X	X	X	X		X	X	
Return and accountability of study medication					M		X	X	X	X	X		X	X	X
Return and review of patient diary					M		X	X	X	X	X		X	X	X

[1] Dose adjustment will be made according to weight measured on three monthly bases.
[2] Heart rate, blood pressure, body temperature, respiratory rate.
[3] Only for patients for which the insulin-stimulation test has not been used or glucagon test has shown peak cortisol level below 500 nmol/l. Will be done at any point during the study if there is suspicion of de novo hypoadrenalism.

[4] Earlier if there are clinical signs of intracranial hypertension.
[5] Vital signs: for all patients allocated to cohorts 1- 3 (MOD) - Pre-dose and at 30 mins, 2h (±20 mins) and 4h (±20mins); for patients in cohorts 4 (Genotropin) at any time during the visit.
[6] Injection site reaction: 30 min and 4h (±20 min) post dosing for MOD-4023 cohorts and at any time during the visit for patients in cohort 4 (Genotropin).
[7] Insulin tolerance test, with cortisol response to hypoglycemia if insulin stimulation test is chosen / Arginine test / Clonidine test / Glucagon test (plus or without propranolol) / L-dopa plus propranolol. At least one of the two stimulation tests must be analyzed by the central lab.
[8] with Lp(a) lipoprotein.
[9] Last MOD-4023 dosing 4 (-1) days before V12.
[10] Last Genotropin dosing 1 day before V12.

MOD-4023 Dose Cohorts (Cohorts 1-3) PK/PD Sampling Scheme

Visit	a			b	c	d	e	f	g
Time after dosing(h)/ Block number	0h	6h	12h	24h	48h	72h	96h	120h	168h
Block 1	3.5 ml			3.5 ml	3.5 ml		3.5 ml		
Block 2		3.5 ml			3.5 ml	3.5 ml		3.5 ml	
Block 3			3.5 ml	3.5 ml		3.5 ml			3.5 ml

Genotropin Dose Cohort (Cohort 4) PK/PD Sampling Scheme

Time after dosing(h)/ Block number	0h	1h	2h	4h	6h	12h	16h	20h	24h
Block 1	3.5 ml		3.5 ml	3.5 ml			3.5 ml		
Block 2		3.5 ml		3.5 ml	3.5 ml			3.5 ml	
Block 3			3.5 ml		3.5 ml	3.5 ml			3.5 ml

Appendix 2: Schedule of Assessments – 12-Month Open Label Extension (Ole) – Period III

	FIRST YEAR OLE STUDY MONTH					
	follow up Visit[1]	Day 1 & Month 1[2]	Month 3	Month 6	Month 9	Month 12
Assessments OLE visit #	**Visit 0**	**Visits 1-2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Previous and concomitant medication		X	X	X	X	X
Actual height		X	X	X	X	X
Body weight		X	X	X	X	X
Physical examination		X	X	X	X	X
Vital signs		X	X	X	X	X
Injection Site Reaction (local tolerability)		X	X	X	X	X
ECG						X
Pubertal status (Tanner)						X
Bone age (Greulich-Pyle)						X
Routine safety biochemistry/hematology and urinalysis	X	X	X	X	X	X
IGF-I and IGFBP-3	X	X	X	X	X	X
MOD-4023 serum levels	X	X	X	X	X	X
Anti-MOD- 4023 antibodies	X[3]			X		X
Thyroid status (free T4, free T3, TSH)		X	X	X	X	X
Cortisol levels		X	X	X	X	X
Fasting glucose, fasting insulin	X	X	X	X	X	X
HbA1C	X	X	X	X	X	X
Lipid panel		X	X	X	X	X
Lipoprotein						X
AE assessment		X	X	X	X	X
Fundoscopy						X[4]
MOD-4023 administration		X				
Training for study medication administration		X				
Dispense study medication	X	X	X	X	X	X
Dispense patient diary	X	X	X	X	X	X
Return and accountability of study medication		X	X	X	X	X
Return and review of patient diary		X	X	X	X	X

[1] Applicable only to patients who were off-treatment for over [redacted] between Main Study Month 12 and Visit 1 OLE.
[2] Applicable only patients who received Genotropin in the Main Study and switched to MOD-4023 will attend the following visits:
Day 1 is Month 12 visit of the Main Study in which the patient will be trained on medication administration and Visit 2/OLE will be 28 days + 4 (-1) days after the first MOD-4023 injection.
[3] Applicable for Genotropin patients
[4] Earlier if there are clinical signs of intracranial hypertension.

