Clinical trial results:
A phase II, randomized, active controlled, open label study of safety and efficacy of HM10560A a Long-acting rhGH-HMC001 conjugate in treatment of subjects suffering from adult growth hormone deficiency (AGHD)

Summary

EudraCT number	2011-001826-61
Trial protocol	HU PL BG
Global end of trial date	29 June 2015

Results information

Result version number	v1 (current)
This version publication date	02 November 2016
First version publication date	02 November 2016

Trial information

Trial identification

Sponsor protocol code	11HM10560A201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	HANMI Pharmaceutical Co., Ltd.
Sponsor organisation address	14, Wiryeseong-daero, Songpa-gu, Seoul, Korea, Republic of, 138-724
Public contact	Executive Director, HANMI Pharmaceutical Co., Ltd., +82 24109041, jhkang@hanmi.co.kr
Scientific contact	Executive Director, HANMI Pharmaceutical Co., Ltd., +82 24109041, jhkang@hanmi.co.kr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2015
Global end of trial reached?	Yes
Global end of trial date	29 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1.To assess the safety, tolerability and Pharmacokinetic/ Pharmacodynamic (PK/PD) profile of three doses of HM10560A on an every week (EW) regime and one dose on every other week(EOW) regime administered for a period of 24 weeks initial study
2.To select the optimal dose and dosing regimen of HM10560A for the subsequent phase III study on the basis of the safety and PK/PD profile after 24 weeks of treatment
3.To assess the long term safety of HM10560A when administered in optimal dose range and dose frequency for additional 48 weeks (followed with 2 weeks safety follow up)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Serbia: 8
Worldwide total number of subjects	69
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial took place at 16 centres in 8 countries: Poland-3 sites, Romania-3 sites, Ukraine-3 sites, Hungary-2 sites, Russia-2 sites, Bulgaria-1 site, Korea-1 site, and Serbia-1 site.
The first subject was enrolled on 21 November 2011 and the last study visit occurred on 29 June 2015.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	169[1]
Number of subjects completed	69

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 97
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: It is the number of subjects screened indicated as starters of the pre-assignment period and the number of subjects treated as the worldwide number of subjects, therefore the difference.

Period 1

Period 1 title	24-week dose finding period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

HM10560A 0.03 mg/kg EW

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

HM10560A 0.03 mg/kg EW. Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject’s body weight at each regularly scheduled visit.

Arm title	Cohort 2

Arm description:

HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 20 weeks

Arm type	Experimental

Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 20 weeks. Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject's body weight at each regularly scheduled visit.

Arm title	Cohort 3

Arm description:

HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 4 weeks then 0.10 mg/kg EW for 16 weeks

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 4 weeks then 0.10 mg/kg EW for 16 weeks. Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject's body weight at each regularly scheduled visit.

Arm title	Cohort 4

Arm description:

HM10560A 0.04 mg/kg EOW for 4 weeks then 0.08 mg/kg EOW for 4 weeks then 0.12 mg/kg EOW for 16 weeks

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

HM10560A 0.04 mg/kg EOW for 4 weeks then 0.08 mg/kg EOW for 4 weeks then 0.12 mg/kg EOW for 16 weeks. Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject's body weight at each regularly scheduled visit.

Arm title	Cohort 5

Arm description:

standard daily rhGH

Arm type	Active comparator
Investigational medicinal product name	Genotropin®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Genotropin® was administered at a dose of 0.04 mg/kg/week (0.006 mg/kg/day), divided and administered as a daily SC dose (7X/week), at bedtime, and that dose was then adjusted on every 4 weeks with 25% increments or decrements (0.01 mg/kg/week) up to the maximal dose of 0.08 mg/kg/week, with the aim to stabilize IGF-1 levels between 0 and +2 SDS (standard deviation score).

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	15	14	14
Completed	13	14	14
Not completed	2	0	0
Consent withdrawn by subject	1	-	-
Military actions	1	-	-

Number of subjects in period 1	Cohort 4	Cohort 5
Started	12	14
Completed	11	14
Not completed	1	0
Consent withdrawn by subject	1	-
Military actions	-	-

Period 2 title	Long-term safety: 48 weeks treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	

lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject's body weight at each regularly scheduled visit.

Arm title	Cohort 2 SFU

Arm description:

0.06 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.06 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject's body weight at each regularly scheduled visit.

Arm title	Cohort 3 SFU

Arm description:

0.10 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.10 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU)

Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject's body weight at each regularly scheduled visit.

Arm title	Cohort 4 SFU

Arm description:

0.12 mg/kg EOW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.12 mg/kg EOW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject'

s body weight at each regularly scheduled visit.

Arm title	Cohort 5 SFU

Arm description:

Switched from Genotropin to 0.03 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Switched from Genotropin to 0.03 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1).

Study treatment was administered as SC injections in the region of right or left thigh and right or left lower abdominal wall, always alternating the injection site. Dose calculation was adjusted to the subject's body weight at each regularly scheduled visit.

Number of subjects in period 2	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU
Started	13	14	14
Completed	13	12	14
Not completed	0	2	0
Personal reasons	-	1	-
Consent withdrawn by subject	-	-	-
Own reasons	-	-	-
Lost to follow-up	-	1	-
Growth of an intracranial tumor during study	-	-	-

Number of subjects in period 2	Cohort 4 SFU	Cohort 5 SFU
Started	11	14
Completed	10	12
Not completed	1	2
Personal reasons	-	-
Consent withdrawn by subject	-	1
Own reasons	1	-
Lost to follow-up	-	-
Growth of an intracranial tumor during study	-	1

Period 3

Period 3 title	Single dose PK/PD run-in period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 PK-PD

Arm description:

Single dose 0.04 mg/kg HM10560A (total body weight)

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose 0.04 mg/kg HM10560A (total body weight). Subjects received a single dose administered in the abdominal wall.

Arm title	Cohort 2 PK-PD

Arm description:

Single dose 0.08 mg/kg HM10560A

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose 0.08 mg/kg HM10560A (total body weight). Subjects received a single dose administered in the abdominal wall.

Arm title	Cohort 3 PK-PD

Arm description:

Single dose 0.12 mg/kg HM10560A

Arm type	Experimental
Investigational medicinal product name	HM10560A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose 0.12 mg/kg HM10560A (total body weight). Subjects received a single dose administered in the abdominal wall.

Number of subjects in period 3[2]	Cohort 1 PK-PD	Cohort 2 PK-PD	Cohort 3 PK-PD
Started	3	3	3
Completed	3	3	3

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The PK-PD substudy was conducted in a subgroup of patients prior to the dose finding period.

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
HM10560A 0.03 mg/kg EW	
Reporting group title	Cohort 2
Reporting group description:	
HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 20 weeks	
Reporting group title	Cohort 3
Reporting group description:	
HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 4 weeks then 0.10 mg/kg EW for 16 weeks	
Reporting group title	Cohort 4
Reporting group description:	
HM10560A 0.04 mg/kg EOW for 4 weeks then 0.08 mg/kg EOW for 4 weeks then 0.12 mg/kg EOW for 16 weeks	
Reporting group title	Cohort 5
Reporting group description:	
standard daily rhGH	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	15	14	14
Age categorical Units: Subjects			
Adults (18-64 years)	15	14	14
Age continuous Units: years			
arithmetic mean	38.2	38.6	36.2
standard deviation	± 12.01	± 12.73	± 9.74
Gender categorical Units: Subjects			
Female	5	6	6
Male	10	8	8
Race Units: Subjects			
Asian	0	0	0
Caucasian	15	14	14
GHD history Units: Subjects			
Childhood onset	7	7	7
Adult onset	8	7	7
IGF-1 Units: µg/l			
arithmetic mean	50.5	52.5	61.9
standard deviation	± 30.35	± 28.79	± 33.43
IGF-1 SDS Units: SDS			
arithmetic mean	-2.84	-2.72	-2.49

standard deviation	± 1.57	± 1.275	± 1.452
IGFBP3 SDS			
Units: SDS			
arithmetic mean	-2.21	-2.36	-2.26
standard deviation	± 1.932	± 1.505	± 1.539
Body fat mass			
Units: kg			
arithmetic mean	22.591	23.243	23.188
standard deviation	± 6.0256	± 6.7088	± 4.0353
Lean body mass			
Units: kg			
arithmetic mean	43.677	41.88	41.201
standard deviation	± 8.5766	± 13.201	± 10.4357
Trunk fat mass			
Units: kg			
arithmetic mean	12.715	12.747	12.353
standard deviation	± 3.6182	± 3.5907	± 2.3455
Bone mineral density			
Units: g/cm2			
arithmetic mean	1.086	1.087	1.094
standard deviation	± 0.1613	± 0.1611	± 0.116

Reporting group values	Cohort 4	Cohort 5	Total
Number of subjects	12	14	69
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	14	69
Age continuous			
Units: years			
arithmetic mean	41.7	37.4	
standard deviation	± 11.42	± 9.29	-
Gender categorical			
Units: Subjects			
Female	6	6	29
Male	6	8	40
Race			
Units: Subjects			
Asian	0	1	1
Caucasian	12	13	68
GHD history			
Units: Subjects			
Childhood onset	6	5	32
Adult onset	6	9	37
IGF-1			
Units: µg/l			
arithmetic mean	44.3	44.6	
standard deviation	± 27.91	± 28.73	-
IGF-1 SDS			
Units: SDS			
arithmetic mean	-2.97	-3.14	
standard deviation	± 1.58	± 1.264	-

IGFBP3 SDS			
Units: SDS			
arithmetic mean	-2.69	-2.55	
standard deviation	± 1.992	± 1.595	-
Body fat mass			
Units: kg			
arithmetic mean	24.335	29.113	
standard deviation	± 8.4133	± 9.5614	-
Lean body mass			
Units: kg			
arithmetic mean	41.73	44.261	
standard deviation	± 15.4269	± 12.5819	-
Trunk fat mass			
Units: kg			
arithmetic mean	13.827	15.847	
standard deviation	± 4.6946	± 5.8307	-
Bone mineral density			
Units: g/cm2			
arithmetic mean	1.076	1.126	
standard deviation	± 0.1523	± 0.1798	-

Subject analysis sets	
Subject analysis set title	SAS
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who had received at least one dose of the active treatment	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects who had received at least one dose of the active treatment and who provided any follow-up data for the primary target variables	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects with major protocol deviations in the dose-finding period were excluded.	
Subject analysis set title	SAS-SFU
Subject analysis set type	Safety analysis
Subject analysis set description:	
Includes all randomized patients who have completed the dose finding period and have received at least one dose of active treatment in the safety follow-up period.	
Subject analysis set title	FAS-SFU
Subject analysis set type	Full analysis
Subject analysis set description:	
Comprises all randomized patients who have completed the dose finding period, and who have received at least one dose of active treatment in the safety follow-up period and who provide any follow-up data for the primary target variables in the safety follow-up period.	

Reporting group values	SAS	FAS	PP
Number of subjects	69	69	58

Age categorical Units: Subjects			
Adults (18-64 years)	69	69	58
Age continuous Units: years			
arithmetic mean	38.3	38.3	38.8
standard deviation	± 10.93	± 10.93	± 11.19
Gender categorical Units: Subjects			
Female	29	29	26
Male	40	40	32
Race Units: Subjects			
Asian	1	1	1
Caucasian	68	68	57
GHD history Units: Subjects			
Childhood onset	32	32	29
Adult onset	37	37	29
IGF-1 Units: µg/l			
arithmetic mean	51	51	50.2
standard deviation	± 29.78	± 29.78	± 27.92
IGF-1 SDS Units: SDS			
arithmetic mean	-2.83	-2.83	-2.83
standard deviation	± 1.407	± 1.407	± 1.35
IGFBP3 SDS Units: SDS			
arithmetic mean	-2.4	-2.4	-2.42
standard deviation	± 1.675	± 1.675	± 1.658
Body fat mass Units: kg			
arithmetic mean	24.49	24.49	24.288
standard deviation	± 7.3842	± 7.3842	± 6.8127
Lean body mass Units: kg			
arithmetic mean	42.61	42.61	42.033
standard deviation	± 11.8294	± 11.8294	± 11.6529
Trunk fat mass Units: kg			
arithmetic mean	13.493	13.493	13.259
standard deviation	± 4.2566	± 4.2566	± 3.7528
Bone mineral density Units: g/cm2			
arithmetic mean	1.094	1.094	1.087
standard deviation	± 0.1525	± 0.1525	± 0.1552

Reporting group values	SAS-SFU	FAS-SFU	
Number of subjects	66	65	

Age categorical Units: Subjects			
Adults (18-64 years)	66	65	
Age continuous Units: years			
arithmetic mean	38.5	38.5	
standard deviation	± 10.99	± 11.08	
Gender categorical Units: Subjects			
Female	27	26	
Male	39	39	
Race Units: Subjects			
Asian	1	1	
Caucasian	65	64	
GHD history Units: Subjects			
Childhood onset	30	30	
Adult onset	36	35	
IGF-1 Units: µg/l			
arithmetic mean			
standard deviation	±	±	
IGF-1 SDS Units: SDS			
arithmetic mean			
standard deviation	±	±	
IGFBP3 SDS Units: SDS			
arithmetic mean			
standard deviation	±	±	
Body fat mass Units: kg			
arithmetic mean			
standard deviation	±	±	
Lean body mass Units: kg			
arithmetic mean			
standard deviation	±	±	
Trunk fat mass Units: kg			
arithmetic mean			
standard deviation	±	±	
Bone mineral density Units: g/cm2			
arithmetic mean			
standard deviation	±	±	

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: HM10560A 0.03 mg/kg EW	
Reporting group title	Cohort 2
Reporting group description: HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 20 weeks	
Reporting group title	Cohort 3
Reporting group description: HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 4 weeks then 0.10 mg/kg EW for 16 weeks	
Reporting group title	Cohort 4
Reporting group description: HM10560A 0.04 mg/kg EOW for 4 weeks then 0.08 mg/kg EOW for 4 weeks then 0.12 mg/kg EOW for 16 weeks	
Reporting group title	Cohort 5
Reporting group description: standard daily rhGH	
Reporting group title	Cohort 1 SFU
Reporting group description: 0.03 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum insulin-like growth factor- 1 (IGF-1) as follows: IGF-1 < -0.5 SDS dose increased 50% IGF-1 between -0.5 and +1.5 SDS dose maintained IGF-1 > 1.5 SDS dose decreased 25% IGF-1 >2 SDS dose decreased 50%.	
Reporting group title	Cohort 2 SFU
Reporting group description: 0.06 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).	
Reporting group title	Cohort 3 SFU
Reporting group description: 0.10 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).	
Reporting group title	Cohort 4 SFU
Reporting group description: 0.12 mg/kg EOW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).	
Reporting group title	Cohort 5 SFU
Reporting group description: Switched from Genotropin to 0.03 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).	
Reporting group title	Cohort 1 PK-PD
Reporting group description: Single dose 0.04 mg/kg HM10560A (total body weight)	
Reporting group title	Cohort 2 PK-PD
Reporting group description: Single dose 0.08 mg/kg HM10560A	
Reporting group title	Cohort 3 PK-PD
Reporting group description: Single dose 0.12 mg/kg HM10560A	

Subject analysis set title	SAS
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who had received at least one dose of the active treatment

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who had received at least one dose of the active treatment and who provided any follow-up data for the primary target variables

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects with major protocol deviations in the dose-finding period were excluded.

Subject analysis set title	SAS-SFU
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes all randomized patients who have completed the dose finding period and have received at least one dose of active treatment in the safety follow-up period.

Subject analysis set title	FAS-SFU
Subject analysis set type	Full analysis

Subject analysis set description:

Comprises all randomized patients who have completed the dose finding period, and who have received at least one dose of active treatment in the safety follow-up period and who provide any follow-up data for the primary target variables in the safety follow-up period.