Appendix 3: Schedule of Assessments – Long-Term OLE (LT-OLE) Period IV from Second Year of OLE/Third Year of Treatment until switch to LT-OLE-PEN period

Assessments	follow up Visit[1]	First Month 3 visit[2] (on day 3 or 4 post-dosing)	Early termination visit[3]		LT OLE visits by Month over each year until switch to LT-OLE-PEN period				
					Month 3 visit	Month 6 visit	Month 9 visit	Month 12 each year and End of Study Visit	
	Visit 0	Visit 1a	On Dosing Day	day 4 (-1) post dose	day 4 (-1) post dose	day 4 (-1) post dose	day 4 (-1) post dose	On Dosing Day	day 4 (-1) post dose
Auxology measurements: Actual height measured on a calibrated stadiometer and body weight measurement		X	X		X	X	X	X	
Adjustment of dose for weight			X		X	X	X	X	
AEs			X		X	X	X	X	
Local tolerability			X		X	X	X	X	
Concomitant medication		X	X		X	X	X	X	
Dispensing of drug					X	X	X	X	
IGF-I, IGFBP-3 and MOD-4023 serum levels	X	X		**X**		**X**			**X**
MOD-4023 serum levels			X					X	
Anti-MOD-4023 antibodies	X	X	X					X	
Physical examination		X	X					X	
Vital signs		X	X					X	
Glucose metabolism (fasting glucose & insulin, HbA1c)	X	X	X					X	
Other hormonal levels (TSH, free T4, free T3, cortisol)			X					X	

[1] Applicable only to patients who were off-treatment for over 60 days between OLE Month 12 and Visit 1 LT-OLE.
[2] This visit applies only to patients in Cohorts 1 and 2 who switch to MOD-4023 0.66 mg/kg/week; this will be their first visit after the switch. Selected group of patients may be switched during the 2nd year and will be required to undergo this visit three months after their switch.
[3] This visit applies to patients who discontinue the study prematurely for any reason (including not switching to higher dose).

	follow up Visit[1]	First Month 3 visit[2] (on day 3 or 4 post-dosing)	Early termination visit[3]		LT OLE visits by Month over each year until switch to LT-OLE-PEN period				
					Month 3 visit	Month 6 visit	Month 9 visit	Month 12 each year and End of Study Visit	
Parameters of lipid metabolism			X					X	
Routine safety laboratory (biochemistry, hematology and urinalysis)	X	X	X					X	
Pubertal status			X					X	
ECG			X					X	
Bone age			X					X	
LH, FSH and Testosterone[4]			X					X	
LH, FSH and Estradiol[5]			X					X	
Patient diary dispensing and return of completed diaries					X	X	X	X	X

[4] For male patients that are at the age of 13 years and above.
[5] For female patients that are at the age of 12 years and above.

Appendix 4: Schedule of Assessments – Long-Term OLE PEN (LT-OLE-PEN) Period V first year

Assessments	PEN Visit 1 (PEN V1)	PEN Visit 2 (PEN V2) 4 weeks (+1) after PEN visit V1	LT OLE PEN visits by Month over the first year				
			Month 3 visit (±2 week)	Month 6 visit (±2 week)	Month 9 visit (±2 week)	Month 12 (±2 week)[1]	
	On Dosing Day (pre-dose)	day 4 (-1) post dose	day 4 (-1) post dose	day 4 (-1) post dose	day 4 (-1) post dose	On Dosing Day	day 4 (-1) post dose
Informed consent/ assent	X						
Auxology measurements (actual height measured on calibrated stadiometer)	X		X	X	X	X	
Body Weight measurement	X	X	X	X	X	X	
Adjustment of dose for weight	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	
Local tolerability	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	
Dispensing of drug	X	X	X	X	X	X	
Return of used drugs	X[2]	X	X	X	X	X	
Training on PEN	X	X[3]					
Fundoscopy- If required	X	X	X	X	X	X	
IGF-I, IGFBP-3	X	X	X	**X**	X		**X**
MOD- 4023 serum levels	X	X	X	**X**	X	X	
Anti-MOD-4023 antibodies	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	
Glucose metabolism (fasting glucose & insulin, HbA1c)	X		X	X		X	
Other hormonal levels (TSH, free T4, cortisol)	X		X	X		X	
Parameters of lipid metabolism	X		X	X		X	
Routine safety laboratory (biochemistry, hematology and urinalysis)	X		X	X		X	
Urine pregnancy test[4]	X	X	X	X	X	X	

[1] In case ET/EOS visit is conducted all assessment should be done at one visit with no split.
[2] Return of used and unused MOD-4023 vials.
[3] If required.
[4] For females of child bearing potential. In case urine pregnancy test is positive, please refer to section 7.4 in the protocol.