Primary: Period 1: Change in IGF-1 over time (FAS)

End point title	Period 1: Change in IGF-1 over time (FAS)

End point description:

95% confidence intervals (CIs) for least-square mean (LSM) changes from baseline (coupled with standard error (SE) and degrees of freedom) at Week 24 in IGF-1 levels were calculated within a repeated mixed model analysis (MMRM) with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 level, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Primary

End point timeframe:

Baseline to Weeks 2, 4, 8, 12, 16, 20 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: µg/l				
least squares mean (standard error)				
Week 2	24.02 (± 10.31)	27.5 (± 10.234)	25.33 (± 10.31)	5.4 (± 11.105)
Week 4	23.02 (± 9.182)	24.38 (± 9.097)	11.74 (± 9.182)	7.52 (± 10.074)
Week 8	31.64 (± 8.855)	47.21 (± 8.674)	32.23 (± 8.763)	14.92 (± 9.428)
Week 12	34.52 (± 10.262)			

Week 20	39.37 (± 10.273)	43.84 (± 10.011)	61.1 (± 10.089)	15.17 (± 11.107)
Week 24	37.25 (± 9.643)	44.35 (± 9.439)	75.85 (± 9.521)	23.51 (± 10.416)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[1]		
Units: µg/l				
least squares mean (standard error)				
Week 2	86.47 (± 10.384)	()		
Week 4	98.15 (± 9.266)	()		
Week 8	110.65 (± 8.85)	()		
Week 12	91.49 (± 10.337)	()		
Week 16	115.23 (± 9.077)	()		
Week 20	104 (± 10.165)	()		
Week 24	96.99 (± 9.602)	()		

Notes:

[1] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24
Statistical analysis description: Difference in IGF-1 change from baseline to Week 24 between Cohort 1 and Cohort 5	
Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-59.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-86.87
upper limit	-32.61
Variability estimate	Standard error of the mean
Dispersion value	13.559

Notes:

[2] - Comparison of LSMs across treatment groups (Cohort 1 vs. Cohort 5) using the same MMRM (with standard error of the mean [SEM], 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24

Statistical analysis description:	
Difference in IGF-1 change from baseline to Week 24 between Cohort 2 and Cohort 5	
Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-52.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-79.6
upper limit	-25.68
Variability estimate	Standard error of the mean
Dispersion value	13.475

Notes:

[3] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in IGF-1 change from baseline to Week 24 between Cohorts 3 and Cohort 5	
Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.125
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-21.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.32
upper limit	6.04
Variability estimate	Standard error of the mean
Dispersion value	13.584

Notes:

[4] - Comparison of LSMs across treatment groups (Cohort 3 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in IGF-1 change from baseline to Week 24 between Cohorts 4 and Cohort 5	
Comparison groups	Cohort 4 v Cohort 5

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-73.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-101.82
upper limit	-45.13
Variability estimate	Standard error of the mean
Dispersion value	14.167

Notes:

[5] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with standard error of the mean [SEM], 95% CI and p value).

Primary: Period 1: Change in IGF-1 over time (PP)

End point title	Period 1: Change in IGF-1 over time (PP)

End point description:

95% CIs for LSM changes from baseline (coupled with SE and degrees of freedom) at Week 24 in IGF-1 levels were calculated within a MMRM with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 level, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Primary

End point timeframe:

Baseline to Weeks 2, 4, 8, 12, 16, 20 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	11	8
Units: µg/l				
least squares mean (standard error)				
Week 2	24.38 (± 10.574)	27.22 (± 9.736)	12.27 (± 11.282)	2.3 (± 13.008)
Week 4	22.74 (± 9.683)	24.1 (± 8.906)	9.11 (± 10.372)	4.07 (± 11.922)
Week 8	31.37 (± 9.766)	46.94 (± 8.984)	26.67 (± 10.457)	10.17 (± 12.024)
Week 12	33.98 (± 11.139)	49.84 (± 10.261)	53.76 (± 11.859)	11.69 (± 13.697)
Week 16	37.48 (± 9.565)	44.56 (± 8.796)	53.41 (± 10.252)	15.17 (± 11.778)
Week 20	40.13 (± 9.994)	43.57 (± 9.196)	43.29 (± 10.689)	12.63 (± 12.301)
Week 24	37.97 (± 9.929)	44.07 (± 9.135)	64.2 (± 10.623)	20.59 (± 12.222)

End point values	Cohort 5	PP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	0[6]		
Units: µg/l				
least squares mean (standard error)				
Week 2	81.91 (± 10.377)	()		
Week 4	91.6 (± 9.541)	()		
Week 8	107.65 (± 9.619)	()		
Week 12	93.05 (± 10.909)	()		
Week 16	112.68 (± 9.43)	()		
Week 20	109.74 (± 9.832)	()		
Week 24	102.29 (± 9.771)	()		

Notes:

[6] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGF-1 change from baseline to Week 24 between Cohort 1 and Cohort 5

Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-64.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-92.14
upper limit	-36.49
Variability estimate	Standard error of the mean
Dispersion value	13.847

Notes:

[7] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGF-1 change from baseline to Week 24 between Cohorts 2 and Cohort 5

Comparison groups	Cohort 2 v Cohort 5

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-58.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-85.19
upper limit	-31.24
Variability estimate	Standard error of the mean
Dispersion value	13.424

Notes:

[8] - Comparison of LSMs across treatment groups (Cohort 2vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGF-1 change from baseline to Week 24 between Cohorts 3 and Cohort 5

Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.014
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-38.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.96
upper limit	-8.22
Variability estimate	Standard error of the mean
Dispersion value	14.865

Notes:

[9] - Comparison of LSMs across treatment groups (Cohort 3 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGF-1 change from baseline to Week 24 between Cohorts 4 and Cohort 5

Comparison groups	Cohort 4 v Cohort 5
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-81.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-113.32
upper limit	-50.08
Variability estimate	Standard error of the mean
Dispersion value	15.733

Notes:

[10] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Primary: Period 2: Change in IGF-1 from Week 24 to 74 (FAS-SFU)

End point title	Period 2: Change in IGF-1 from Week 24 to 74 (FAS-SFU)

End point description:

95% CIs for LSM changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an analysis of covariance (ANCOVA) model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Primary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: µg/l				
least squares mean (standard error)	9.06 (± 12.103)	9.13 (± 12.083)	14.57 (± 11.543)	-8.64 (± 14.226)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[11]		
Units: µg/l				
least squares mean (standard error)	-50.92 (± 13.305)	()		

Notes:

[11] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 change from Week 24 to Week 72 between Cohorts 1-4 SFU and Cohort 5 SFU

Comparison groups	Cohort 5 SFU v Cohort 1 SFU

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	59.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.37
upper limit	96.6
Variability estimate	Standard error of the mean
Dispersion value	18.238

Notes:

[12] - Comparison of LSMs across treatment groups (Cohort 1-4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 change from Week 24 to Week 72 between Cohorts 2 SFU and Cohort 5 SFU

Comparison groups	Cohort 2 SFU v Cohort 5 SFU
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	59.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.37
upper limit	96.6
Variability estimate	Standard error of the mean
Dispersion value	18.238

Notes:

[13] - Comparison of LSMs across treatment groups (Cohort 2 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 change from Week 24 to Week 72 between Cohorts 3 SFU and Cohort 5 SFU

Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	65.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	31.69
upper limit	99.29
Variability estimate	Standard error of the mean
Dispersion value	16.835

Notes:

[14] - Comparison of LSMs across treatment groups (Cohort 3 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 change from Week 24 to Week 72 between Cohorts 4 SFU and Cohort 5 SFU

Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.044
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	42.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	83.31
Variability estimate	Standard error of the mean
Dispersion value	20.439

Notes:

[15] - Comparison of LSMs across treatment groups (Cohort 4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Primary: Period 3: Change in IGF-1 over time (FAS)

End point title	Period 3: Change in IGF-1 over time (FAS)[16]

End point description:

Actual change in IGF-1 over time (observed cases)

End point type	Primary

End point timeframe:

0 hours to 672 hours

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a Phase II study of exloratory nature, therefore statistical analysis of each endpoint is not completely necessary. However, statistical analyses of the same measured variable (IGF-1) are ready in other study periods.

End point values	Cohort 1 PK-PD	Cohort 2 PK-PD	Cohort 3 PK-PD	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	3	0[17]
Units: µ/l				
arithmetic mean (standard deviation)				
0.5-1.5 hours	-4.7 (± 6.79)	-3.6 (± 1.23)	-0.5 (± 2.16)	()

2-4 hours	-3.6 (± 4.48)	-3.1 (± 4.83)	-2.9 (± 4.54)	()
7-12 hours	4.5 (± 7.09)	12 (± 4.78)	23.5 (± 9.24)	()
16-30 hours	21.9 (± 16.21)	69.9 (± 7.71)	80.8 (± 31.12)	()
30-60 hours	34 (± 22.14)	91.2 (± 12.76)	109.7 (± 48.58)	()
72-100 hours	37.7 (± 26.8)	73.5 (± 44.77)	84.3 (± 64.37)	()
120-150 hours	25.2 (± 16.35)	61.2 (± 29.75)	53.2 (± 53.34)	()
200-250 hours	19.5 (± 5.75)	40.1 (± 19.54)	18.3 (± 25.37)	()
400-450 hours	-7 (± 11.03)	8.1 (± 12.28)	0.1 (± 9.98)	()
600-672 hours	-4.2 (± 8.85)	3.4 (± 5.49)	-4.1 (± 8.7)	()

Notes:

[17] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

No statistical analyses for this end point

Secondary: Period 1: Change in IGF-1 SDS (FAS)

End point title	Period 1: Change in IGF-1 SDS (FAS)

End point description:

95% CIs for LSM changes from baseline (coupled with SE and degrees of freedom) at Week 24 in IGF-1 SDS were calculated within a MMRM with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 SDS, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 2, 4, 8, 12, 16, 20 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: SDS				
least squares mean (standard error)				
Week 2	1.01 (± 0.265)	0.87 (± 0.263)	0.98 (± 0.264)	0.06 (± 0.285)
Week 4	1.02 (± 0.229)	1.01 (± 0.227)	0.61 (± 0.229)	0.13 (± 0.252)
Week 8	1.27 (± 0.244)	1.52 (± 0.238)	1.28 (± 0.24)	0.45 (± 0.259)
Week 12	1.35 (± 0.288)	1.7 (± 0.286)	1.87 (± 0.287)	0.35 (± 0.31)
Week 16	1.39 (± 0.255)	1.52 (± 0.253)	2 (± 0.254)	0.69 (± 0.275)
Week 20	1.41 (± 0.253)	1.56 (± 0.247)	2 (± 0.248)	0.46 (± 0.273)
Week 24	1.37 (± 0.241)	1.52 (± 0.235)	2.35 (± 0.237)	0.8 (± 0.259)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[18]		
Units: SDS				
least squares mean (standard error)				

Week 2	2.55 (± 0.267)	()		
Week 4	2.84 (± 0.232)	()		
Week 8	3.17 (± 0.243)	()		
Week 12	2.52 (± 0.289)	()		
Week 16	3.24 (± 0.257)	()		
Week 20	3.19 (± 0.251)	()		
Week 24	2.97 (± 0.24)	()		

Notes:

[18] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in IGF-1 SDS change from baseline to Week 24 between Cohorts 1 and Cohort 5	
Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	-0.92
Variability estimate	Standard error of the mean
Dispersion value	0.338

Notes:

[19] - Comparison of LSMs across treatment groups (Cohort 1 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in IGF-1 SDS change from baseline to Week 24 between Cohorts 2 and Cohort 5	
Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	-0.78
Variability estimate	Standard error of the mean
Dispersion value	0.336

Notes:

[20] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGF-1 SDS change from baseline to Week 24 between Cohorts 3 and Cohort 5

Cohort 3 v Cohort 5

and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 SDS, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 2, 4, 8, 12, 16, 20 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: SDS				
least squares mean (standard error)				
Week 2	0.58 (± 0.197)	0.53 (± 0.195)	0.55 (± 0.196)	0.08 (± 0.212)
Week 4	0.55 (± 0.168)	0.45 (± 0.166)	0.26 (± 0.167)	-0.1 (± 0.185)
Week 8	0.7 (± 0.173)	0.64 (± 0.169)	0.47 (± 0.169)	0.12 (± 0.183)
Week 12	0.59 (± 0.202)	0.8 (± 0.2)	0.9 (± 0.2)	0.05 (± 0.217)
Week 16	0.53 (± 0.176)	0.7 (± 0.174)	0.99 (± 0.174)	0.36 (± 0.189)
Week 20	0.56 (± 0.178)	0.75 (± 0.172)	1 (± 0.173)	0.18 (± 0.192)
Week 24	0.8 (± 0.19)	0.63 (± 0.184)	1.09 (± 0.185)	0.4 (± 0.205)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[23]		
Units: SDS				
least squares mean (standard error)				
Week 2	1.61 (± 0.197)	()		
Week 4	1.65 (± 0.169)	()		
Week 8	1.53 (± 0.171)	()		
Week 12	1.4 (± 0.202)	()		
Week 16	1.76 (± 0.176)	()		
Week 20	1.8 (± 0.175)	()		
Week 24	1.67 (± 0.186)	()		

Notes:

[23] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGFBP3 SDS change from baseline to Week 24 between cohorts

Comparison groups	Cohort 1 v Cohort 5

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.266

Notes:

[24] - Comparison of LSMs across treatment groups (Cohort 1-4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGFBP3 SDS change from baseline to Week 24 between cohorts

Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.262

Notes:

[25] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGFBP3 SDS change from baseline to Week 24 between cohorts

Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.028
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.262

Notes:

[26] - Comparison of LSMs across treatment groups (Cohort 3 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in IGFBP3 SDS change from baseline to Week 24 between cohorts

Comparison groups	Cohort 4 v Cohort 5
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	-0.72
Variability estimate	Standard error of the mean
Dispersion value	0.277

Notes:

[27] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Secondary: Period 1: Change in lean body mass (LBM) (FAS)	
End point title	Period 1: Change in lean body mass (LBM) (FAS)

End point description:

95% CIs for LSM changes from baseline (coupled with SE and degrees of freedom) at Week 24 in LBM were calculated within a MMRM with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 SDS, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 12 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: kg				
least squares mean (standard error)				

Week 12	0.575 (± 0.4054)	1.749 (± 0.3868)	0.436 (± 0.4021)	0.599 (± 0.4192)
Week 24	1.078 (± 0.4408)	1.675 (± 0.4239)	1.286 (± 0.4405)	1.1 (± 0.4739)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[28]		
Units: kg				
least squares mean (standard error)				
Week 12	1.709 (± 0.3895)	()		
Week 24	2.357 (± 0.4263)	()		

Notes:

[28] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in LBM change from baseline to Week 24 between Cohort 1 and Cohort 5

Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.04
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.279
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.497
upper limit	-0.061
Variability estimate	Standard error of the mean
Dispersion value	0.6086

Notes:

[29] - Comparison of LSMs across treatment groups (Cohort 1 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in LBM change from baseline to Week 24 between Cohorts 2 and Cohort 5

Comparison groups	Cohort 2 v Cohort 5

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.26
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.682
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.882
upper limit	0.519
Variability estimate	Standard error of the mean
Dispersion value	0.5997

Notes:

[30] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in LBM change from baseline to Week 24 between Cohort 3 and Cohort 5

Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.085
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.293
upper limit	0.151
Variability estimate	Standard error of the mean
Dispersion value	0.6106

Notes:

[31] - Comparison of LSMs across treatment groups (Cohort 3 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in LBM change from baseline to Week 24 between Cohort 4 and Cohort 5

Comparison groups	Cohort 4 v Cohort 5
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.054
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.257

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.538
upper limit	0.024
Variability estimate	Standard error of the mean
Dispersion value	0.6399

Notes:

[32] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Secondary: Period 1: Change in body fat mass (FM) (FAS)

End point title	Period 1: Change in body fat mass (FM) (FAS)