	PEN Visit 1 (PEN V1)	PEN Visit 2 (PEN V2) 4 weeks (+1) after PEN visit V1	LT OLE PEN visits by Month over the first year				
			Month 3 visit (±2 week)	Month 6 visit (±2 week)	Month 9 visit (±2 week)	Month 12 (±2 week)[1]	
Pubertal status [1]	X		X	X	X	X	
ECG around Tmax (7-12 hours post dose)[2]						X	
Bone age	X[3]					X	
LH, FSH and Testosterone[4]	X					X	
LH, FSH and Estradiol[5]	X					X	
Provide patient diary and return of completed diaries	X	X	X	X	X	X	

[1] In case the patient becomes pubertal, childbearing potential and refraining from sexual activity will be discussed with the patient.
[2] In case not possible to conduct the ECG around Tmax at the 12 months visit, it can be performed on month 12± 3 weeks (7-12 hours post dose).
[3] Bone age measurement will be performed in case the previous assessment was done more than 6 months prior to this visit.
[4] For male patients that are at the age of 13 years and above.
[5] For female patients that are at the age of 12 years and above.

Appendix 5: Schedule of Assessments – Long-Term OLE PEN (LT-OLE-PEN) Period V from 2nd year until marketing approval

	LT OLE PEN visits by Month over each year the study is running			
	Month 3 visit (±2 week)	Month 6 visit (±2 week)	Month 9 visit (±2 week)	Month 12 (±2 week)[1]
Assessments	day 4 (-1) post dose	day 4 (-1) post dose	day 4 (-1) post dose	day 4 (-1) post dose
Auxology measurements: actual height measured on calibrated stadiometer	X	X	X	X
Body weight measurement	X	X	X	X
Adjustment of dose for weight	X	X	X	X
AEs	X	X	X	X
Local tolerability	X	X	X	X
Concomitant medication	X	X	X	X
Dispensing of drug	X	X	X	X
Return of used drugs	X	X	X	X
Fundoscopy - If required	X	X	X	X
IGF-I, IGFBP-3	X	**X**	X	X
MOD- 4023 serum levels		**X**		X
Anti-MOD-4023 antibodies		X		X
Physical examination	X	X	X	X
Vital signs	X	X	X	X
Glucose metabolism (fasting glucose & insulin, HbA1c)		X		X
Other hormonal levels (TSH, free T4, cortisol)		X		X
Parameters of lipid metabolism		X		X
Routine safety laboratory (biochemistry, hematology and urinalysis)		X		X
Urine pregnancy test[2]	X	X	X	X
Pubertal status[3]	X	X	X	X
ECG				X
Bone age				X
LH, FSH and Testosterone[4]				X
LH, FSH and Estradiol[5]				X
Provide patient diary and return of completed diaries	X	X	X	X[6]

[1] In case ET/EOS visit is conducted all assessment should be done as one with no split.
[2] For females of child bearing potential. In case urine pregnancy test is positive, please refer to section 7.4 in the protocol.
[3] In case the patient becomes pubertal, childbearing potential and refraining from sexual activity will be discussed with the patient.
[4] For male patients that are at the age of 13 years and above.
[5] For female patients that are at the age of 12 years and above.
[6] Dispensing patient diary is not applicable for termination visit, only return of completed diaries.

Appendix 6: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI - Ethical Principles for Medical Research Involving Human Subjects

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 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

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 not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. 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."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. 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 current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should 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.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. 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.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any

other undue influence. 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 change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, 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, 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.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should 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 should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent 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.

29. 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 population. In such circumstances the physician should 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 should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research 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.

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

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the 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 interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or 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 judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix 7: Growth Hormone Stimulation Tests and Other Assessments

Growth Hormone Stimulation Tests

As stated in the 2000 Growth Hormone Research Society Consensus Guideline: "In a child with clinical criteria for GHD, a peak ***GH concentration less than [redacted] ng/ml has traditionally been used to support the diagnosis***. At the present time, a new GH reference standard is being introduced that may require a downward adjustment of the lower limit of normal" (Growth Hormone Research Society Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence (2000))[1].

The new standard is currently used in the USA and EU. However, the common clinical practice remains to treat patients with GH below [redacted] ng/ml. The cutoff for this study is in line with this common clinical practice.

Two different GH-stimulation tests will be done to confirm the diagnosis and eligibility of patients. At least one of the two stimulation tests (and preferably both) will be analyzed by the central laboratory.

Sex Hormone Priming

Prior to the stimulation tests performed during the screening period, sex hormone priming will be performed as follows:

Boys - A single dose of 100 mg intramuscular depo-testosterone will be administered 5 days before the stimulation test.

Girls - Ethinylestradiol will be given as 25 µg p.o. twice a day over 5 days before the stimulation test (a total of 10 doses) or Beta estradiol will be given as 2 mg p.o. once a day for 3 days before the stimulation test (a total of 3 doses).

If the patient requires sex hormone priming (due to the age) and both stimulation tests must be performed during the Screening (no historical samples were kept, or the test was without priming), it is recommended to perform stimulation tests in one of the following two settings, so as to avoid priming the patient twice. Local historical tests without sex-steroid priming will not be accepted for patients that require sex steroid priming according to the protocol.

It is possible to perform combined growth hormone stimulation tests, in the two following ways, so as to avoid priming the patient twice:

a) Perform two GH stimulation tests in a consecutive setting, in one day: immediately after drawing the last sample of the first test the stimulating agent of the second test will be given (there is no need for the -30 sample for the second test). After most of the tests, patients need some time to rest (ITT, glucagon), and are even sleepy (clonidine), so the second test performed immediately after the first one brings no additional discomfort. In this setting, one priming is to be performed, before the first test only.

b) Perform two GH stimulation tests in two consecutive days, with the sex hormone priming before the first test only; female patients should then have one additional day of receiving

[1] JCEM 2000. Vol. 85 (11): 3990-3993.

Ethinylestradiol (2 additional doses) or Beta estradiol (1 additional dose), before the second stimulation test.

The investigator, together with parents/legal guardians, will make the decision which one is more convenient for the patient.

Insulin Tolerance Test

Regular human insulin (0.10-0.15 IU/kg) will be administered intravenously (i.v.) at time point 0. The test will be interpretable if the blood glucose level decreases below 40 mg/dL. Administration of i.v. 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 = – 30, 0, 15, 30, 45, 60, 90, and 120 min (8 sampling points) for glucose, hGH and cortisol determination.

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

Clonidine test

After fasting overnight, clonidine (0.15 mg/m^2 body surface, given orally) will be given at time t = 0, and venous blood will be obtained by an indwelling catheter inserted in a cubital vein and kept patent by slow infusion of isotonic saline. Blood will be collected at 30 min intervals, between t = - 30 to +150 min (7 sampling points) 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.

Arginine test

Soluble arginine hydrochloride (0.5 g/kg) will be given i.v. 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 = –30, 0, 15, 30, 45, 60, 90, and 120 min (8 sampling points) for hGH measurement.

Glucagon test

After fasting overnight, glucagon (0.03 mg/kg with a maximal total dose of 1 mg) will be given i.m. or s.c. at time t = 0, and venous blood will be obtained by an indwelling catheter inserted in a cubital vein and kept patent by slow infusion of isotonic saline. Blood will be collected for hGH measurement at -30, 0, 60, 90, 120, 150 and 180 min relative to the time of glucagon administration.

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

L-Dopa test

After fasting overnight L-Dopa will be given orally at time-point t=0 in dose of 125 mg if body weight is less than 15 kg, else 250 mg if body weight is less than 35 kg, else 500 mg if body weight is greater than 35 kg. 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: –30, 0, 30, 60, 90 and 120 minutes.

Cortisol levels

Screening serum cortisol (in conjunction with a screening ITT for GH reserve; or glucagon test) and routine follow-up serum cortisol will be determined in ALL screened patients with/without pre-existing central hypoadrenalism, and additional serum cortisol will be determined when there is suspicion of either de novo central hypoadrenalism or exacerbation of pre-existing central hypoadrenalism. Screening ACTH stimulation (Standard Dose Short ACTH test) will be performed only in patients without pre-existing central hypoadrenalism, and additional ACTH stimulation tests will be performed when there is suspicion of de novo central hypoadrenalism.

The Standard Dose Short ACTH test will be performed after overnight fasting. An i.v. catheter will be inserted into the cubital vein; a baseline sample for serum cortisol will be taken and then the set will be heparinized. Subsequently, 250 µg of alpha 1-24 ACTH will be injected intravenously as a bolus and blood samples for serum cortisol will be taken at 30 and 60 min post dose.