End point description:

95% CIs for LSM changes from baseline (coupled with SE and degrees of freedom) at Week 24 in FM were calculated within a MMRM with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 SDS, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 12 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: kg				
least squares mean (standard error)				
Week 12	-0.713 (± 0.5672)	-0.956 (± 0.5452)	0.923 (± 0.5671)	-0.506 (± 0.5913)
Week 24	-0.468 (± 0.7144)	-1.337 (± 0.6944)	1.137 (± 0.7216)	-0.599 (± 0.7648)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[33]		
Units: kg				
least squares mean (standard error)				
Week 12	-1.418 (± 0.5675)	()		
Week 24	-0.831 (± 0.712)	()		

Notes:

[33] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in FM change from baseline to Week 24 between Cohort 1 and Cohort 5	
Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.722
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.363
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	2.396
Variability estimate	Standard error of the mean
Dispersion value	1.0156

Notes:

[34] - Comparison of LSMs across treatment groups (Cohort 1 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in FM change from baseline to Week 24 between Cohort 2 and Cohort 5	
Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.615
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.506
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.511
upper limit	1.498
Variability estimate	Standard error of the mean
Dispersion value	1.0012

Notes:

[35] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in FM change from baseline to Week 24 between Cohort 3 and Cohort 5	
Comparison groups	Cohort 3 v Cohort 5

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.058
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.968
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.071
upper limit	4.007
Variability estimate	Standard error of the mean
Dispersion value	1.0187

Notes:

[36] - Comparison of LSMs across treatment groups (Cohort 3 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24

Statistical analysis description:

Difference in FM change from baseline to Week 24 between Cohorts 4 and Cohort 5

Comparison groups	Cohort 4 v Cohort 5
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.826
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.232
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	2.334
Variability estimate	Standard error of the mean
Dispersion value	1.0502

Notes:

[37] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Secondary: Period 1: Relative change in body fat mass (FM) (FAS)

End point title	Period 1: Relative change in body fat mass (FM) (FAS)

End point description:

95% CIs for LSM % changes from baseline (coupled with SE and degrees of freedom) at Week 24 in FM were calculated within a MMRM with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 SDS, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 12 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: percent				
least squares mean (standard error)				
Week 12	-1.173 (± 0.61)	-1.922 (± 0.5884)	0.467 (± 0.6124)	-0.964 (± 0.6418)
Week 24	-1.164 (± 0.7327)	-2.175 (± 0.7134)	0.244 (± 0.7418)	-1.21 (± 0.7896)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[38]		
Units: percent				
least squares mean (standard error)				
Week 12	-1.98 (± 0.6219)	()		
Week 24	-2.081 (± 0.7412)	()		

Notes:

[38] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change in FM from baseline to Week 24 between Cohorts 1 and Cohort 5	
Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.383 [40]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.169
upper limit	3.002
Variability estimate	Standard error of the mean
Dispersion value	1.0418

Notes:

[39] - Comparison of LSMs across treatment groups (Cohort 1 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

[40] - Comparison of LSMs across treatment groups (Cohort 1 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change in FM from baseline to Week 24 between Cohorts 2 and Cohort 5	
Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.927
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.152
upper limit	1.963
Variability estimate	Standard error of the mean
Dispersion value	1.0277

Notes:

[41] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change in FM from baseline to Week 24 between Cohorts 3 and Cohort 5	
Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	= 0.03
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.325
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.233
upper limit	4.416
Variability estimate	Standard error of the mean
Dispersion value	1.0449

Notes:

[42] - Comparison of LSMs across treatment groups (Cohort 3 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change in FM from baseline to Week 24 between Cohort 4 and Cohort 5	
Comparison groups	Cohort 4 v Cohort 5

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.425
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.296
upper limit	3.036

Notes:

[44] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in trunk fat change from baseline to Week 24 between Cohort 1 and Cohort 5	
Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.735
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.022
upper limit	1.441
Variability estimate	Standard error of the mean
Dispersion value	0.6151

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in trunk fat change from baseline to Week 24 between Cohorts 2 and Cohort 5	
Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.543
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.373
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.594
upper limit	0.847
Variability estimate	Standard error of the mean
Dispersion value	0.6096

Notes:

[45] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in trunk fat change from baseline to Week 24 between Cohort 3 and Cohort 5	
Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.147
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.915
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.332
upper limit	2.162
Variability estimate	Standard error of the mean
Dispersion value	0.6229

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in trunk fat change from baseline to Week 24 between Cohorts 4 and Cohort 5	
Comparison groups	Cohort 4 v Cohort 5
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.959
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.244
upper limit	1.31
Variability estimate	Standard error of the mean
Dispersion value	0.6381

Notes:

[46] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Secondary: Period 1: Relative change in trunk fat (FAS)

End point title	Period 1: Relative change in trunk fat (FAS)

End point description:

95% CIs for LSM % changes from baseline (coupled with SE and degrees of freedom) at Week 24 in trunk fat were calculated within a MMRM with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 SDS, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 12 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: percent				
least squares mean (standard error)				
Week 12	-2.012 (± 0.7492)	-2.516 (± 0.7226)	-0.124 (± 0.7532)	-1.463 (± 0.7904)
Week 24	-1.799 (± 0.8373)	-3.184 (± 0.8135)	-0.574 (± 0.8472)	-1.932 (± 0.9063)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[47]		
Units: percent				
least squares mean (standard error)				
Week 12	-2.94 (± 0.754)	()		
Week 24	-2.847 (± 0.8416)	()		

Notes:

[47] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change from baseline to Week 24 between Cohorts 1 and Cohort 5	
Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.379
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.317
upper limit	3.413
Variability estimate	Standard error of the mean
Dispersion value	1.1816

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change from baseline to Week 24 between Cohorts 2 and Cohort 5	
Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	= 0.775
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.337
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	2.007
Variability estimate	Standard error of the mean
Dispersion value	1.1708

Notes:

[48] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change from baseline to Week 24 between Cohorts 3 and Cohort 5	
Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.063
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.273
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.124
upper limit	4.671
Variability estimate	Standard error of the mean
Dispersion value	1.1979

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in relative change from baseline to Week 24 between Cohort 4 and Cohort 5	
Comparison groups	Cohort 4 v Cohort 5

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.46
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.916
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.548
upper limit	3.379
Variability estimate	Standard error of the mean
Dispersion value	1.2307

Notes:

[49] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Secondary: Period 1: Change in bone mineral density (BMD) (FAS)

End point title	Period 1: Change in bone mineral density (BMD) (FAS)

End point description:

95% CIs for LSM changes from baseline (coupled with SE and degrees of freedom) at Week 24 in BMD were calculated within a MMRM with random subject effect, class variables: cohort, gender, and GHD onset type (Childhood or Adult), and continuous covariates: baseline IGF-1 SDS, age at screening (in years). An unstructured covariance structure was assumed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 12 and 24

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	12
Units: kg				
least squares mean (standard error)				
Week 12	-0.003 (± 0.006)	0.004 (± 0.0058)	-0.006 (± 0.006)	0.013 (± 0.0063)
Week 24	0 (± 0.0053)	-0.005 (± 0.005)	-0.002 (± 0.0052)	0.002 (± 0.0057)

End point values	Cohort 5	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	0[50]		
Units: kg				
least squares mean (standard error)				
Week 12	-0.006 (± 0.0058)	()		
Week 24	-0.01 (± 0.0051)	()		

Notes:

[50] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in BMD change from baseline to Week 24 between Cohorts 1 and Cohort 5	
Comparison groups	Cohort 1 v Cohort 5
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.187
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.024
Variability estimate	Standard error of the mean
Dispersion value	0.0073

Notes:

[51] - Comparison of LSMs across treatment groups (Cohort 1 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in BMD change from baseline to Week 24 between Cohorts 2 and Cohort 5	
Comparison groups	Cohort 2 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	= 0.521
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.019
Variability estimate	Standard error of the mean
Dispersion value	0.0071

Notes:

[52] - Comparison of LSMs across treatment groups (Cohort 2 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in BMD change from baseline to Week 24 between Cohort 3 and Cohort 5	
Comparison groups	Cohort 3 v Cohort 5
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.275
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.023
Variability estimate	Standard error of the mean
Dispersion value	0.0073

Notes:

[53] - Comparison of LSMs across treatment groups (Cohort 3 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 24
Statistical analysis description:	
Difference in BMD change from baseline to Week 24 between Cohorts 4 and Cohort 5	
Comparison groups	Cohort 4 v Cohort 5
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.152
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.026
Variability estimate	Standard error of the mean
Dispersion value	0.0077

Notes:

[54] - Comparison of LSMs across treatment groups (Cohort 4 vs. Cohort 5) using the same MMRM (with SEM, 95% CI and p value).

Secondary: Period 2: Change in IGF-1 SDS from Week 24 to 72 (FAS-SFU)

End point title	Period 2: Change in IGF-1 SDS from Week 24 to 72 (FAS-SFU)

End point description:

95% CIs for LSM changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an ANCOVA model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Secondary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: SDS				
least squares mean (standard error)	0.36 (± 0.301)	0.22 (± 0.301)	0.58 (± 0.286)	-0.09 (± 0.358)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[55]		
Units: SDS				
least squares mean (standard error)	-1.3 (± 0.33)	()		

Notes:

[55] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 SDS change from Week 24 to 72 between Cohorts 1 SFU and Cohort 5 SFU

Comparison groups	Cohort 1 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.56
Variability estimate	Standard error of the mean
Dispersion value	0.45

Notes:

[56] - Comparison of LSMs across treatment groups (Cohort 1 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 SDS change from Week 24 to 72 between Cohorts 2 SFU and Cohort 5 SFU

Comparison groups	Cohort 2 SFU v Cohort 5 SFU

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	2.41
Variability estimate	Standard error of the mean
Dispersion value	0.446

Notes:

[57] - Comparison of LSMs across treatment groups (Cohort 2 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 SDS change from Week 24 to 72 between Cohorts 3 SFU and Cohort 5 SFU

Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.72
Variability estimate	Standard error of the mean
Dispersion value	0.421

Notes:

[58] - Comparison of LSMs across treatment groups (Cohort 3 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGF-1 SDS change from Week 24 to 72 between Cohorts 4 SFU and Cohort 5 SFU

Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.022
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	2.23
Variability estimate	Standard error of the mean
Dispersion value	0.511

Notes:

[59] - Comparison of LSMs across treatment groups (Cohort 4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Secondary: Period 2: Change in IGFBP3 SDS from Week 24 to 72 (FAS-SFU)

End point title	Period 2: Change in IGFBP3 SDS from Week 24 to 72 (FAS-SFU)

End point description:

95% CIs for LSM changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an ANCOVA model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Secondary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: SDS				
least squares mean (standard error)	0.32 (± 0.23)	0.31 (± 0.236)	0.83 (± 0.22)	0.04 (± 0.272)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[60]		
Units: SDS				
least squares mean (standard error)	-0.44 (± 0.255)	()		

Notes:

[60] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGFBP3 SDS change from Week 24 to 72 between Cohorts 1 SFU and Cohort 5 SFU

Comparison groups	Cohort 1 SFU v Cohort 5 SFU

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	= 0.028
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.76

lower limit	0.09
upper limit	1.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.94
Variability estimate	Standard error of the mean
Dispersion value	0.332

Notes:

[63] - Comparison of LSMs across treatment groups (Cohort 3 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in IGFBP3 SDS change from Week 24 to 72 between Cohorts 4 SFU and Cohort 5 SFU

Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[64]
P-value	= 0.215
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	1.25
Variability estimate	Standard error of the mean
Dispersion value	0.384

Notes:

[64] - Comparison of LSMs across treatment groups (Cohort 4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Secondary: Period 2: Change in lean body mass (LBM) from Week 24 to 72 (FAS-SFU)

End point title	Period 2: Change in lean body mass (LBM) from Week 24 to 72 (FAS-SFU)

End point description:

95% CIs for LSM changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an ANCOVA model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Secondary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: kg				
least squares mean (standard error)	0.26 (± 0.612)	0.18 (± 0.608)	0.92 (± 0.58)	0.75 (± 0.682)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[65]		
Units: kg				
least squares mean (standard error)	0.31 (± 0.617)	()		

Notes:

[65] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in LBM change from Week 24 to 72 between Cohort 1 SFU and Cohort 5 SFU

Comparison groups	Cohort 1 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	= 0.951
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	1.64
Variability estimate	Standard error of the mean
Dispersion value	0.845

Notes:

[66] - Comparison of LSMs across treatment groups (Cohort 1 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in LBM change from Week 24 to 72 between Cohorts 1-4 SFU and Cohort 5 SFU

Comparison groups	Cohort 2 SFU v Cohort 5 SFU

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	= 0.872
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	1.58
Variability estimate	Standard error of the mean
Dispersion value	0.856

Notes:

[67] - Comparison of LSMs across treatment groups (Cohort 2 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in LBM change from Week 24 to 72 between Cohorts 1-4 SFU and Cohort 5 SFU

Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[68]
P-value	= 0.465
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	2.27
Variability estimate	Standard error of the mean
Dispersion value	0.829

Notes:

[68] - Comparison of LSMs across treatment groups (Cohort 1-4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in LBM change from Week 24 to 72 between Cohort 4 SFU and Cohort 5 SFU

Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	= 0.644
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.932

Notes:

[69] - Comparison of LSMs across treatment groups (Cohort 4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Secondary: Period 2: Change in body fat mass (FM) from Week 24 to 72 (FAS-SFU)

End point title	Period 2: Change in body fat mass (FM) from Week 24 to 72 (FAS-SFU)

End point description:

95% CIs for LSM changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an ANCOVA model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Secondary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: kg				
least squares mean (standard error)	0.88 (± 0.863)	-1.32 (± 0.885)	-0.47 (± 0.815)	0.46 (± 0.986)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[70]		
Units: kg				
least squares mean (standard error)	0.94 (± 0.901)	()		

Notes:

[70] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in body FM change from Week 24 to 72 between Cohorts 1 SFU and Cohort 5 SFU

Comparison groups	Cohort 1 SFU v Cohort 5 SFU

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	= 0.965
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.55
upper limit	2.45
Variability estimate	Standard error of the mean
Dispersion value	1.246

Notes:

[71] - Comparison of LSMs across treatment groups (Cohort 1 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in body FM change from Week 24 to 72 between Cohorts 2 SFU and Cohort 5 SFU

Comparison groups	Cohort 2 SFU v Cohort 5 SFU
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[72]
P-value	= 0.081
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	1.269

Notes:

[72] - Comparison of LSMs across treatment groups (Cohort 2 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in body FM change from Week 24 to 72 between Cohort 3 SFU and Cohort 5 SFU

Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.246
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.81
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	1.199

Notes:

[73] - Comparison of LSMs across treatment groups (Cohort 1-4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in body FM change from Week 24 to 72 between Cohorts 4 SFU and Cohort 5 SFU

Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[74]
P-value	= 0.728
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.17
upper limit	2.23
Variability estimate	Standard error of the mean
Dispersion value	1.346

Notes:

[74] - Comparison of LSMs across treatment groups (Cohort 4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Secondary: Period 2: Relative change in body fat mass (FM) from Week 24 to 72 (FAS-SFU)

End point title	Period 2: Relative change in body fat mass (FM) from Week 24 to 72 (FAS-SFU)

End point description:

95% CIs for LSM % changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an ANCOVA model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Secondary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: percent				
least squares mean (standard error)	0.75 (± 0.9)	-1.54 (± 0.929)	-0.85 (± 0.883)	0.09 (± 1.043)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[75]		
Units: percent				
least squares mean (standard error)	0.86 (± 0.959)	()		

Notes:

[75] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in FM relative change from Week 24 to 72 between Cohort 1 SFU and Cohort 5 SFU

Comparison groups	Cohort 1 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[76]
P-value	= 0.93
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	2.48
Variability estimate	Standard error of the mean
Dispersion value	1.292

Notes:

[76] - Comparison of LSMs across treatment groups (Cohort 1 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in FM relative change from Week 24 to 72 between Cohorts 2 SFU and Cohort 5 SFU

Comparison groups	Cohort 2 SFU v Cohort 5 SFU

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	= 0.078
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.09
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	1.337

Notes:

[77] - Comparison of LSMs across treatment groups (Cohort 2 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in FM relative change from Week 24 to 72 between Cohort 3 SFU and Cohort 5 SFU

Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[78]
P-value	= 0.179
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.24
upper limit	0.81
Variability estimate	Standard error of the mean
Dispersion value	1.258

Notes:

[78] - Comparison of LSMs across treatment groups (Cohort 3 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in FM relative change from Week 24 to 72 between Cohorts 4 SFU and Cohort 5 SFU

Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[79]
P-value	= 0.592
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.62
upper limit	2.09
Variability estimate	Standard error of the mean
Dispersion value	1.423

Notes:

[79] - Comparison of LSMs across treatment groups (Cohort 4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Secondary: Period 2: Change in trunk fat from Week 24 to 72 (FAS-SFU)

End point title	Period 2: Change in trunk fat from Week 24 to 72 (FAS-SFU)

End point description:

95% CIs for LSM changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an ANCOVA model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Secondary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: kg				
least squares mean (standard error)	0.44 (± 0.486)	-0.61 (± 0.503)	-0.22 (± 0.462)	0.18 (± 0.56)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[80]		
Units: kg				
least squares mean (standard error)	0.18 (± 0.508)	()		

Notes:

[80] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in trunk fat change from Week 24 to 72 between Cohort 1 SFU and Cohort 5 SFU

Comparison groups	Cohort 1 SFU v Cohort 5 SFU

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[81]
P-value	= 0.71
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	1.66
Variability estimate	Standard error of the mean
Dispersion value	0.698

Notes:

[81] - Comparison of LSMs across treatment groups (Cohort 1 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in trunk fat change from Week 24 to 72 between Cohort 2 SFU and Cohort 5 SFU

Comparison groups	Cohort 2 SFU v Cohort 5 SFU
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[82]
P-value	= 0.276
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.718

Notes:

[82] - Comparison of LSMs across treatment groups (Cohort 2 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in trunk fat change from Week 24 to 72 between Cohorts 3 SFU and Cohort 5 SFU

Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[83]
P-value	= 0.554
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.41

&RQILGHQFH LQWHUYDO	
OHYHO	
VLGHV	VLGHG
ORZHU OLPLW	
XSSHU OLPLW	
9DULDELOLW\ HVWLPDWH	6WDQGDUG HUURU RI WKH PHDQ
'LVSHUVLRQ YDOXH	

1RWHV

> @ &RPSDULVRQ RI /60V DFURVV WUHDWPHQW JURXSV &RKRUW 6)8 YV &RK $1&29$ PRGHO ZLWK 6(0 &, DQG S YDOXH

Statistical analysis title	&RKRUW YV &RKRUW DW :HHN

6WDWLVWLFDO DQDO\VLV GHVFULSWLRQ

'LIIHUHQFH LQ WUXQN IDW FKDQJH IURP :HHN WR EHWZHHQ &RKRUWV 6)8

&RPSDULVRQ JURXSV	&RKRUW 6)8 Y &RKRUW 6)8
1XPEHU RI VXEMHFWV LQFOXGHG LQ DQDO\VLV	
$QDO\VLV VSHFLILFDWLRQ	3UH VSHFLILHG
$QDO\VLV W\SH	RWKHU> @
3 YDOXH	
0HWKRG	$1&29$
3DUDPHWHU HVWLPDWH	0HDQ GLIIHUHQFH ILQDO YDOXHV
3RLQW HVWLPDWH	

&RQILGHQFH LQWHUYDO	
OHYHO	
VLGHV	VLGHG
ORZHU OLPLW	
XSSHU OLPLW	
9DULDELOLW\ HVWLPDWH	6WDQGDUG HUURU RI WKH PHDQ
'LVSHUVLRQ YDOXH	

1RWHV

> @ &RPSDULVRQ RI /60V DFURVV WUHDWPHQW JURXSV &RKRUW 6)8 YV &RK $1&29$ PRGHO ZLWK 6(0 &, DQG S YDOXH

Secondary: Period 2: Relative change in trunk fat from Week 24 to 72 (FAS-SFU)	
(QG SRLQW WLWOH	3HUFHQWDJH FKDQJH LQ WUXQN IDW IURP :HHN)$6 6)8

(QG SRLQW GHVFULSWLRQ

&,V IRU /60 FKDQJHV IURP :HHN FRXSOHG ZLWK 6(DQG GHJUHHV RI IUHH HYDOXDWHG LQ DQ $1&29$ PRGHO ZLWK FODVV YDULDEOHV FRKRUW JHQGHU $GXOW DQG FRQWLQXRXV FRYDULDWHV FKDQJH LQ +0 $ GRVH ZHHN UH \HDUV

(QG SRLQW W\SH	6HFRQGDU\

(QG SRLQW WLPHIUDPH

:HHNV WR

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: percent				
least squares mean (standard error)	0.79 (± 1.086)	-1.75 (± 1.126)	-1.27 (± 1.047)	-0.05 (± 1.262)

End point values	Cohort 5 SFU	FAS-SFU		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	0[85]		
Units: percent				
least squares mean (standard error)	0.02 (± 1.149)	()		

Notes:

[85] - It is not reasonable to summarize results across cohorts (except for baseline, reported separately).

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in relative change in trunk fat from Week 24 to 72 between Cohort 1 SFU and Cohort 5 SFU

Comparison groups	Cohort 1 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[86]
P-value	= 0.622
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	3.87
Variability estimate	Standard error of the mean
Dispersion value	1.548

Notes:

[86] - Comparison of LSMs across treatment groComparison of LSMs across treatment groups (Cohort 1 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).ups (Cohort 1-4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in relative change in trunk fat from Week 24 to 72 between Cohorts 2 SFU and Cohort 5 SFU

Comparison groups	Cohort 2 SFU v Cohort 5 SFU

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[87]
P-value	= 0.278
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.02
upper limit	1.47
Variability estimate	Standard error of the mean
Dispersion value	1.616

Notes:

[87] - Comparison of LSMs across treatment groups (Cohort 2 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in relative change in trunk fat from Week 24 to 72 between Cohort 3 SFU and Cohort 5 SFU

Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[88]
P-value	= 0.401
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.33
upper limit	1.76
Variability estimate	Standard error of the mean
Dispersion value	1.518

Notes:

[88] - Comparison of LSMs across treatment groups (Cohort 3 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72

Statistical analysis description:

Difference in relative change in trunk fat from Week 24 to 72 between Cohort 4 SFU and Cohort 5 SFU

Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[89]
P-value	= 0.97
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	3.37
Variability estimate	Standard error of the mean
Dispersion value	1.71

Notes:

[89] - Comparison of LSMs across treatment groups (Cohort 4 SFU vs Cohort 5 SFU) using the same ANCOVA model (with SEM, 95% CI and p-value).

Secondary: Period 2: Change in bone mineral density (BMD) from Week 24 to 72 (FAS-SFU)

End point title	Period 2: Change in bone mineral density (BMD) from Week 24 to 72 (FAS-SFU)

End point description:

95% CIs for LSM changes from Week 24 (coupled with SE and degrees of freedom) at Week 72 were evaluated in an ANCOVA model with class variables: cohort, gender and GHD onset type (Childhood or Adult), and continuous covariates: change in HM10560A dose, week 24 result, age at screening (in years).