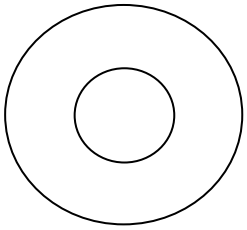
If the cortisol level remains below 18 µg/dL (500 nmol/L) at both post-dose time-points, the child should be investigated outside of this protocol for primary or secondary adrenal insufficiency. Associated clinical symptoms like lethargy, weight loss, anorexia, nausea, vomiting, hyperpigmentation, shock, hypoglycaemia, eosinophylia and electrolyte imbalance will further emerge the need for the investigation of adrenal insufficiency.

Assessment of pubertal status

Pubertal status will be documented by physical examination according to the schedule in Appendix 1. Boys will be assessed for descent of the testes and testis volumes, girls for the breast development according to Tanner stages (Tanner JM, 1976). Pubic hair rating will also be recorded according to Tanner stages.

Appendix 8: Injection Site Assessment Table (Local Reactions)

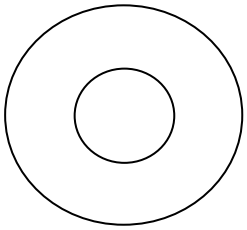
Redness



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.

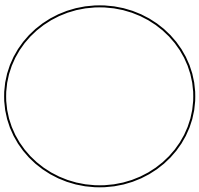
Bruising



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

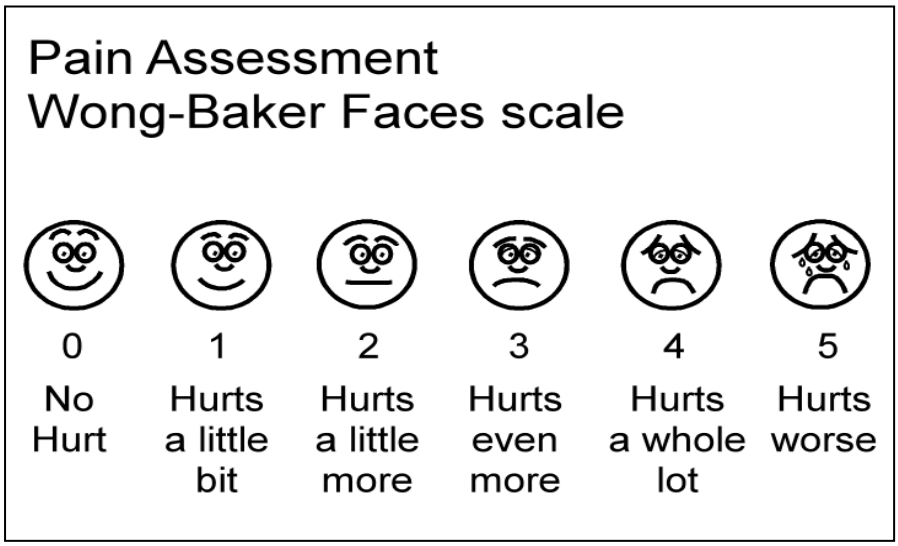
Swelling will be assessed by a member of the study staff. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe.

Itching

Grade	Description
0	NONE
1	MILD
2	MODERATE
3	SEVERE

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

Pain



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 9: Instructions for Obtaining Height Measurements

Use the following instructions when obtaining height measurements:

1. Use a wall-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 0.5 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 10: Instructions for Obtaining X-Ray Films

It is necessary to have a good assessment of the skeletal age from an X-ray of the hand. The X-ray should be taken of the left hand, which is placed palm down, wrist and hand flat on the film holder, fingers should be slightly separate and the axis of the hand, wrist and forearm should be a straight line. Center the tube half way between the tips of the fingers at least 3 cm of the radius, in order to obtain a picture of the hand epiphyses and the distal radius, the longitudinal axis should meet the 3rd finger ray and the horizontal axis should cross the head of the 3rd metacarpal. A 24/30 cm no-screen card board holder should be used. A small focus should be used with a film-focus distance of 1.00 m.

Films should only be identified by center number, patient number and the gender of the patient.

Historical films (if not older than 6 months at Screening), should mask the patient's identification details, and contain only the center number, patient number and the gender of the patient.

Either originals or high quality copies should be sent to central bone age reader.

Detailed study specific instructions will describe the handling and circulation of X-ray films.

Appendix 11: List of Central Technical Facilities

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Testing USA

[redacted]

[redacted]

13. References

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