End point type	Secondary

End point timeframe:

Weeks 24 to 72

End point values	Cohort 1 SFU	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	13	10
Units: g/cm2				
least squares mean (standard error)	0 (± 0.01)	-0.01 (± 0.01)	0 (± 0.01)	0.01 (± 0.012)

End point values	Cohort 5 SFU			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: g/cm2				
least squares mean (standard error)	0 (± 0.01)			

Statistical analyses

Statistical analysis title	Cohort 1 vs Cohort 5 at Week 72
Comparison groups	Cohort 1 SFU v Cohort 5 SFU

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.802
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	Cohort 2 vs Cohort 5 at Week 72
Comparison groups	Cohort 2 SFU v Cohort 5 SFU
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.354
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.015

Statistical analysis title	Cohort 3 vs Cohort 5 at Week 72
Comparison groups	Cohort 3 SFU v Cohort 5 SFU
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.898
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.03

Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	Cohort 4 vs Cohort 5 at Week 72
Comparison groups	Cohort 4 SFU v Cohort 5 SFU
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.366
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.016

Adverse events information

Timeframe for reporting adverse events:

AEs were collected beginning after starting the study treatment and continued until 2 weeks after the subject received the last dose of the study treatment. SAEs, reporting started after the subject had provided IC until the same timeframe as AEs.

Adverse event reporting additional description:

Reported AEs(SAEs) are Treatment-emergent adverse events(TEAEs). TEAEs are summarized by the following study periods: Single Dose Run-in and 24-week Dose Finding Periods (Periods 3 and 1) pooled, and for the 48+2 weeks Long-term Safety Period (Period 2).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

HM10560A 0.03 mg/kg EW

Reporting group title	Cohort 2

Reporting group description:

HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 20 weeks

Reporting group title	Cohort 3

Reporting group description:

HM10560A 0.03 mg/kg EW for 4 weeks then 0.06 mg/kg EW for 4 weeks then 0.10 mg/kg EW for 16 weeks

Reporting group title	Cohort 4

Reporting group description:

HM10560A 0.04 mg/kg EOW for 4 weeks then 0.08 mg/kg EOW for 4 weeks then 0.12 mg/kg EOW for 16 weeks

Reporting group title	Cohort 5

Reporting group description:

standard daily rhGH

Reporting group title	Cohort 1 SFU

Reporting group description:

0.03 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum insulin-like growth factor- 1 (IGF-1) as follows: IGF-1 < -0.5 SDS dose increased 50% IGF-1 between -0.5 and +1.5 SDS dose maintained IGF-1 > 1.5 SDS dose decreased 25% IGF-1 >2 SDS dose decreased 50%.

Reporting group title	Cohort 2 SFU

Reporting group description:

0.06 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Reporting group title	Cohort 3 SFU

Reporting group description:

0.10 mg/kg HM10560A EW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Reporting group title	Cohort 4 SFU

Reporting group description:

0.12 mg/kg EOW initially then adjusted up to 6 times following monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Reporting group title	Cohort 5 SFU

Reporting group description:

Switched from Genotropin to 0.03 mg/kg HM10560A EW initially then adjusted up to 6 times following

monthly visits, according to subjects' age and gender-adjusted serum IGF-1 (as detailed for cohort 1 SFU).

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric volvulus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Acute tonsillitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4	Cohort 5	Cohort 1 SFU
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric volvulus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	1 / 11 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric volvulus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 5 SFU		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric volvulus			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	11 / 14 (78.57%)	8 / 14 (57.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour recurrent			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injection site atrophy			
subjects affected / exposed	1 / 15 (6.67%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	1	2	2
Injection site erythema			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Injection site haematoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injection site nodule			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	3	1
Injection site pruritus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	3 / 14 (21.43%)
occurrences (all)	0	2	3
Oedema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	2

Dysmenorrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pharyngeal erythema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Food aversion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Thyroxine free decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Thyroxine increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Palpitations			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Hypoaesthesia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Lymphadenopathy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Abdominal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	4	0
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Dermatitis atopic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Diabetic dermopathy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dyshidrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypercorticoidism			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperthyroidism			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Adrenal insufficiency			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Salpingo-oophoritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	2
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Acute tonsillitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4	Cohort 5	Cohort 1 SFU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	8 / 14 (57.14%)	4 / 13 (30.77%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour recurrent			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injection site atrophy			
subjects affected / exposed	2 / 12 (16.67%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	5	0	2
Injection site erythema			
subjects affected / exposed	1 / 12 (8.33%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Injection site haematoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Injection site nodule			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	2 / 13 (15.38%)
occurrences (all)	4	0	9
Injection site pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			

subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pharyngeal erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Food aversion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Thyroxine free decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Thyroxine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed			0 / 13 (0.00%)

subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)	2 / 14 (14.29%)	0 / 13 (0.00%)
occurrences (all)	3	4	0
Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Blepharospasm			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Inguinal hernia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Diabetic dermopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dyshidrosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypercorticoidism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hyperthyroidism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Adrenal insufficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 14 (7.14%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 14 (14.29%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Limb discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Osteoporosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	1 / 14 (7.14%)	1 / 13 (7.69%)
occurrences (all)	1	2	2
Tendonitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Influenza			

subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 14 (14.29%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Salpingo-oophoritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 14 (14.29%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Acute tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort 2 SFU	Cohort 3 SFU	Cohort 4 SFU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	8 / 14 (57.14%)	4 / 11 (36.36%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour recurrent			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injection site atrophy			
subjects affected / exposed	5 / 14 (35.71%)	3 / 14 (21.43%)	1 / 11 (9.09%)
occurrences (all)	8	9	1
Injection site erythema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injection site haematoma			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injection site induration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Injection site nodule			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 11 (9.09%)
occurrences (all)	0	2	2
Injection site pruritus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Cough			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Pharyngeal erythema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Food aversion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Thyroxine free decreased			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Thyroxine increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	0 / 11 (0.00%)
occurrences (all)	2	3	0
Hypoaesthesia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Syncope			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0

Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
		0	

subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	0 / 11 (0.00%)
occurrences (all)	3	2	0
Dermatitis atopic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Diabetic dermopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Dry skin			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dyshidrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypercorticoidism			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hyperthyroidism			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Adrenal insufficiency			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Bronchitis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Pharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Rhinitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Salpingo-oophoritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Sinusitis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Acute tonsillitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 5 SFU		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour recurrent			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Exercise tolerance decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injection site atrophy			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Injection site erythema subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site haematoma subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site induration subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site nodule subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site pruritus subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Malaise subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Oedema subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Pyrexia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Pharyngeal erythema subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0		
Psychiatric disorders Food aversion subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood pressure increased subjects affected / exposed occurrences (all) Thyroxine free decreased subjects affected / exposed occurrences (all)	 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0		

Thyroxine increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Ear pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Dyspepsia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Inguinal hernia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Nausea subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Toothache subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Vomiting subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0			
Skin and subcutaneous tissue disorders Acne				

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dermatitis atopic			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Blister			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Diabetic dermopathy			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Dyshidrosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypercorticoidism			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hyperthyroidism			

subjects affected / exposed	0 / 14 (0.00%)			
occurrences (all)	0			
Hypothyroidism				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences (all)	0			
Adrenal insufficiency				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	4			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Salpingo-oophoritis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Viral infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Sinusitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Acute tonsillitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2012	The protocol was revised to reflect the fact that the run-in period had been completed. The number and timing of blood samples for PK/PD analysis was revised Cohorts 1-4. The protocol was amended to address the change of the dose within 24-week-dose finding period after data obtained from single dose PK/PD run-in period. However, this change is addressed only to Cohorts 1-4. Pregnancy and breast-feeding were added to the exclusion criteria and it was clarified that fertile females had to use contraceptives for the duration of study and 20 days after the last dose of study medication. Cohort 5 SFU dose was revised from starting at 0.02-0.04 HM10560A to starting at 0.03 mg/kg EW. The protocol was amended to expand and clarify details of the Interim Analysis and the Final Analysis. Typographic, administrative and clarification changes were also made.
04 June 2013	Raised the upper age permitted for inclusion from 60 to 65 years. Changed methods for measurement of IGF-I and IGFBP3 with addition of IDS iSYS assay. Clarified that in case of severe or serious lipoatrophy a dermatologist should be consulted. Typographic and administrative changes were also made.
25 March 2014	Added a new interim analysis to be performed upon completion of Week 12 Visit of the 24-week-dose finding period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported