NON-INTERVENTIONAL (NI)/ LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) FINAL STUDY REPORT

PASS Information

Title	Pfizer Registry of Outcomes in Growth Hormone RESearch (PROGRES): A Multi-Country, Non-Interventional, Prospective Cohort Study Among Patients With Human Growth Hormone (hGH) Treatments Under Routine Clinical Care
Protocol number	C0311015
Version identifier of the final study report	1.0
Date	15 October 2024
EU Post-Authorization Study (PAS) register number	EUPAS43715
Active substance	Somatropin, Somatrogon
Medicinal product	Genotropin, Ngenla
Product reference	Genotropin: Refer to protocol (Appendix 2) Annex I document #4 for additional Genotropin product reference. Ngenla: Refer to protocol (Appendix 2) Annex I document #5 for additional Ngenla product reference.

Procedure number	Genotropin: Refer to protocol (Appendix 2) Annex I document #4 for additional Genotropin procedure number Ngenla: Refer to protocol (Appendix 2) Annex I document #5 for additional Ngenla procedure number
Marketing Authorization Holder (MAH)	Genotropin: Pfizer Limited Refer to protocol (Appendix 2) Annex I document #4 for additional Genotropin MAH Ngenla: Pfizer Europe MA EEIG Refer to protocol (Appendix 2) Annex I document #5 for additional Ngenla MAH
Joint PASS	No

Research question and objectives	The purpose of this multi-country, non-interventional, prospective cohort study among patients treated according to routine clinical practice, was to assess the long-term safety and effectiveness of Genotropin, Other daily human growth hormone (hGH) treatments of interest (i.e., Norditropin, Humatrope, Omnitrope), and Ngenla, a long--acting hGH, all of which are prescribed at the discretion of the treating physician according to routine clinical care. Primary Objectives: • To estimate incidence rates (IRs) of safety events among patients on Ngenla, Genotropin, and Other daily hGH treatments of interest. • To describe and compare effectiveness of Ngenla, Genotropin, and Other daily hGH treatments of interest. Secondary Objectives: • To evaluate treatment adherence and compliance of Ngenla, Genotropin, and Other daily hGH treatments of interest. • To evaluate the health-related quality of life (HRQoL) and treatment experience of patients on Ngenla, Genotropin, and Other daily hGH treatments of interest (this objective was not applicable in Belgium). • To compare the IRs of safety events among patients on Ngenla, Genotropin, and Other daily hGH treatments of interest by conducting exploratory analysis.
Countries of study	Australia, Belgium, Canada, Czech Republic, France, Germany, Israel, Italy, Japan, South Korea, Slovenia, Spain, Sweden, Taiwan, United Arab Emirates, the United Kingdom, and the United States.

Author	Reese Sy, PhD, MS Director, Global Medical Epidemiology Worldwide Medical & Safety Pfizer Research & Development Cambridge, MA, US

Marketing Authorization Holder(s)

Marketing Authorization Holder(s) (MAH)	Genotropin: Pfizer Limited Ramsgate Road, Sandwich, Kent CT13 9NJ United Kingdom Ngenla: Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
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Annex 1. List of stand-alone documents

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
BIA	Bioelectrical impedance analysis
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
DCOA	Dyad Clinical Outcomes Assessment
DNA	Deoxyribonucleic acid
DXA	Dual energy X-ray absorptiometry
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
EHR	Electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ENR	Enrolled set
ePRO	Electronic patient-reported outcome
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation	Definition
FSH	Follicle-stimulating hormone
FSS	Familial short stature
G&P	Greulich & Pyle
GH	Growth hormone
GHD	Growth hormone deficiency
GPP	Good Pharmacoepidemiology Practices
HDL	High-density lipoprotein
hGH	Human growth hormone
HRQoL	Health-related quality of life
HV	Height velocity
HVSDS	Height velocity standard deviation score
IA	Interim analysis
ICD	Informed consent document
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor-1 binding protein-3
IR	Incidence rate
IRB	Institutional review board
IRR	Incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
ISS	Idiopathic short stature
IUGR	Intrauterine growth restriction
LDL	Low-density lipoprotein

Abbreviation	Definition
LH	Luteinizing hormone
LIQ-GHD	Life Interference Questionnaire for Growth Hormone Deficiency
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Models for Repeated Measures
MSM	Marginal Structural Model
N/A	Not available
NIS	Non-interventional study
PASS	Post-Authorization Safety Study
PRO	Patient-reported outcome
PROGRES	Pfizer Registry of Outcomes in Growth hormone RESearch
PT	Preferred term
QCT	Quantitative computed tomography
QoLISSY	Quality of Life in Short Stature Youth
RoW	Rest of the World
RUS	Radius-ulna-short
RWD	Real-world data
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SAS	Statistical Analysis System
SD	Standard deviation
SDS	Standard deviation score

Abbreviation	Definition
SGA	Small for gestational age
SOC	System organ class
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
US	United States
WHO	World Health Organization

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Reese Sy, PhD MS	Director, Global Medical Epidemiology Worldwide Medical & Safety Pfizer Research & Development Cambridge, MA, US	Pfizer, Inc. Cambridge, MA
Michael P Wajnrajch, MD MPA	Senior Medical Director, Rare Disease, Global Medical Affairs, Pfizer Biopharmaceuticals Group	Pfizer, Inc. New York, NY
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Lead Country Investigator(s) of the Protocol

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Name, degree(s)	Title	Affiliation
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Erdal Eren, MD	Physician at Bursa Uludağ University (BUU) Hospital – Health Practice and Research Center (SUAM) (Department of Pediatrics – Division of Pediatric Endocrinology)	Bursa Uludağ University Bursa, Turkey

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Carly Rodriguez, PhD MPH Lead Epidemiologist, Real-World Solutions, IQVIA	Epidemiologic support

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol	First approval: N/A Last approval: N/A	First approval: 04 June 2021 Last approval: 06 February 2024	The IEC/IRB approval dates for the protocol and any amendments is provided in Appendix 3.2.
Start of data collection	24 September 2021	18 November 2021	
End of data collection	08 December 2030	18 July 2024	
Registration in the HMA-EMA Catalogs of RWD Studies	23 September 2021	14 October 2021	
Annual report I	27 January 2023	27 January 2023	
Annual report II	24 January 2024	29 April 2024	
Final report of study results	26 May 2031	[To be completed]	

EMA: European Medicines Agency; HMA: Heads of Medicines Agencies; N/A: not available; RWD: real-world data.

6. RATIONALE AND BACKGROUND

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates production and release of insulin-like growth factor-1 (IGF-1). Growth hormone (GH) and IGF-1 are the primary mediators of the promotion of growth in children and play a role in the regulation of body composition and metabolism in children and adults. These factors are regulated through complex feedback mechanisms involving hGH, and IGF-1 (Shalet, Toogood et al. 1998; Bach 2004).[12,1] Growth hormone deficiency (GHD) results in inadequate circulating IGF-1 level and is manifested as abnormal growth (linear growth) in children (Krysiak, Gdula-Dymek et al. 2007; Thomas and Monson 2009).[7,15] Childhood GHD can be congenital, acquired, or idiopathic. The underlying causes for congenital GHD may include genetic abnormalities and pituitary dysfunction due to abnormal neurodevelopment in utero of certain brain regions. The etiology for acquired GHD may result from brain tumors in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation, and surgical intervention. Generally, the origin of idiopathic GHD is complex and multifactorial, and thus is not fully understood (Rona and Tanner 1977).[10]

Data on the incidence and prevalence of GHD are limited. A population-based (nationwide) study in Denmark reported average incidence of 2.58 males, and 1.7 females per 100,000 for childhood onset of GHD (Stochholm, Gravholt et al. 2006).[13] For prevalence, rates were comparable in studies conducted in Belgium and the United States (US). The Belgian study, conducted between 1986 and 2001, estimated the prevalence of childhood GHD to be 1/5600. The origin of GHD was idiopathic in 41% of the patients, congenital in 20%, acquired in 35% and 4% of the patients had a defined syndrome accompanying GHD; there was male predominance in all the categories (Thomas, Massa et al. 2004).[14] In the US study, the prevalence of GHD in the 1990's was at least 1:3480, with male predominance (Lindsay, Feldkamp et al. 1994).[8] The incidence of GHD in the US has remained fairly constant over the last 2 decades. Most morbidity in children with GHD relates to short stature. The inability to reach normal height can lead to early onset of severe psychosocial problems. GHD can also present with accompanying problems such as delayed puberty and deficits in facial, dental and (in males) genital development. Lastly, GHD that persists into adulthood is associated with increased risk of cardiovascular morbidity and mortality (Krysiak, Gdula-Dymek et al. 2007).[7]

Genotropin®, which contains the active ingredient somatropin, is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates, and proteins and is a recombinant hGH replacement therapy that has been used since 1987 in thousands of patients (primarily children) and has proved to be safe and effective (Ho 2007; Cohen, Rogol et al. 2008).[6,4] In pediatric patients with inadequate endogenous GH, somatropin stimulates linear growth and increases growth rate which enables short pediatric patients to obtain normal height. In adults, as well as in children, somatropin maintains normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth and by mobilization of body fat. Recombinant hGH has also been approved in many countries around the world for other conditions associated with growth failure and/or abnormal body composition in children or adults with Prader-Willi Syndrome, Noonan syndrome, Turner syndrome, idiopathic short stature (ISS), short stature homeobox containing- gene (Shox) deficiency.

Treatment response is most often assessed by measurement of height and growth velocity and, in pediatric GHD, hGH treatment is usually continued until final height, epiphyseal closure, or both have been recorded. The majority of currently available hGH medications require daily injections. The burden of daily administration and its concomitant side effects (eg, transient edema, injection site discomfort and arthralgia) may cause a reduction in compliance (Rosenfeld and Bakker 2008)[11] and limit the therapeutic utility of existing daily formulations.

Ngenla™ (somatrogon) is a long-acting once-weekly subcutaneously-administered form of hGH developed for use as a long-term treatment in children with growth failure due to an inadequate secretion of endogenous GH. Ngenla is a glycoprotein produced in Chinese Hamster Ovary cells by recombinant deoxyribonucleic acid (DNA) technology. It comprises the amino acid chain of hGH and 1 copy of the C-terminal peptide from the beta chain of human chorionic gonadotropin at the N-terminus and 2 copies at the C--terminus.

As a weekly long-acting hGH, Ngenla maintains the same mode of action as currently prescribed daily hGH treatments. Ngenla binds to the GH receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with GH signaling, Ngenla binding leads to activation of the STAT5b signaling pathway and increases the serum concentration of IGF-1. Insulin-like growth factor-1 was found to increase in a dose-dependent manner during treatment with Ngenla partially mediating the clinical effect. As a result, somatrogon stimulates metabolic changes, linear growth, and enhances growth velocity in pediatric patients with GHD.

The sub-optimal adherence with daily hGH is well established, as is the burden of daily injections for both patients and caregivers. Long-acting hGH may obviate the need for the numerous injections currently required in daily hGH products. As demonstrated in animal models and clinical studies, Ngenla may be injected once per week resulting in similar clinical efficacy as compared to daily injections of hGH. In the Phase 3 clinical trial, the primary objective of non-inferiority (clinically comparable) for weekly Ngenla compared to daily hGH was met (annualized height velocity [HV] at Month 12 for once-weekly Ngenla was 10.10 cm/year versus 9.78 cm/year for daily hGH). Low numbers of serious adverse events (SAEs) were reported in both the weekly Ngenla and daily hGH groups, and the majority of adverse events (AEs) were of mild to moderate severity. Thus, weekly Ngenla administration was generally well-tolerated in pediatric patients.

The purpose of the Pfizer Registry of Outcomes in Growth hormone Research (PROGRES) study was to assess the long-term safety and effectiveness of Genotropin, Other daily hGH treatments of interest, and Ngenla, a long-acting hGH according to routine clinical care and was intended to reflect outcomes that occur in real-world clinical practice.

This non-interventional study (NIS) was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer. The study was terminated early by Pfizer based on a business decision in view of existing competing registries.

Analyses and reports were conducted annually in the first (2022) and second (2023) year of the study. This is the final study report covering the period from 18 November 2021 to database lock on 18 July 2024.

7. RESEARCH QUESTION AND OBJECTIVES

The purpose of this multi-country, non-interventional, prospective cohort study among patients treated according to routine clinical practice was to assess the long-term safety and effectiveness of Ngenla, (a long-acting hGH), Genotropin, and Other daily hGH treatments of interest (Norditropin, Humatrope, Omnitrope) in a real-world setting, all of which were prescribed at the discretion of the treating physician according to routine clinical care.

Research question:

What is the long-term safety and effectiveness of Ngenla, Genotropin, and Other daily hGH treatments of interest (Norditropin, Humatrope, Omnitrope) when used under routine clinical care?

Primary Objectives:

- To estimate incidence rates (IRs) of safety events among patients on Ngenla, Genotropin, and Other daily hGH treatments of interest.
- To describe and compare effectiveness of Ngenla, Genotropin, and Other daily hGH treatments of interest.

Secondary Objectives:

- To evaluate treatment adherence and compliance of Ngenla, Genotropin, and Other daily hGH treatments of interest.
- To evaluate the health-related quality of life (HRQoL) and treatment experience of patients on Ngenla, Genotropin, and Other daily hGH treatments of interest (this objective was not applicable in Belgium).
- To compare the IRs of safety events among patients on Ngenla, Genotropin, and Other daily hGH treatments of interest by conducting exploratory analysis.

8. AMENDMENTS AND UPDATES

Table 1 Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	02 August 2021	Substantial amendment	Abstract; Sections: 4, 6, 7, 8, 9, 9.2, 9.3, 9.3.3.4.3, 9.4.1, 9.5, 9.7.3, 9.9, Appendix 1	Any reference and mention of somatrogon (Ngenla) and its related information was removed. The study objectives, design, data collection schedule, patient-reported outcomes (PRO) collection and analyses were changed accordingly (Abstract, Sections 4, 6, 7, 8, 9, 9.2, 9.3, 9.3.3.4.3, 9.4.1, 9.5, 9.7.3, 9.9, Appendix 1).	Somatrogon (Ngenla) was removed as a study treatment in recognition that data prior to approval would not be eligible for review by the European Medicines Agency Pharmacovigilance Risk Assessment Committee.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				Milestone timelines updated (Abstract, Sections 6 and 9.2). Age group of patients who completed the DCOA was corrected to be 3 to <18 years (Sections 9.3.3.4.3). For non-Genotropin daily hGH treatments, approximate target sample sizes per daily treatment arm were added (Sections 9.5 and 9.9). SAE rates and equivalence bounds were provided per geographic region (Section 9.5).	Due to changes in data collection timelines. To accurately reflect the population used in the DCOA instrument validation study. Provided an approximate indication of the required sample size of the 4 daily hGH treatments supporting the overall target sample size for equivalence. Analyses of SAE data recognized regional variation.
2	25 March 2022	Substantial amendment	Abstract; PASS info, MAH contact persons, Sections: 3, 4, 6, 7, 8, 9.1, 9.2, 9.2.1, 9.3.1, 9.3.2, 9.3.3.2, 9.3.3.3, 9.3.3.4.1, 9.3.3.4.2, 9.5, 9.6.2, 9.7.2, 9.7.3, 9.7.5, 9.9, 11.1, Table 1, Annex 1, 3	[a] EU PAS registration number was added and details of product reference, procedure number, MAH information, and team members were updated (PASS information, Responsible Parties, MAH contact persons, Section 3) Added specification that there is no limit on the number of patients enrolled in the Ngenla treatment group (Section 9.5) [a] Study milestone dates were updated (Section 6, 9.2) Added secondary objective to compare safety event incidence rates across treatment groups (Sections 4, 8, 9.7.3) [a] Addition of inclusion criteria for Germany regarding adherence to summary of product characteristics (SmPC) indications and contraindications (Section 9.2.1) Added *a priori* subgroups (Section 9.1) [a] Specified that history pertains to history of birth, added 'brand' to list of variables collected among patients who change hGH treatment, and collection of race/ethnicity in all countries, where allowable (Sections 9.3.1, 9.3.2) Addition that Quality of Life in Short Stature Youth (QoLISSY) will be collected until the end of study or	Registration was completed after last protocol amendment (1.0); change in Pfizer team members To clarify there are no enrollment targets by treatment group Planned dates were replaced with actual To add objective on comparison of incidence rates of safety outcomes of interest Request from the German regulatory authorities to ensure no off-label use in a non-interventional study design To add additional subgroups of interest Consistency with planned data capture To extend the duration of QoLISSY data collection, clarification of planned statistical analysis

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				participant discontinuation and scoring instruction (Section 9.3.3.4.2)	
				[a] Specified equivalence bounds are per region (Section 9.5)	Consistency with Abstract
				[a] Added frequency assessment for all reported SAEs (Annex 3)	Consistency with planned data capture
				Specify 25-year physician record retention requirement for Canada (Section 9.6.2)	As per local regulatory requirements
				Removed infections from list of AESIs (Table 1, Sections 9.3.3.3, 11.1, Annex 3)	Infections do not fulfill expedited reporting criteria.
				Added age collected in months for participants <18 years (Table 1, Annex 3)	Valid calculation of endpoints requires age in months
				Added reason for switch for patients switching from daily hGH to Ngenla (Section 9.3.3.4.1)	To provide additional data on reasons for switching treatment.
				Reference to somatrogon by brand name (Ngenla) (throughout)	All treatments will be summarized by their brand names.
				Revision of inclusion criteria that Ngenla does not need to be for GHD (Section 9.2.1)	To include patients who have been prescribed Ngenla for conditions other than GHD.
				Added specification that the Full Analysis Set be comprised of all enrolled patients who initiated Genotropin, Other daily hGH and Ngenla (Section 9.7.2)	To clearly define FAS.
				Clarification that the primary effectiveness outcome of height include height, height standard deviation score, height velocity, and height velocity standard deviation score (Section 9.3.3.2, 9.7.3, Annex 3)	To clearly define primary effectiveness outcome for height.
				Addition of section on scientific steering committee (Section 9.7.5)	To provide additional detail
				Removal of lack of generalizability by region limitation (Section 9.9)	To remove this as a limitation given the multi-country study design.
				Update of non-serious AE list (Section 11.1)	To include only non-serious AEs most important in the Risk Management Plan.
				Added document reference number 5 “Ngenla line listing in participating sites from 33 countries” (Annex 1)	Due to addition of Ngenla to protocol.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
3	15 September 2023	Administrative	PASS information, Abstract, Sections: 3.0, 5, 7, 8, 9.1, 9.2, 9.2.1, 9.2.4, 9.3, 9.3.1, 9.3.2, 9.3.3.2, 9.3.3.4.1, 9.3.3.4.2, 9.3.3.4.3, 9.4.1, 9.5, 9.6, 9.7.2, 9.7.3, 9.8, 9.9, 9.10.1, 10.2, 11.1.1, 11.2, 18, Annex 1, 2, 3	Replaced Yun Gu with Reese Sy as author [b] Monica Nijher changed to Daria La Torre [b] "Other daily hGH treatment" changed to "Other daily hGH treatments of interest" Added Amendment type and changed amendment number to version identifier Replaced DCOA with LIQ-GHD (also known as DCOA) Replaced "IBM Clinical Development" to "Zelta" Primary and secondary objectives: replaced "safety events of interest" to "safety events". Replaced "gender" with "sex" Added "with GHD" to the sample size calculation Revisions made to clarify that there is no enrollment cap on the number of patients enrolled in the Ngenla and Genotropin treatment groups Reordered primary effectiveness outcomes Replaced PDF attachments (documents 3 and 4) Added Table 1: Schedule of activities Removed Table entitled Key variables and associated Roles Revised text to clarify that all 8 domains of the QoLISSY will be collected, not just the 3 core domains and the 3 additional domains of coping, beliefs, and treatment Added research question	Change in Pfizer team members involved in the PROGRES study Change in Pfizer team members involved in the PROGRES study To clarify that only specific daily hGH treatments are of interest and permissible Required by Pfizer's new protocol template dated August 2023 To ensure consistency throughout the protocol To reflect change in the name of electronic data capture (EDC) platform. Both serious adverse events and safety events of interest will be studied, objective was revised to accurately reflect what is already being collected and studied To clarify that the variable of interest is sex and not gender, and to reflect what is already being collected To clarify that the 600 sample size requirement refers to patients with GHD Clarification of enrollment caps To present the outcomes based on their clinical importance To update the product line listing Required by Pfizer's new Protocol template dated August 2023 The new Table required by the template (added under Section 9.2) includes this information. Correction made to reflect the data that is being collected To ensure that the study research question is clear and explicitly mentioned

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				Independent Ethics Committee changed to Ethics Committee	To comply with language in Pfizer's new template
				Indicated that drugs under study also includes "Other daily hGH treatments of interest"	To clarify that "drugs under study" refers to Ngenla, Genotropin as well as Other daily hGH treatments of interest
				Single reference safety document section was updated to include "EU SmPC English version."	To comply with the new Pfizer template
				Added information on country coordinating investigators	Required per Pfizer's new template.
				Annex 3 removed	New Table 1 added in Section 9.2 outlines all the information previously presented in Annex 3. Annex 3 was hence removed to avoid duplicate presentation of information
				ENCePP checklist updated	Section numbers updated to reflect the updates made to the protocol
				Incidence rate formula revised to indicate that the number will be multiplied by 1000 instead of 100	Considering the sample size, incident rates are expected to be small and hence more appropriately presented if multiplied by 1000
3	15 September 2023	Substantial	PASS Information, Abstract, Sections: 8, 9.1, 9.2, 9.2.1, 9.2.2, 9.2.3, 9.2.4, 9.3, 9.3.1, 9.3.2, 9.3.2.1, 9.3.3.1, 9.3.3.2, 9.3.3.4, 9.3.3.4.1, 9.3.3.4.2, 9.3.3.4.3, 9.4.1, 9.5, 9.7.3, 10.2, 11, 11.1.4, 11.1.5, 11.3,	Added text to clarify that PROs will not be collected in Belgium. These include: The LIQ-GHD, to assess treatment experience and QoLISSY, to assess HRQoL [b]	To comply with the requirements of the local Ethics Committee in Belgium
				Added more details with respect to follow-up of patients who switch their therapy	To provide clarification on data collection for those who go through a switch
				Changed sequence of treatment presentation as "Ngenla, Genotropin, and Other daily hGH treatments of interest"	Ngenla is the drug of interest, other medications are included as comparators
				Added names of Other daily hGH treatments of interest (i.e., Norditropin, Humatrope, Omnitrope)	To provide clarity on the approved daily hGH treatments for this study
				Edited geographic regions which now include Europe, Japan, North America, and Rest of the World (RoW)	To provide clarification
				Removed GHD from inclusion criteria 1 for Genotropin users	To capture all Genotropin users who receive hGH in the real-world setting regardless of their diagnoses
				Removed pyridinoline cross links and deoxy-pyridinoline cross links	These data will not be collected

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				Removed "GH stimulation test and value" as a primary effectiveness outcome and presented it as a clinical characteristic	GH stimulation test is not an effectiveness outcome
				Added frequency under "hGH treatment details" and "change in hGH treatment"	Frequency of treatment will be collected to provide more information on hGH treatment
				Removed "US only" for race/ethnicity data collection	Race and ethnicity data will be collected as per local regulations in participating countries
				Added "primary" and "secondary" behind AESI	To distinguish the 2 AESI lists
				Replaced "growth hormone concentration" with "growth factor concentration"	IGF-1 and IGFBP-3 are growth factors not growth hormone
				Corrected Height velocity standard deviation score (HVSDS) formula and interpretation and added information on height standard deviation score	To provide correction and distinguish height velocity standard deviation score (SDS) from height SDS
				Removed cognitive function as secondary effectiveness outcome	Cognitive function is not an appropriate effectiveness outcome
				Revised text regarding QoLISSY implementation rules for different age groups and scoring	To provide clarity on when QoLISSY should be triggered and how it should be scored
				Revised text regarding LIQ-GHD implementation rules based on age groups	To provide clarity on when LIQ-GHD should be triggered and to provide corrections
				Details on ePRO trigger rules removed	Other study documentations will be used to outline the ePRO trigger rules in more detail.
				Added equivalence bounds for RoW	To provide clarification
				Added additional information regarding the process of obtaining informed consent	To provide clarification
				The following information was removed from the hospitalization section "Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)"	Safety information was updated to comply with the new Pfizer template
				The following additional information was added under exposure during pregnancy (EDP): "For EDP in studies of pregnant women, data on the exposure to drug under study during pregnancy, are not reportable unless	Safety information was updated to comply with the new Pfizer template

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				associated with serious or non-serious AEs." " As a general rule, prospective and retrospective EDP reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events." The following subsections were removed: "Safety reporting for sites using EHR to EDC integration" and "Unsolicited safety reporting from patient-reported outcomes instrument" Exclusion criteria changed from "Participation in any interventional clinical trials at study enrollment" to "Participation in any interventional clinical trials at study enrollment" Reporting restricted to Pfizer products updated to represent all drugs under study	To clarify that enrollment in clinical trials is not allowed anytime during the study To comply with Pfizer safety reporting

a. These protocol updates were implemented in an earlier amendment specific to Germany only (Protocol Amendment Version 1.1, dated 08 December 2021).
b. These protocol updates were implemented in an earlier amendment specific to Belgium only (Protocol Amendment 2.1, dated 16 June 2023)

9. RESEARCH METHODS

9.1. Study Design

As described in the protocol (Appendix 2), this was a multi-country, non-interventional, prospective cohort study of patients exposed to Ngenla (a long-acting hGH treatment), Genotropin, and Other daily hGH treatments of interest, as prescribed by the treating physician according to routine clinical care in a real-world setting. Patient treatment with a particular therapeutic regimen was determined at the discretion of the treating physician or other healthcare provider specialties in the countries where this NIS was conducted, according to routine clinical care.

This multi-country, multi-site prospective cohort study in a real-world population provides results generalizable to the respective countries included in the study. As well, the large sample size enables the evaluation of key endpoints within numerous prespecified strata or

subgroups across countries. To evaluate the safety and effectiveness of Ngenla, Genotropin, and Other daily hGH treatments of interest within the study population, patients were stratified by selecting *a priori* subgroups, including but not limited to: age group, sex, puberty status, follow-up time, initial disease/treatment indications, peak GH levels, and study region (Europe, Japan, North America, and Rest of the World [RoW])/country.

IQVIA was contracted by Pfizer as a vendor to conduct this study.

9.2. Setting

Physicians from 173 participating sites across 17 countries in 4 regions (Europe, Japan, North America, and RoW) attempted to recruit eligible patients in this study to collect data in order to assess the long-term safety and effectiveness, maintenance, and discontinuation of Ngenla, Genotropin, and Other daily hGH treatments of interest, and other study objectives under a routine clinical care setting. Appendix 3 details study site and investigator information. The start date of data collection was 18 November 2021 and final database lock was 18 July 2024. The study population were patients of any age meeting inclusion/exclusion criteria who received care from participating study sites during the enrollment period. Patients were followed up until the end of the study, withdrawal of consent, death, switch to non-Ngenla long-acting hGH, switch to a daily hGH that was not one of the prespecified daily hGH treatments of interest, or loss to follow-up, whichever occurred first.

Patients treated with Ngenla, Genotropin, and Other daily hGH treatments of interest were followed by the treating physician as per routine clinical practice, who collected and entered relevant patient data into electronic case report forms (eCRFs). All treatment information, including dosage, administration date, and reasons for discontinuation, along with any other treatment information or changes that occurred throughout participation in the study, were recorded in the eCRFs or extracted from the electronic health record (EHR).

Data collected during routine clinical care visits were entered in the eCRFs or extracted from the EHR, which included data related to safety, hGH treatment effectiveness, and other research outcomes of interest. As routine clinical practice was at the discretion of the treating physician, which was expected to vary by site and country, it was anticipated that the information collected from routine clinical care could vary to some degree from one physician to another. Collected data was anonymized and de-identified, and analyzed by study vendors and physicians, in collaboration with Pfizer, to evaluate safety, treatment effectiveness, and other research outcomes of interest.

9.3. Subjects

9.3.1. Inclusion Criteria

Male and female patients of any age who met all the following inclusion criteria were eligible for inclusion in the study:

1. Prescription of Ngenla, a long-acting hGH per local diagnostic guidelines, prescription of Genotropin daily hGH per local diagnostic guidelines, or prescription of Other daily hGH treatments of interest (i.e., Norditropin, Humatrope, Omnitrope) per local diagnostic guidelines.

2. Evidence of a personally signed and dated informed consent document (ICD) indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study. Assent was also sought from children of applicable age in line with national guidance. In all cases, the treating physician responsible for enrolling the patient into the registry assessed the appropriateness of gaining assent from a patient (or a legally acceptable representative) at their discretion during routine clinical care.

3. Germany only: The treating clinician confirmed that the patient receiving a prescription treatment for GHD was eligible according to the summary of product characteristics (SmPC) indications and contraindications.

9.3.2. Exclusion Criteria

Patients who met any of the following criteria were not included in the study:

1. Participation in any interventional clinical trials.

9.3.3. Patient Enrollment

Physicians who were routinely involved in the care of patients, prescribed hGH, were invited to participate and considered for inclusion into the study.

Eligible patients were enrolled in the study at the time of presentation for a routine clinic visit. No additional clinic visits were required as part of participation in this study. All assessments were intended to be performed at the time of a routine clinical encounter or by referencing the medical record.

All patients who presented during the enrollment period were assessed for eligibility according to the defined selection criteria and all eligible patients were proposed to be enrolled in the study.

9.3.4. Patient Early Termination

Patients who had not initiated Ngenla, Genotropin, or Other daily hGH treatments of interest as planned within 6 months after signing the study consent, were discontinued from the study. Patients who switched from Ngenla, or Genotropin, or one of the Other daily hGH treatments of interest (i.e., Norditropin, Humatrope, Omnitrope) to a non-Ngenla long-acting hGH or to a daily hGH treatment that is not one of the prespecified daily hGH formulations during the study period, were discontinued from the study. These patients were followed up for 28 days after the date of switch, as per Pfizer standard for safety assessment. In all other cases of switching (from daily hGH treatment to Ngenla or vice versa, or between prespecified daily hGH treatments) and in cases of treatment discontinuation, early termination did not occur, and follow-up was continued until the administrative end of the study.

9.4. Variables

The study collected data resulting from routine clinical care on variables pertaining to patient demographics, clinical characteristics, medical history, concomitant medications, current GH treatment, safety outcomes, effectiveness outcomes, treatment adherence and compliance,

treatment experience and HRQoL. Treatment experience and HRQoL were not collected in Belgium, in order to comply with the requirements of the local Ethics Committee (EC).

The full list of variables and their associated role along with the schedule of assessments is presented in Table 1 of the protocol (Appendix 2).

Table 2 Key Variables and Associated Roles

Variables[0]	**Role**
Date of visit	
Year of birth (yyyy)[2]	Demographics
Age at enrollment[3]	Demographics
Sex	Demographics
Race/Ethnicity[4]	Demographics
Country of residence	Demographics
Puberty	Clinical characteristics
History of birth	Clinical characteristics
Medical history and comorbidities	Clinical characteristics
Relevant family history	Clinical characteristics
Concomitant medications	Clinical characteristics
GH stimulation test and values	Clinical characteristics
hGH diagnosis - Growth hormone deficiency - Idiopathic short stature - Prader-Willi syndrome - Small for gestational age - Turner syndrome - Other	Clinical characteristics
Auxological measures - Height - Weight - Sitting height - Height standard deviation score (SDS) (derived) - BMI (derived) - Annual HV (derived) - HVSDS (derived) -	 Clinical characteristics Clinical characteristics Clinical characteristics Primary effectiveness Primary effectiveness Primary effectiveness Primary effectiveness Clinical characteristics
hGH treatment - Type	Exposure/treatment/medications

Variables[0]	**Role**
- Dose - Start/end date of treatment - Frequency - Brand of daily hGH treatment	
Change in hGH treatment - Reason - New hGH treatment type - Dose - Frequency - Start/end date - Brand of daily hGH treatment	Exposure/treatment/medications
Discontinuation in hGH treatment - Date of last hGH injection - Reason for discontinuing hGH treatment - Plan for future management	Exposure/treatment/medications
Dose adjustment necessary for targeted increase or decrease in insulin-like growth factor-1 (IGF-1) response	Primary effectiveness
Treatment adherence - Missed injections	Secondary–treatment adherence
Growth factor concentrations - IGF-1 - IGFBP-3	Primary effectiveness
Bone age	Secondary effectiveness
Body composition - Lean tissue, kg - Fat tissue - Resistance, ohm (BIA) - BMC, kg (DXA) - Total potassium, mmol (total body K) - Overall interpretation of results (normal, abnormal, not known)	Secondary effectiveness
BMD - Date of examination - Instrument used - BMD - BMC	Primary effectiveness
All reported SAEs	Primary safety
AESIs - Acute critical illness - Adrenal cortical hypofunction - Bone fractures - Glucose intolerance - Hypersensitivity reactions - Injection site reactions - Immunogenicity	Primary safety

Variables[0]	Role
- Thyroid dysfunction - Intracranial hypertension - Metabolic syndrome - Neoplasms (intracranial tumors, meningiomas, other sites) - Type 1 or type 2 diabetes mellitus - Slipped capital femoral epiphysis	
AESIs - Arthralgia - Fluid retention (edema, arthralgia, myalgia, nerve compression syndromes) - Gynecomastia - Hyperglycemia - Hypoadrenalism - Immune system reactions - Non-neutralizing antibody response Progression of pre-existing scoliosis	Secondary safety
All other reported non-serious AEs	Secondary safety
Lab measures (if available)	Clinical characteristics
QoLISSY (not applicable in Belgium)[5]	Secondary HRQoL
DCOA/LIQ-GHD (not applicable in Belgium)[6]	Secondary–treatment experience

AE: Adverse Event; AESI: Adverse Event of Special Interest; BIA: Bioelectrical Impedance Analysis; BMC: Bone Mineral Content; BMD: Bone Mineral Density; BMI: Body Mass Index; DCOA: Dyad Clinical Outcome Assessment; DXA: Dual Energy X-Ray Absorptiometry; EHR: Electronic Health Record; GH: Growth Hormone; hGH: Human Growth Hormone; HRQoL: Health-Related Quality Of Life; HV: Height Velocity; HVSDS: Height Velocity Standard Deviation Score; IGF-1: Insulin-Like growth factor-1; IGFBP-3: Insulin-Like growth factor binding protein 3; LIQ-GHD: Life Interference Questionnaire for Growth Hormone Deficiency; QoLISSY: Quality Of Life In Short Stature Youth; SAE: Serious Adverse Event; SDS: Standard Deviation Score.

1. No diagnostic or monitoring procedures are required, per protocol, to be performed in this observational study. However, if information for a variable is available as part of the participant's routine clinical care, that information should, per protocol, be entered into the data collection tool by the site/the treating physician or extracted from the EHR.
2. Year of birth is collected when permitted according to local regulations.
3. Age in months is collected for participants <18 years of age; age in years is collected for participants ≥18 years of age.
4. Collection of data on race/ethnicity dependent on local regulations.
5. QoLISSY is not applicable in Belgium. In the other countries, QoLISSY will be completed at both study enrollment, and annually (i.e., every 12 months) until end of study or participant discontinuation. QoLISSY-Child is completed by patients who are >8 years and ≤18 years. QoLISSY-Parent is completed by parents of patients who are ≥4 and ≤18 years.
6. LIQ-GHD is not applicable in Belgium. LIQ-GHD measures treatment experience and is collected for patients who are aged ≥3 to ≤17 years. Age at enrollment will be used to determine eligibility for LIQ-GHD. It contains several modules, intended to be completed by the patient, the caregiver, or the patient and caregiver together (as a "dyad").

9.4.1. Demographic and Clinical Characteristics

Demographics and clinical characteristics data were collected at the study enrollment, including year of birth, age, sex, race/ethnicity (depending on local regulations), country of residence, puberty, history of birth, medical history and comorbidities, relevant family history, GH stimulation test values, and diagnosis that necessitated hGH treatment. Concomitant medications, and auxological measures (including height, weight, and sitting height) were collected at the study enrollment and all routine clinical care visits.

9.4.2. Exposure/Treatment

This was a NIS. Treatment information of Ngenla, Genotropin, and Other daily hGH treatments of interest was collected at the enrollment and all routine follow-up visits according to real-world clinical care, including hGH treatment type, dose, start and end dates, frequency, and brand of daily hGH treatment. If a patient changed hGH treatment after enrollment, the reason for change, new hGH treatment type, brand, dose, frequency, start and end date were collected. If a patient discontinued hGH treatment after enrollment, the reason for discontinuation, date of last injection, and plan for future management were also collected, all of which were prescribed at the discretion of the treating physicians according to routine clinical care.

9.4.3. Outcomes

9.4.3.1. Primary Safety Outcomes

Primary safety outcomes were reported at any point of time during the study, including all reported SAEs, and primary adverse event of special interests (AESIs), including acute critical illness, adrenal cortical hypofunction, bone fractures, glucose intolerance, hypersensitivity reactions, injection site reactions, immunogenicity, thyroid dysfunction, intracranial hypertension, metabolic syndrome, neoplasms (intracranial tumors, meningiomas, other sites), type 1 or type 2 diabetes mellitus, and slipped capital femoral epiphysis.

9.4.3.2. Primary Effectiveness Outcomes

Primary effectiveness outcomes included:

- Annual HV, which was calculated as the annual height gain
- Height standard deviation score (SDS) and change in height SDS; Height SDS was calculated as (height – mean)/standard deviation (SD)
- Height velocity standard deviation score (HVSDS), which was calculated as (HV – mean)/SD
- Amount of dose adjustment necessary for targeted increase or decrease in IGF-1 response
- Change in Body mass index (BMI), calculated as the annual BMI gain, where BMI is calculated as weight (kg)/height(m)^2
- Bone mineral density (BMD), measured by Dual energy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT)
- Growth factor concentrations

9.4.3.3. Secondary Safety Outcomes

Secondary safety outcomes included secondary AESIs including arthralgia, fluid retention (edema, arthralgia, myalgia, nerve compression syndromes), gynecomastia, hyperglycemia, hypoadrenalism, immune system reactions, non-neutralizing antibody response, progression

of pre-existing scoliosis, and all reported other non-serious AEs. These were reported at any point of time during the study.

9.4.3.4. Secondary Effectiveness Outcomes

Secondary effectiveness outcomes included:

- Bone age, measured by Greulich & Pyle (G&P) or Tanner-Whitehouse methods, including radius-ulna-short bones, carpus, and 20-bones method.

- Body composition, including lean tissue, fat tissue, resistance, body mass composition, total potassium, and overall interpretation of results (normal, abnormal, not known).

9.4.3.4.1. Treatment Adherence and Compliance Outcomes

Treatment adherence and compliance outcomes included compliance with Ngenla, Genotropin, and Other daily hGH treatments of interest, discontinuation of Genotropin or Ngenla treatment (indicator, reason, and date), and the first and the last date of daily hGH treatment and the reason for switch for patients who switched from daily hGH to Ngenla and missed injections. The number of missed injections since the last visit were evaluated by the treating physician by asking patients at routine clinical visits. The number of missed injections over the last 4 weeks was also collected from the patient and/or the caregiver via the Life Interference Questionnaire for Growth Hormone Deficiency ([LIQ-GHD], also known as Dyad Clinical Outcomes Assessment [DCOA]) questionnaire (Section 9.4.3.4.3), not applicable in Belgium.

9.4.3.4.2. Health-Related Quality of Life

The HRQoL data were not collected in Belgium. In other countries, HRQoL was measured by the Quality of Life in Short Stature Youth (QoLISSY). The QoLISSY is a patient- and parent reported outcome questionnaire measuring HRQoL in short stature youth. The age at enrollment was used to determine eligibility for QoLISSY. QoLISSY-Child was available in self-report form for patients aged >8 years to ≤18. QoLISSY-Parent was available for caregivers of patients aged ≥4 to ≤18 years. As such, for patients aged >8 years, both the parent and the child version were completed. For all enrolled patients (and their caregivers) aged ≥4 to ≤18 years, QoLISSY was collected at study enrollment and annually (i.e., every 12 months) until end of study or participant discontinuation.

Both child- and parent-report versions of QoLISSY comprised 3 core domains (including 22 items), assessing physical (6 items), social (8 items), and emotional functions (8 items), and 3 additional domains (including 28 items) which measure predictors of HRQoL in coping (10 items), beliefs (4 items), and treatment (14 items). The parent-report version also included 2 supplementary domains: (i) parent's perception of child's worries about their future (5 items), and (ii) the impact of the child's condition on the parent's wellbeing (11 items). For this study all 8 domains were collected.

The response scale consists of a five-point Likert scale ranging from "not at all/never" to "extremely/always". The QoLISSY scores (core domains and sub-scale levels) were calculated per QoLISSY scoring manual developed by Pfizer and the University Medical Centre Hamburg-Eppendorf. The QoLISSY instrument has satisfactory reliability in both

parent-report and self-report forms, and moderate parent-child agreement (Bullinger, Quitmann et al. 2013).[3] The QoLISSY questionnaire also detects changes of HRQoL within the course of GH treatment. Larger increases in body heights were also associated with greater improvement in total HRQoL, which reflects physical, social, and emotional HRQoL (Bloemeke, Sommer et al. 2019).[2]

9.4.3.4.3. Treatment Experience

Treatment experience data was not collected in Belgium. In other countries, treatment experience was measured by the LIQ-GHD instrument. The LIQ-GHD was administered as an electronic patient-reported outcome (ePRO). It contains several modules, intended to be completed by the patient, the caregiver, or the patient and the caregiver together (as a "dyad"). It is a validated questionnaire (Turner-Bowker, Yaworsky et al. 2020).[16] LIQ-GHD was collected for patients who were aged ≥3 to ≤17 years. Age at enrollment was used to determine eligibility for LIQ-GHD.

The LIQ-GHD section I assessed 6 domains: injection pen assessment which comprised the pen ease of use, and ease of injection schedule, patient life interference, caregiver life interference, patient satisfaction and willingness to continue, missed injections, and injection signs and symptoms. Only patients who were ≥8 to ≤17 years completed the injection signs and symptoms questionnaire; for children <8 years, the caregiver answered the caregiver assessment of signs instead. The missed injection questions included the number of missed injections over the previous 4-week period, and the reasons for missing injections using a predetermined list. The majority of questions were scored via a 5-point scale (for example, 'very easy to very difficult' or 'never to always'); the 'convenience' question (as part of the 'ease of injection schedule' questions) used a 7-point scale (extremely convenient to extremely inconvenient) and the 4 injection signs and symptoms questions (pain, bleeding, bruising, stinging) used a numerical rating scale 0–10. All scores were transformed from raw scores and converted to a 0 to 100 scale.

The LIQ-GHD section II was a comparative assessment administered after a patient experienced both daily injections and the long-acting (administered once -weekly) hGH, Ngenla. LIQ-GHD section II assessed the following domains: Caregiver life interference, patient life interference, patient satisfaction and willingness to continue, the injection pen assessment questionnaire, and patient intention to comply with treatment.

9.5. Data Sources and Measurement

This was an NIS and did not impose a therapy protocol, diagnostic/therapeutic procedure, or a trial visit schedule. Patients were treated at the discretion of the treating physician in terms of visit frequency and types of routine assessments were performed as per routine clinical care.

Data were collected at study enrollment, with follow-up information collected at routine clinical visits approximately every year, and at the end of follow-up or early termination. All data were entered into the electronic data capture (EDC) using eCRFs each time a clinical follow-up visit occurred.

In February 2024, a mid-study update of the EDC was issued requesting data from sites to inform whether patients were naïve or non-naïve to hGH treatment at baseline. These data

were added to datasets in March 2024 and used to update naïve and non-naïve subgroup tables in the second interim analysis (IA) and in the final analysis.

9.5.1. Data Collection

The schedule of assessments for the study is presented in Table 1 of the protocol (Appendix 2). All data elements in the eCRF were collected from information routinely recorded during routine clinical practice.

QoLISSY and LIQ-GHD were not collected in Belgium. In the other countries, QoLISSY and LIQ-GHD were administered as ePRO.

Additionally, any SAEs/AEs that were observed by or reported to the treating physician at any time outside of a routine clinical follow-up visit were reported by the treating physician as per the protocol.

9.6. Bias

As a NIS, this study has several potential limitations. Although this was a prospective cohort study with primary data collection, without randomization, confounding and biases cannot be entirely eliminated, and determination of causation is limited. Enrollment bias is possible, though sites were expected to enroll all eligible patients treated with Ngenla, Genotropin, and Other daily hGH treatments of interest. Follow-up bias is a potential limitation as well, especially if patients with AEs were less likely to return to the treating physician or site for follow-up.

There is a potential risk of underestimating the safety and effectiveness outcomes due to underreporting, misreporting or missing data from the eCRFs, and/or EHR. However, all data that was collected in Table 2 (Section 9.4) is part of routine clinical care for GHD, thus information bias pertaining to any safety or effectiveness outcomes is likely to be low in the present study and have minimal impact on the interpretation of the results.

9.7. Study Size

One of the study objectives was to estimate IRs of safety events among patients on Ngenla, Genotropin, and Other daily hGH treatments of interest. IRs of safety events were assessed from a prior multicenter observational database study, Pfizer International Growth Database (known as KIGS) (Maghnie, Ranke et al. 2022).[9] In KIGS, the safety data showed that the SAE rate for patients with idiopathic GHD was approximately 0.67, 0.49, 0.17, and 0.74 in Europe, North America, Japan, and RoW, respectively per 100 patient years of exposure. For the current study, a similar SAE rate was assumed for the daily hGH brands with the equivalence bounds set at 0.55 to 0.75 for Europe, 0.40 to 0.60 for North America, 0.10 to 0.30 for Japan, and 0.65 to 0.85 for RoW (per 100 patient years of exposure).

Assuming that each patient in the daily hGH brands will contribute at least 6 months of exposure and using a 2-sided exact equivalence test for binomial proportion with a 0.05 significance level, a sample size of approximately 600 patients with GHD (per geographic region: Europe, North America, Japan, and RoW) in the daily hGH brands was determined to be required to achieve at least 90% power to demonstrate that the SAE rate was equivalent to the SAE rate in the KIGS study, within the equivalence bounds for each region. Considering the attrition rate of 10%, a total of approximately 667 GHD patients (per

geographic region) in the combined daily hGH brands were targeted for the study, had the study not been terminated early.

When 667 GHD patients (per geographic region: Europe, North America, Japan, and RoW) on the daily hGH brands were enrolled in the study, an IA focusing on the primary safety endpoints was planned to assess the equivalence of the SAE rates, using the equivalence bounds for each region, as shown above. However, due to early termination, no IA focusing on primary safety endpoints and their equivalence bounds for each region was conducted. Ngenla

As all eligible patients treated with Ngenla and Genotropin were planned to be enrolled in the study, there was no limit on the number of patients enrolled in the Ngenla and Genotropin treatment group.

All sample size and power calculations were performed using the Statistical Analysis System (SAS), version 9.4.

9.8. Data Transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the Sponsor (Appendix 4).

For the first annual report, naïve and non-naïve patients were defined according to whether they had been exposed to GH product prior to enrollment. Specifically, a naïve patient was defined as any patient with at least one current hGH treatment entered with the injection date on or after ICD date. Non-naïve was defined as any patient with at least one hGH treatment entered prior to the ICD date. For the second annual report, naïve and non-naïve were derived using variables from the February 2024 mid-study update of the EDC and were defined according to whether they were exposed to GH product for at least 28 days including current and prior hGH treatments. Specifically, sites were asked “Has the patient ever been treated with GH for at least 28 days, including current and prior GH treatment?” If the site answered “no”, the patient was classified as naïve; if the site answered “yes”, the patient was classified as non-naïve. This derivation was maintained for data analyzed and presented in this final report.

9.9. Statistical Methods

Detailed methodology for summary and statistical analyses of data collected in this study, and suitable subgroup analyses is documented in the SAP, which is dated, filed, and maintained by Pfizer (Appendix 4). No hypotheses were tested for this NIS study.

Two analysis sets were used for this study: All patients Enrolled Set (ENR), and Full Analysis Set (FAS).

- All patients ENR contained all patients who provided informed consent and met all eligibility criteria to participate in this study.

- The FAS contained all enrolled patients who initiated Ngenla, Genotropin, and Other daily hGH treatments of interest, and had at least one effectiveness or safety outcome available. This set was also used for safety and effectiveness analysis.

The analysis was conducted after database lock and included the available baseline and follow-up data for patients enrolled. The final report focuses on the descriptive analysis of the data collected up to database lock (18 July 2024) for patients in the FAS. Primary and secondary safety and effectiveness endpoints were analyzed and presented to the extent possible given limited follow-up due to early study termination. Assessment of the equivalence of the SAE rates across geographic regions and hGH brands was not conducted due to limited sample size resulting from early study termination.

9.9.1. Main Summary Measures

Descriptive analyses were performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Unless otherwise specified, data were summarized by treatment and overall.

Continuous/quantitative variables were summarized using descriptive statistics which included the number of patients with data to be summarized (n), mean, SD, median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations.

Descriptive statistics for categorical/qualitative variables were presented with the number of patients (count) and percentage and these were presented in the format ‘n (%)’. Percentages did not include the missing category and were calculated over the number of patients with available (non-missing) data. The count of missing observations and the number of patients in each category is provided in all tables.

Safety data are presented in tabular and/or listing format and summarized descriptively, where appropriate. Event count and AE frequency are reported. Number (% of patients) with AEs, SAEs, and discontinuations due to an AE are reported.

SAS®, Version 9.4 was used for all statistical analyses described.

9.9.2. Main Statistical Methods

Analyses of primary and secondary effectiveness and safety outcomes are summarized in Table 3 and Table 4 below. Details on these analyses are available in the SAP (Appendix 4).

Table 3 Overview of Safety Analysis

Outcome	Primary/Secondary	Subgroups (yes/No)	Statistical Method 1	Statistical Method 2	Statistical Method 3
SAEs	Primary	Yes	Descriptive stats	IR, IRR	Equivalence Test*
AESIs	Primary	Yes	Descriptive stats	IR, IRR	NA
AESIs	Secondary	No	Descriptive stats	IR, IRR	NA

Outcome	Primary/Secondary	Subgroups (yes/No)	Statistical Method 1	Statistical Method 2	Statistical Method 3
Non-SAEs	Secondary	No	Descriptive stats	NA	NA
Laboratory results	Secondary	No	Descriptive stats	NA	NA

*Planned to be performed after achieving the optimal sample size for an interim analysis, but not conducted due to limited sample size and study termination
AESI: Adverse Events of Special Interest; IR: Incidence Rates; IRR: Incidence Rate Ratio; NA: Not applicable; SAE: Serious adverse event.

Table 4 Overview of Effectiveness Analysis

Outcome	Primary/Secondary	Subgroups (yes/No)	Statistical Method 1	Statistical Method 2	Statistical Method 3
Annual HV	Primary	Yes	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
Height SDS	Primary	Yes	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
HVSDS	Primary	Yes	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
Change in height SDS	Primary	Yes	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
Amount of dose adjustment	Primary	No	-	-	Descriptive stats
Change in annual BMI	Primary	No	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
Change in annual BMI SDS	Primary	No	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
Change in BMD	Primary	No	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
Growth factor concentration	Primary	No	-	-	Descriptive stats
BMI SDS	Primary	No	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats
Bone age (overall combined and by age groups: 0–2, 3–8, 9–18 and ≥19 years)	Secondary	No	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats

Outcome	Primary/Secondary	Subgroups (yes/No)	Statistical Method 1	Statistical Method 2	Statistical Method 3
Body composition (e.g., lean tissue, fat tissue, resistance, body mass composition, total potassium) (overall combined and by age groups: 0–2, 3–8, 9–18 and ≥19 years)	Secondary	No	MMRM*, 95% CI*	MSM*, 95% CI*	Descriptive stats*

*Not conducted due to limited sample size and study termination.
BMD: Bone Mineral Density; BMI: Body Mass Index; CI: Confidence Interval; HV: Height Velocity; HVSDS: Height Velocity Standard Deviation Score; MMRM: Mixed Models For Repeated Measures; MSM: Marginal Structural Model; SDS: Standard Deviation Score.

9.9.2.1. Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 – March 2024.

Definitions for treatment-emergent adverse events (TEAE), summary of TEAEs by specific system organ class (SOC) and preferred term (PT), handling of missing values, and handling of partial dates are described in the SAP (Appendix 4).

9.9.2.2. Serious Adverse Events and Other Significant Adverse Events

SAEs are those events recorded as “Serious” on the AEs Form of the eCRF. Statistics used to summarize SAEs are described in the SAP (Appendix 4).

9.9.2.3. Treatment Adherence and Compliance Outcomes

An exposure summary, duration of treatment, and type of hGH treatment with Ngenla, Genotropin, and Other daily hGH treatments of interest was summarized for the FAS.

Compliance was summarized descriptively as continuous data.

9.9.2.4. Treatment Experience

Treatment burden was planned to be assessed as the difference in mean overall life interference total scores between the weekly injection schedule and daily injection schedule as assessed by the Patient Life Interference Questionnaire (as part of LIQ-GHD and comprises 7 items: daily activities/social activities/leisure/night away from home/travel/bother and change to life routine) completed by the Subject/Caregiver Dyad, and also by a separate caregiver life interference questionnaire, at baseline and after each post-treatment visit experience. This analysis was not performed due to small sample sizes and study termination.

Treatment experience was planned to be assessed as the difference in mean scores between the weekly injection schedule experience and daily injection schedule experience in each of the following variables within LIQ-GHD questionnaires completed at baseline and after subjects have experienced both treatment schedules. However, this analysis was not performed due to small sample sizes and study termination.

9.9.2.5. Health-Related Quality of Life

QoLISSY item responses and resulting scores are presented in a listing. The 3 core domains (physical, social, and emotional), the 3 additional domains (coping, beliefs, and treatment) and the 2 supplementary domains (future and impact) as part of the QoLISSY-Parent only were calculated individually. A total score was calculated by the sum of the means in the physical, social, and emotional sub-scale divided by 3 based on the QoLISSY scoring manual. All scores were transformed from raw scores to 0 to 100 scores.

Separate tables for QoLISSY-Child and QoLISSY-Parent are presented. Summary statistics are presented by study visit and change from baseline is presented for post-treatment visits. The mean change from baseline to post baseline assessment analyzed by Mixed Models for Repeated Measure (MMRM) and Marginal Structural Model (MSM) as described in the SAP (Appendix 4) was planned but not performed due to small sample sizes and study termination.

9.9.2.6. Subgroups

Selected results are stratified by whether patients were naïve or non--naïve to hGH treatment prior to enrollment, which are presented in full in Appendix 8 and discussed within this report. Derivation of this variable is described in Section 9.8.

Selected data were also analyzed by subgroups such as age group, sex, race, duration of primary diagnosis of hGH, primary diagnosis, puberty status, peak baseline GH level, and study region (Europe, Japan, North America, and RoW)/country. Details on subgroup analyses are described in the SAP.

9.9.3. Missing Values

In general, missing data were not imputed and data were analyzed as they were recorded in the study eCRF and as they were entered in the study database following resolution of all queries from data management.

The number of non-missing observations for all variables are indicated in descriptive tables. The number of missing cases was reported for each variable of interest in the analysis. Patients with completely missing data for a variable were excluded from the denominator when calculating proportions involving observed data for that variable.

All questionnaires used standard scoring rules, which included any information for the handling of missing data. Details on the handling of partial dates and missing dates are detailed in the SAP (Appendix 4).

9.9.4. Sensitivity Analyses

None.

9.9.5. Amendments to the Statistical Analysis Plan

The SAP was amended on 22 May 2024 to make updates following protocol amendment 3 (protocol version 4.0) and eCRF mid-study updates. Revisions to the SAP from version 1.0 (01 August 2022) included minor phrasing changes, removal of cognitive function as an endpoint, the addition of definitions for naïve and non-naïve patients, and details on the early termination of study.

9.10. Quality Control

IQVIA performed clinical monitoring, including review of the data within the eCRF to ensure compliance with the protocol, the accuracy and completeness of submitted clinical data. High data quality standards were maintained, and processes and procedures utilized to repeatedly ensure that the data were as clean and accurate as possible when presented for analysis. Data quality was enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data. No system checks were in place for laboratory values due to the diversity of units reported across sites and countries. Ad hoc queries were generated within the EDC system and followed up for resolution.

Treating physicians entered their study data into the eCRF database, a web-based system, customized for this study in a timely manner and reported SAEs and Exposure In utero as described in protocol.

9.11. Protection of Human Subjects

Subject information and consent

All parties complied with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures included omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Written informed consent (Appendix 6) was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an ICD.

The informed consent and assent documents used during the informed consent process and any patient recruitment materials were reviewed and approved by Pfizer, approved by the Institutional Review Board (IRB)/EC before use, and are available for inspection.

Patient withdrawal

Patients could withdraw from the study at any time at their own request, or they could be withdrawn at any time at the discretion of the physician or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort was made to document patient outcomes, if applicable. The physician inquired about the reason for withdrawal and follow-up with the patient regarding any unresolved AEs.

If the patient withdrew from the study, and also withdrew consent for disclosure of future information, no further evaluations were performed, and no additional data were collected. The Sponsor retained and continued to use any data collected before such withdrawal of consent.

Institutional review board/ethics committee

It was the responsibility of the physician to have prospective approval of the study protocol, protocol amendments, and ICDs, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/EC. All correspondence with the IRB/EC was retained by the physician. Copies of IRB/EC approvals were forwarded to Pfizer.

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an IRB(s) and/or EC(s) for each site participating in the study.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and US Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. RESULTS

10.1. Participants

There were 1559 patients who were enrolled in the study between 18 November 2021 to database lock on 18 July 2024. A total of 1516 patients were included in the FAS with 716 patients in the Genotropin group, 359 patients in the Other daily hGH group, and 441 patients enrolled in the Ngenla group (Table 5). No treatment details were available for 7 patients and no outcome data were available for 36 patients, hence they were not included in the FAS (Source Table 16.2.3, Appendix 8).

At the time of database lock, 1557 patients had discontinued the study for reasons of study terminated by sponsor (n=1488), loss to follow-up (n=5), poor compliance to protocol (n=1), AEs (n=3), and “Other” reasons (n=60), including parents changing their minds, not initiating treatment, switching to a non-Ngenla weekly treatment or daily treatment not of interest (some due to global shortage of Genotropin), withdrawal of consent, or patient leaving the practice (Table 5) (Source Table 16.2.4.2, Appendix 8). Two patients did not have their study disposition eCRF completed at time of database lock and therefore are not represented in the aforementioned counts.

Table 5 Patient Disposition

	Genotropin (N=743)	Other daily hGH				Ngenla (N=448)	Overall (N=1576)
		Humatrope (N=28)	Norditropin (N=156)	Omnitrope (N=187)	Total (N=371)		
Number of Screened Patients, n	-	-	-	-	-	-	1576
Number of Screened Failures, n	-	-	-	-	-	-	17
Population, n (%)							
All Patients Enrolled Set	738 (100)	28 (100)	155 (100)	183 (100)	366 (100)	448 (100)	1559 (100)
Full Analysis Set[1]	716 (97.0)	28 (100)	150 (96.8)	181 (98.9)	359 (98.1)	441 (98.4)	1516 (97.2)
Missing treatment patients[1]	-	-	-	-	-	-	7 (0.4)
Missing outcome patients[1]	-	-	-	-	-	-	36 (2.3)
Patients ongoing the study, n (%)[1]	0	0	0	0	0	0	0
Patients completing the study, n (%)[1]	0	0	0	0	0	0	0
Prematurely discontinuing the study, n (%)[1]	738 (100)	28 (100)	155 (100)	183 (100)	366 (100)	446 (99.6)	1557 (99.9)
Primary reason for study discontinuation, n (%)[2]							
Adverse Event	1 (0.1)	1 (3.6)	0	0	1 (0.3)	1 (0.2)	3 (0.2)
Death	0	0	0	0	0	0	0
Lost to Follow-up	3 (0.4)	1 (3.6)	1 (0.6)	0	2 (0.5)	0	5 (0.3)
Poor compliance to protocol	0	0	1 (0.6)	0	1 (0.3)	0	1 (0.1)
Study terminated by sponsor	694 (94.0)	21 (75.0)	142 (91.6)	180 (98.4)	343 (93.7)	445 (99.8)	1488 (95.6)

	Genotropin (N=743)	Other daily hGH				Ngenla (N=448)	Overall (N=1576)
		Humatrope (N=28)	Norditropin (N=156)	Omnitrope (N=187)	Total (N=371)		
Did not meet Eligibility Criteria	0	0	0	0	0	0	0
Other	40 (5.4)	5 (17.9)	11 (7.1)	3 (1.6)	19 (5.2)	0	60 (3.9)
Relationship of death to treatment, n (%)[3]							
Related	0	0	0	0	0	0	0
Unrelated	0	0	0	0	0	0	0
Primary cause of death, n (%)[4]							
No data to report	0	0	0	0	0	0	0

CRF: Case Report Form; hGH: Human Growth Hormone.
Screened subjects are those with signed informed consent.
Percentages are calculated using non-missing values as denominator.
1.Percentages calculated based on the number of enrolled patients.
2.Percentages calculated based on the number of patients who discontinued the study.
3.Related: Possibly Related and Related; Unrelated: Not Related and Unlikely Related.
4.Percentages calculated based on the number of patients who died.
All Patients Enrolled Set: all patients who provided informed consent and met all eligibility criteria.
Full Analysis Set: all enrolled patients who initiated Genotropin, Other daily hGH treatments, or Ngenla, and have at least one effectiveness or safety outcome.
Missing treatment patients for whom the current treatment details are missing at the time of clinical cut-off.
Missing outcome patients for whom the safety or effectiveness outcomes are missing at the time of clinical cut-off.
Note: disposition CRF form is missing for 2 patients. The patient '31026002' is not a part of 'Full Analysis Set' since he received treatment, but safety/effectiveness outcome is missing.
The patients '13009023', '14002001', '16002020', '26036008, '29004003', '29004004', '29004005' are enrolled but the treatment details are missing.
Source: Table 15.1.1.1, Appendix 8: Additional documents.

10.2. Descriptive Data

10.2.1. Demographic and Baseline Characteristics

The mean (SD) age at enrollment for patients overall was 11.1 (3.49) years. The mean (SD) age at enrollment was 11.6 (3.32) years among patients in the Genotropin group, 11.0 (3.82) years in the Other daily hGH group and 10.5 (3.38) years in the Ngenla group. The majority of patients were in the 9 to 18 years age group at enrollment overall (n=1106, 73.0%), and in each respective treatment group (Table 6).

The mean (SD) age at primary diagnosis of GHD for patients overall was 7.7 (4.19) years. The mean (SD) age at primary diagnosis was 8.3 (4.14) years in the Genotropin group, 6.9 (4.42) years in the Other daily hGH group, and 7.4 (3.95) years in the Ngenla group. The mean (SD) duration since primary diagnosis was 3.9 (3.59) years in patients overall, 3.8 (3.61) years in the Genotropin group, 4.5 (3.72) in the Other daily hGH group, and 3.6 (3.37) years in the Ngenla group (Table 6).

The majority of patients overall were non-naïve, defined as patients who have been exposed to a GH product for at least 28 days prior to enrollment including current and prior GH treatments (n=1325, 87.4%). Similarly, compared to naïve patients, there were more non-naïve patients in the Genotropin (n=654, 91.3%), Other daily hGH (n=331, 92.2%), and Ngenla (n=340, 77.1%) groups (Table 6). Subgroup analyses by naïve and non-naïve are included in Source Tables 15.1.2a (Demographic and Baseline Characteristics), 15.1.5a (Birth History), and 15.1.7a (hGH Diagnosis) in Appendix 8.

Overall, males were represented to a greater proportion (n=1023, 67.5%) than females. Similarly, there were more male patients in the Genotropin (n=490, 68.4%), Other daily hGH (n=237, 66.0%), and Ngenla (n=296, 67.1%) groups (Table 6).

Approximately half of the patients were White (n=754, 50.8%) and more than half of the patients were not of Hispanic or Latino ethnicity (n=915, 61.5%). Almost half of the patients were from Europe (n=700, 46.2%) followed by North America (n=406, 26.8%), Japan (n=241, 15.9%) and RoW (n=169, 11.1%) (Table 6).

Out of 1516 patients in FAS, data on bone age using the Tanner-Whitehouse approach were missing for 1063 patients at enrollment. Overall, 453 patients had data for bone age and reported a mean (SD) bone age of 10.0 (3.90) years. The chronological age of these patients had a mean (SD) of 10.9 (3.62) years. In the Genotropin group, 213 had data for bone age and reported a mean (SD) bone age of 10.6 (3.71) years. In the Other daily hGH group, 123 had data for bone age and reported a mean (SD) bone age of 10.2 (3.74) years. In the Ngenla group, 117 had data for bone age and reported a mean (SD) bone age of 8.6 (4.07) years (Table 6).

The mean (SD) height for patients at enrollment overall was 136.4 (21.17) cm. The mean (SD) height was 139.6 (20.08) cm in the Genotropin group, 136.0 (22.83) cm in the daily hGH group, and 131.7 (20.59) cm in the Ngenla group. For all patients the mean (SD) height SDS was -1.3 (1.20). The mean (SD) height SDS was -1.2 (1.14) in the Genotropin group, -1.2 (1.16) in the Other daily hGH group, and -1.5 (1.31) in the Ngenla group (Table 6).

The mean (SD) weight for patients at enrollment overall was 35.6 (15.91) kg. The mean (SD) weight at enrollment was 37.5 (15.79) kg in the Genotropin group, 35.8 (17.03) kg in the Other daily hGH group, and 32.5 (14.66) kg in the Ngenla group. For patients overall, the mean (SD) weight SDS at enrollment was 0.6 (1.84). The mean (SD) weight SDS at enrollment was 0.8 (1.74) in the Genotropin group, 0.7 (1.85) in the Other daily hGH group, and 0.1 (1.90) in the Ngenla group (Table 6).

The mean (SD) BMI for patients at enrollment overall was 18.1 (3.71) kg/m^2. The mean (SD) BMI was 18.3 (3.83) kg/m^2 in the Genotropin group, 18.2 (3.72) kg/m^2 in the Other daily hGH group, and 17.7 (3.47) kg/m^2 in the Ngenla group (Table 6).

Ngenla. The mean (SD) peak GH for patients at enrollment overall was 6.0 (5.77) ng/mL. The mean (SD) peak GH was 6.4 (6.43) ng/mL in the Genotropin group, 5.8 (4.10) ng/mL in the Other daily hGH group, and 5.7 (5.74) ng/mL in the Ngenla group. Approximately half of the patients had peak GH levels >3 ng/mL to ≤7 ng/mL (n=492, 51.8%), followed by peak

GH levels ≤3 ng/mL (n=199, 21.0%) and peak GH levels >7 ng/mL to 10 ng/mL (n=185, 19.5%) (Table 6).

The mean (SD) hGH treatment dose with mg/kg/week unit at enrollment was 0.24 (0.062) in the Genotropin group, 0.24 (0.081) in the Other daily hGH group, and 0.63 (0.051) in the Ngenla group (Table 6). The treatment doses at enrollment for 12 patients with a dose unit other than mg/kg/week are in Source Table 16.2.6.1a, Appendix 8.

Table 6 Demographic and Baseline Characteristics by Treatment Groups

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Age at enrollment (years)							
n	716	28	150	181	359	441	1516
Mean (SD)	11.6 (3.32)	11.4 (3.47)	11.1 (3.92)	10.8 (3.80)	11.0 (3.82)	10.5 (3.38)	11.1 (3.49)
Median	12.2	12.5	11.8	11.4	11.6	10.8	11.6
Q1; Q3	9.6; 14.0	8.7; 14.4	8.1; 13.9	7.8; 13.5	8.1; 13.8	8.2; 13.3	8.8; 13.8
Min; Max	0.3; 21.2	4.3; 15.8	2.3; 19.6	1.2; 19.4	1.2; 19.6	1.8; 17.9	0.3; 21.2
Missing	0	0	0	0	0	0	0
Age group at enrollment (years), n (%)							
Age grouping							
0 to 2	7 (1.0)	0	2 (1.3)	2 (1.1)	4 (1.1)	1 (0.2)	12 (0.8)
3 to 8	147 (20.5)	8 (28.6)	42 (28.0)	55 (30.4)	105 (29.2)	141 (32.0)	393 (25.9)
9 to 18	560 (78.2)	20 (71.4)	104 (69.3)	123 (68.0)	247 (68.8)	299 (67.8)	1106 (73.0)
≥19	2 (0.3)	0	2 (1.3)	1 (0.6)	3 (0.8)	0	5 (0.3)
Age at primary diagnosis (years)							
n	707	28	145	178	351	437	1495
Mean (SD)	8.3 (4.14)	6.8 (4.29)	6.7 (4.37)	7.1 (4.50)	6.9 (4.42)	7.4 (3.95)	7.7 (4.19)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Median	9.0	6.0	7.0	7.0	7.0	7.0	8.0
Q1; Q3	5.0; 12.0	3.5; 10.5	3.0; 10.0	4.0; 11.0	3.0; 10.0	4.0; 11.0	5.0; 11.0
Min; Max	0.0; 18.0	0.0; 15.0	0.0; 15.0	0.0; 17.0	0.0; 17.0	0.0; 17.0	0.0; 18.0
Missing	9	0	5	3	8	4	21
Duration of primary diagnosis (years)							
n	707	28	145	178	351	437	1495
Mean (SD)	3.8 (3.61)	5.0 (4.40)	4.8 (3.85)	4.2 (3.50)	4.5 (3.72)	3.6 (3.37)	3.9 (3.59)
Median	3.0	3.0	4.0	3.5	4.0	3.0	3.0
Q1; Q3	1.0; 5.0	1.5; 8.5	2.0; 6.0	2.0; 6.0	2.0; 6.0	1.0; 6.0	1.0; 6.0
Min; Max	0.0; 21.0	0.0; 16.0	0.0; 20.0	0.0; 17.0	0.0; 20.0	0.0; 14.0	0.0; 21.0
Missing	9	0	5	3	8	4	21
GH types, n (%)							
Naïve	62 (8.7)	3 (10.7)	11 (7.3)	13 (7.2)	27 (7.5)	101 (22.9)	190 (12.5)
Non-naïve	654 (91.3)	25 (89.3)	139 (92.7)	167 (92.3)	331 (92.2)	340 (77.1)	1325 (87.4)
Missing	0	0	0	1	1	0	1
Sex, n (%)							
Male	490 (68.4)	19 (67.9)	99 (66.0)	119 (65.7)	237 (66.0)	296 (67.1)	1023 (67.5)
Female	226 (31.6)	9 (32.1)	51 (34.0)	62 (34.3)	122 (34.0)	145 (32.9)	493 (32.5)
Race, n (%)							
American Indian or Alaska Native	2 (0.3)	0	0	0	0	1 (0.2)	3 (0.2)
Asian	177 (25.1)	7 (25.0)	17 (11.5)	10 (5.7)	34 (9.7)	108 (25.4)	319 (21.5)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Black or African American	6 (0.8)	0	1 (0.7)	1 (0.6)	2 (0.6)	1 (0.2)	9 (0.6)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (0.6)	1 (0.3)	0	1 (0.1)
White	308 (43.6)	19 (67.9)	97 (65.5)	111 (63.4)	227 (64.7)	219 (51.4)	754 (50.8)
Unknown/ Not Available/ Not Reported	178 (25.2)	1 (3.6)	22 (14.9)	41 (23.4)	64 (18.2)	28 (6.6)	270 (18.2)
Not applicable/ collected per local regulations	29 (4.1)	0	11 (7.4)	9 (5.1)	20 (5.7)	60 (14.1)	109 (7.3)
Other	9 (1.3)	2 (7.1)	2 (1.4)	3 (1.7)	7 (2.0)	11 (2.6)	27 (1.8)
Missing	10	0	2	6	8	15	33
Ethnicity, n (%)							
Hispanic or Latino	55 (7.7)	3 (10.7)	4 (2.7)	17 (9.6)	24 (6.8)	53 (12.5)	132 (8.9)
Not Hispanic or Latino	418 (58.8)	22 (78.6)	108 (73.5)	106 (59.9)	236 (67.0)	261 (61.4)	915 (61.5)
Not Reported	129 (18.1)	2 (7.1)	14 (9.5)	29 (16.4)	45 (12.8)	33 (7.8)	207 (13.9)
Not Applicable	34 (4.8)	0	9 (6.1)	11 (6.2)	20 (5.7)	45 (10.6)	99 (6.7)
Unknown	75 (10.5)	1 (3.6)	12 (8.2)	14 (7.9)	27 (7.7)	33 (7.8)	135 (9.1)
Missing	5	0	3	4	7	16	28
Region/ Country of residence, n (%)							
Europe	244 (34.1)	3 (10.7)	37 (24.7)	120 (66.3)	160 (44.6)	296 (67.1)	700 (46.2)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Belgium	1 (0.1)	0	0	0	0	4 (0.9)	5 (0.3)
Czech Republic	1 (0.1)	0	1 (0.7)	0	1 (0.3)	71 (16.1)	73 (4.8)
Denmark	0	0	0	0	0	1 (0.2)	1 (0.1)
France	99 (13.8)	0	23 (15.3)	39 (21.5)	62 (17.3)	89 (20.2)	250 (16.5)
Germany	1 (0.1)	0	5 (3.3)	9 (5.0)	14 (3.9)	18 (4.1)	33 (2.2)
Italy	0	0	2 (1.3)	10 (5.5)	12 (3.3)	7 (1.6)	19 (1.3)
Slovenia	0	0	0	0	0	9 (2.0)	9 (0.6)
Spain	116 (16.2)	3 (10.7)	2 (1.3)	43 (23.8)	48 (13.4)	85 (19.3)	249 (16.4)
Sweden	8 (1.1)	0	0	0	0	3 (0.7)	11 (0.7)
United Kingdom	18 (2.5)	0	4 (2.7)	19 (10.5)	23 (6.4)	9 (2.0)	50 (3.3)
Japan	124 (17.3)	7 (25.0)	13 (8.7)	7 (3.9)	27 (7.5)	90 (20.4)	241 (15.9)
North America	229 (32.0)	18 (64.3)	88 (58.7)	51 (28.2)	157 (43.7)	20 (4.5)	406 (26.8)
Canada	19 (2.7)	2 (7.1)	15 (10.0)	12 (6.6)	29 (8.1)	15 (3.4)	63 (4.2)
United States	210 (29.3)	16 (57.1)	73 (48.7)	39 (21.5)	128 (35.7)	5 (1.1)	343 (22.6)
Rest of the World	119 (16.6)	0	12 (8.0)	3 (1.7)	15 (4.2)	35 (7.9)	169 (11.1)
Australia	13 (1.8)	0	2 (1.3)	3 (1.7)	5 (1.4)	7 (1.6)	25 (1.6)
Israel	63 (8.8)	0	10 (6.7)	0	10 (2.8)	0	73 (4.8)
Taiwan	40 (5.6)	0	0	0	0	16 (3.6)	56 (3.7)
United Arab Emirates	2 (0.3)	0	0	0	0	9 (2.0)	11 (0.7)
Bone age (years)							
N	213	7	51	65	123	117	453
Mean (SD)	10.6 (3.71)	12.1 (4.00)	10.9 (3.65)	9.6 (3.69)	10.2 (3.74)	8.6 (4.07)	10.0 (3.90)
Median	11.6	13.0	11.6	10.0	11.0	8.6	10.9
Q1; Q3	8.5; 13.0	10.5; 15.0	8.3; 14.0	7.6; 12.5	8.0; 13.5	5.4; 12.0	7.5; 13.0
Min; Max	1.5; 18.0	4.3; 16.5	1.0; 17.0	2.0; 16.3	1.0; 17.0	0.0; 17.0	0.0; 18.0
Missing	503	21	99	116	236	324	1063

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Chronological age for patients with Bone age (years)[1]							
N	213	7	51	65	123	117	453
Mean (SD)	11.4 (3.46)	12.3 (3.21)	11.8 (3.48)	10.6 (3.57)	11.2 (3.55)	9.7 (3.72)	10.9 (3.62)
Median	12.2	13.4	12.5	11.3	11.8	10.3	11.5
Q1; Q3	9.2; 13.8	11.2; 14.7	9.2; 14.2	8.1; 13.1	9.0; 13.5	7.3; 12.3	8.6; 13.5
Min; Max	1.1; 18.2	5.8; 15.4	3.6; 17.8	3.7; 17.7	3.6; 17.8	0.9; 16.8	0.9; 18.2
Missing	0	0	0	0	0	0	0
Height (cm)							
N	684	27	146	176	349	423	1456
Mean (SD)	139.6 (20.08)	139.0 (22.21)	137.4 (23.11)	134.4 (22.71)	136.0 (22.83)	131.7 (20.59)	136.4 (21.17)
Median	142.0	144.0	139.8	136.5	138.8	133.0	138.7
Q1; Q3	128.4; 154.7	122.5; 158.9	121.0; 155.1	116.6; 153.1	118.6; 153.9	117.0; 146.6	122.0; 152.5
Min; Max	53.5; 182.1	93.4; 170.1	80.9; 179.0	68.0; 180.3	68.0; 180.3	78.6; 182.5	53.5; 182.5
Missing	32	1	4	5	10	18	60
Height SDS							
N	684	27	146	176	349	423	1456
Mean (SD)	-1.2 (1.14)	-1.1 (1.16)	-1.1 (1.15)	-1.3 (1.17)	-1.2 (1.16)	-1.5 (1.31)	-1.3 (1.20)
Median	-1.2	-0.9	-1.1	-1.3	-1.1	-1.6	-1.3
Q1; Q3	-1.9; -0.6	-2.0; -0.4	-1.7; -0.4	-2.0; -0.6	-1.9; -0.5	-2.2; -0.7	-2.0; -0.6
Min; Max	-5.2; 4.5	-4.1; 1.1	-4.5; 2.8	-7.9; 1.7	-7.9; 2.8	-10.4; 2.3	-10.4; 4.5
Missing	32	1	4	5	10	18	60
Weight (kg)							
N	684	27	146	175	348	424	1456
Mean (SD)	37.5 (15.79)	39.0 (18.89)	36.0 (15.89)	35.2 (17.69)	35.8 (17.03)	32.5 (14.66)	35.6 (15.91)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Median	35.8	35.3	34.0	33.0	33.7	29.6	33.5
Q1; Q3	26.3; 46.8	24.3; 52.4	23.0; 45.8	21.3; 44.4	22.3; 45.0	21.4; 40.8	23.6; 44.8
Min; Max	4.7; 134.2	14.4; 87.5	10.7; 95.3	7.0; 96.3	7.0; 96.3	9.3; 90.4	4.7; 134.2
Missing	32	1	4	6	11	17	60
Weight SDS							
N	684	27	146	175	348	424	1456
Mean (SD)	0.8 (1.74)	0.9 (1.90)	0.8 (1.72)	0.5 (1.94)	0.7 (1.85)	0.1 (1.90)	0.6 (1.84)
Median	0.9	0.6	0.7	0.5	0.6	-0.0	0.6
Q1; Q3	-0.6; 2.1	-0.7; 2.7	-0.5; 2.1	-0.8; 1.9	-0.8; 2.0	-1.2; 1.5	-0.8; 1.9
Min; Max	-4.1; 5.7	-2.2; 4.6	-3.7; 4.8	-7.1; 4.8	-7.1; 4.8	-9.2; 4.7	-9.2; 5.7
Missing	32	1	4	6	11	17	60
Body Mass Index (BMI) (kg/m^2)							
N	684	27	146	175	348	423	1455
Mean (SD)	18.3 (3.83)	18.9 (4.42)	18.0 (2.97)	18.2 (4.15)	18.2 (3.72)	17.7 (3.47)	18.1 (3.71)
Median	17.5	17.6	17.6	17.6	17.6	16.9	17.3
Q1; Q3	15.8; 19.8	15.6; 20.8	15.9; 19.6	15.3; 19.5	15.6; 19.6	15.4; 19.0	15.7; 19.6
Min; Max	12.8; 42.7	14.2; 32.9	11.9; 31.7	11.7; 36.2	11.7; 36.2	12.0; 35.7	11.7; 42.7
Missing	32	1	4	6	11	18	61
Peak GH (ng/mL)							
n	440	7	73	129	209	300	949
Mean (SD)	6.4 (6.43)	6.4 (5.93)	6.1 (4.53)	5.6 (3.74)	5.8 (4.10)	5.7 (5.74)	6.0 (5.77)
Median	5.4	4.7	4.9	5.1	5.1	5.1	5.2
Q1; Q3	3.6; 7.6	2.5; 6.9	3.2; 7.7	3.0; 7.1	3.1; 7.3	3.3; 6.8	3.4; 7.2
Min; Max	0.0; 83.0	1.5; 19.2	0.6; 28.0	0.0; 22.4	0.0; 28.0	0.1; 76.0	0.0; 83.0
Missing	276	21	77	52	150	141	567

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Peak GH levels*, n (%)							
≤3 ng/mL	79 (18.0)	2 (28.6)	17 (23.3)	33 (25.6)	52 (24.9)	68 (22.7)	199 (21.0)
>3 ng/mL to ≤7 ng/mL	226 (51.4)	4 (57.1)	33 (45.2)	63 (48.8)	100 (47.8)	166 (55.3)	492 (51.8)
>7 ng/mL to 10 ng/mL	100 (22.7)	0	16 (21.9)	22 (17.1)	38 (18.2)	47 (15.7)	185 (19.5)
>10 ng/mL	35 (8.0)	1 (14.3)	7 (9.6)	11 (8.5)	19 (9.1)	19 (6.3)	73 (7.7)
Missing	276	21	77	52	150	141	567
hGH Treatment dose at enrollment							
mg/kg/week, n (%)	277 (38.7)	12 (42.9)	81 (54.0)	113 (62.4)	206 (57.4)	293 (66.4)	NA
Mean (SD)	0.24 (0.062)	0.26 (0.131)	0.25 (0.071)	0.24 (0.081)	0.24 (0.081)	0.63 (0.051)	
Median	0.23	0.21	0.24	0.22	0.23	0.66	
Q1; Q3	0.19; 0.28	0.18; 0.30	0.21; 0.30	0.19; 0.26	0.19; 0.28	0.61; 0.66	
Min; Max	0.13; 0.43	0.14; 0.63	0.12; 0.53	0.13; 0.70	0.12; 0.70	0.41; 0.77	
hGH Treatment dose at enrollment							
Other, n (%)	2 (0.3)	0	2 (1.3)	2 (1.1)	4 (1.1)	6 (1.4)	NA
Mean (SD)	1.50 (1.273)	- (-)	1.25 (1.061)	1.50 (0.990)	1.38 (0.850)	24.77 (7.537)	
Median	1.50	-	1.25	1.50	1.40	27.00	
Q1; Q3	0.60; 2.40	-;-	0.50; 2.00	0.80; 2.20	0.65; 2.10	24.00; 30.00	
Min; Max	0.60; 2.40	-;-	0.50; 2.00	0.80; 2.20	0.50; 2.20	10.60; 30.00	

CRF: Case Report Form; hGH: Human Growth Hormone; BMI: Body Mass Index; IGF-I: Insulin-like growth factor-1; IGFBP-3: Insulin-like growth factor-1 binding protein 3; GH: Growth Hormone; Min: Minimum; Max: Maximum; SDS: Standard Deviation Score; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; WHO: World Health Organization.
Percentages are calculated using non-missing values as denominator.
[1] Chronological age among patients with bone age using Tanner-Whitehouse method.
*The peak GH is calculated based on GH test. If there are 2 GH tests performed, the higher value in the 2 different tests was used as the baseline peak GH value.
Naïve: Those patients who were not exposed to GH product for at least 28 days including current and prior GH treatments.
Non-naïve: Those patients who were exposed to GH product for at least 28 days including current and prior GH treatments.
1 pt 10001011 was having missing GH Type information.
Bone Age based on the Tanner-Whitehouse approach. '13009007', '17019001', '17019002', '30003001' have been removed due to data quality issues.
Reference population from Growth Analyzer for Height, Weight and BMI: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined)
Note: For Race, multiple options can be selected per CRF.
Peak GH, Peak GH levels have been removed for patients '29002001', '29002002', '29002003', '29002006', '29002007', '29002009', '29002010', '29002011', '29002012', '29002014', '29002015', '29002016', '29002017', '29002018','29002019', '22013007' due to data quality issues.
The output excluded any hGH treatment dosage data beyond the following ranges: Daily hGH Dose: 0.12 – 0.70 mg/kg/week and Ngenla hGH dose: 0.40 – 0.80 mg/kg/week. There were few patients with Other units such as 'mg/week, mg/weekly, mg every 7 days, mg daily, mg/day, mg/daily, mg per day, mg alternative days'. These units were not converted into the mg/kg/week.
Race and ethnicity were set to Missing when the site did not complete the respective variable in the eCRF. Unknown/Not Available/Not Reported was an option in the eCRF that sites could select when the respective data could not be found in the medical record.
Not applicable/Not collected per local regulation was an option in the eCRF available for sites to select when the local ethics committee did not allow collection of race or the concept and categories of race was not understood by the site in a given country.
Source: Table 15.1.2, Appendix 8: Additional documents.

There were 393 patients in the age category of 3 to 8 years. Out of these patients, majority (n=383, 98.0%) of patients were not in puberty, of which 142 (96.6%) patients were in the Genotropin group, 102 (98.1%) were in the Other daily hGH group, and 139 (99.3%) were in the Ngenla group. A total of 262 (66.7%) patients were in prepuberty, out of which 109 (74.1%) were in Genotropin group, 59 (56.2%) were in Other daily hGH group, and 94 (66.7%) were in the Ngenla group (Table 7).

Overall majority of the patients from 3–8 years category were in pubic hair stage 1 (n=303, 78.1%), of which 123 (84.2%) patients were in the Genotropin group, 69 (67.0%) were in the Other daily hGH group, and 111 (79.9%) were in the Ngenla group. Overall, majority of the male patients were in genital stage 1 (n=172, 76.8%), of which 64 (80.0%) patients were in the Genotropin group, 39 (69.6%) were in the Other daily hGH group, and 69 (78.4%) were in the Ngenla group (Table 7).

The mean (SD) of both left and right testis volume for overall patients was 1.8 (0.75). The mean (SD) of both left and right testis volume for patients in Genotropin group was 1.6 (0.70), for Other daily hGH group was 1.8 (0.92) and for Ngenla group was 2.0 (0.65). The mean (SD) of both left and right testis volume among non-pubertal patients (n=134, 58.8%) overall was 1.8 (0.75). The mean (SD) of both left and right testis volume among non-pubertal patients in the Genotropin group (n=51, 63.8%) was 1.6 (0.70), in the Other daily hGH group (n=30, 51.7%) was 1.8 (0.92), and in the Ngenla group (n=53, 58.9%) was 2.0 (0.65) (Table 7).

Overall, majority of the female patients were in breast stage 1 (n=127, 77.0%), of which 57 (85.1%) patients were in the Genotropin group, 29 (61.7%) were in the Other daily hGH group, and 41 (80.4%) were in the Ngenla group (Table 7). None of the female patients (n=164) were in menarche. Details of their pubertal status are provided in Table 7.

Table 7 Pubertal Status in 3-8 (years) Age Category at Baseline by Treatment Groups

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
No. of patients in 3–8 years of age							393
Patient in puberty, n (%)							
Yes	5 (3.4)	0	1 (2.4)	1 (1.9)	2 (1.9)	1 (0.7)	8 (2.0)
No	142 (96.6)	8 (100)	41 (97.6)	53 (98.1)	102 (98.1)	139 (99.3)	383 (98.0)
Missing	0	0	0	1	1	1	2
Patient in prepuberty (derived), n (%)	109 (74.1)	5 (62.5)	18 (42.9)	36 (65.5)	59 (56.2)	94 (66.7)	262 (66.7)
Tanner breast stage <B2 and puberty induced =“"N"" (for females)	57 (38.8)	1 (12.5)	12 (28.6)	16 (29.1)	29 (27.6)	41 (29.1)	127 (32.3)
Maximum testis volume (left/right) <4 mL and puberty induced =“"N"" (for males)	52 (35.4)	4 (50.0)	6 (14.3)	20 (36.4)	30 (28.6)	53 (37.6)	135 (34.4)
Puberty induced, n (%)							
Yes	3 (2.0)	0	0	0	0	0	3 (0.8)
No	144 (98.0)	8 (100)	41 (100)	54 (100)	103 (100)	140 (100)	387 (99.2)
Missing	0	0	1	1	2	1	3

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Pubic hair stage, n (%)							
1	123 (84.2)	5 (62.5)	22 (53.7)	42 (77.8)	69 (67.0)	111 (79.9)	303 (78.1)
2	0	0	1 (2.4)	0	1 (1.0)	0	1 (0.3)
3	0	0	0	0	0	0	0
4	1 (0.7)	0	0	0	0	0	1 (0.3)
5	0	0	0	0	0	0	0
Unknown	22 (15.1)	3 (37.5)	18 (43.9)	12 (22.2)	33 (32.0)	28 (20.1)	83 (21.4)
Missing	1	0	1	1	2	2	5
Testis volume (left) (mL) [1]							
N	52	4	6	20	30	53	135
Mean (SD)	1.6 (0.70)	1.5 (1.00)	1.5 (1.22)	2.0 (0.83)	1.8 (0.92)	2.0 (0.65)	1.8 (0.75)
Median	1.5	1.0	2.0	2.0	2.0	2.0	2.0
Q1; Q3	1.0; 2.0	1.0; 2.0	0.0; 2.0	1.5; 2.5	1.0; 2.0	2.0; 2.0	1.0; 2.0
Min; Max	0.0; 3.0	1.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0
Missing	28	2	15	11	28	37	93
Testis volume by Pubertal Status (left) (mL), n (%)[1]							
Pubertal patients	1 (1.3)	0	0	0	0	0	1 (0.4)
N	1	0	0	0	0	0	1
Mean (SD)	2.0 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	2.0 (-)
Median	2.0	-	-	-	-	-	2.0
Q1; Q3	2.0; 2.0	-; -	-; -	-; -	-; -	-; -	2.0; 2.0
Min; Max	2.0; 2.0	-; -	-; -	-; -	-; -	-; -	2.0; 2.0
Missing	0	0	0	0	0	1	1

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Not pubertal patients	51 (63.8)	4 (66.7)	6 (28.6)	20 (64.5)	30 (51.7)	53 (58.9)	134 (58.8)
N	51	4	6	20	30	53	134
Mean (SD)	1.6 (0.70)	1.5 (1.00)	1.5 (1.22)	2.0 (0.83)	1.8 (0.92)	2.0 (0.65)	1.8 (0.75)
Median	1.0	1.0	2.0	2.0	2.0	2.0	2.0
Q1; Q3	1.0; 2.0	1.0; 2.0	0.0; 2.0	1.5; 2.5	1.0; 2.0	2.0; 2.0	1.0; 2.0
Min; Max	0.0; 3.0	1.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0
Missing	28	2	15	10	27	36	91
Testis volume (right) (mL) [1]							
N	52	4	6	20	30	53	135
Mean (SD)	1.6 (0.70)	1.5 (1.00)	1.5 (1.22)	2.0 (0.83)	1.8 (0.92)	2.0 (0.65)	1.8 (0.75)
Median	1.5	1.0	2.0	2.0	2.0	2.0	2.0
Q1; Q3	1.0; 2.0	1.0; 2.0	0.0; 2.0	1.5; 2.5	1.0; 2.0	2.0; 2.0	1.0; 2.0
Min; Max	0.0; 3.0	1.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0
Missing	28	2	15	11	28	37	93
Testis volume by Pubertal Status (right) (mL), n (%)[1]							
Pubertal patients	1 (1.3)	0	0	0	0	0	1 (0.4)
N	1	0	0	0	0	0	1
Mean (SD)	2.0 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	2.0 (-)
Median	2.0	-	-	-	-	-	2.0
Q1; Q3	2.0; 2.0	-; -	-; -	-; -	-; -	-; -	2.0; 2.0
Min; Max	2.0; 2.0	-; -	-; -	-; -	-; -	-; -	2.0; 2.0
Missing	0	0	0	0	0	1	1
Not pubertal patients	51 (63.8)	4 (66.7)	6 (28.6)	20 (64.5)	30 (51.7)	53 (58.9)	134 (58.8)
N	51	4	6	20	30	53	134

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Mean (SD)	1.6 (0.70)	1.5 (1.00)	1.5 (1.22)	2.0 (0.83)	1.8 (0.92)	2.0 (0.65)	1.8 (0.75)
Median	1.0	1.0	2.0	2.0	2.0	2.0	2.0
Q1; Q3	1.0; 2.0	1.0; 2.0	0.0; 2.0	1.5; 2.5	1.0; 2.0	2.0; 2.0	1.0; 2.0
Min; Max	0.0; 3.0	1.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0
Missing	28	2	15	10	27	36	91
Genital stage (male), n (%)[1]							
1	64 (80.0)	4 (66.7)	11 (55.0)	24 (80.0)	39 (69.6)	69 (78.4)	172 (76.8)
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0
Unknown	16 (20.0)	2 (33.3)	9 (45.0)	6 (20.0)	17 (30.4)	19 (21.6)	52 (23.2)
Missing	0	0	1	1	2	2	4
Breast stage (female), n (%)[1]							
1	57 (85.1)	1 (50.0)	12 (57.1)	16 (66.7)	29 (61.7)	41 (80.4)	127 (77.0)
2	2 (3.0)	0	1 (4.8)	2 (8.3)	3 (6.4)	1 (2.0)	6 (3.6)
3	2 (3.0)	0	0	0	0	0	2 (1.2)
4	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0
Unknown	6 (9.0)	1 (50.0)	8 (38.1)	6 (25.0)	15 (31.9)	9 (17.6)	30 (18.2)
Missing	0	0	0	0	0	0	0
Breast stage (female) by Pubertal Status, n (%)[2]							

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Pubertal patients	4 (6.0)	0	1 (4.8)	1 (4.2)	2 (4.3)	0	6 (3.6)
1	0	0	0	0	0	0	0
2	2 (3.0)	0	1 (4.8)	0	1 (2.1)	0	3 (1.8)
3	2 (3.0)	0	0	0	0	0	2 (1.2)
4	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0
Unknown	0	0	0	1 (4.2)	1 (2.1)	0	1 (0.6)
Not pubertal patients	63 (94.0)	2 (100)	20 (95.2)	23 (95.8)	45 (95.7)	50 (98.0)	158 (95.8)
1	57 (85.1)	1 (50.0)	12 (57.1)	16 (66.7)	29 (61.7)	41 (80.4)	127 (77.0)
2	0	0	0	2 (8.3)	2 (4.3)	1 (2.0)	3 (1.8)
3	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0
Unknown	6 (9.0)	1 (50.0)	8 (38.1)	5 (20.8)	14 (29.8)	8 (15.7)	28 (17.0)
Menarche, n (%)[2]							
Yes	0	0	0	0	0	0	0
No	67 (100)	2 (100)	21 (100)	24 (100)	47 (100)	50 (100)	164 (100)
Missing	0	0	0	0	0	1	1

hGH: Human Growth Hormone; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard Deviation
Percentages are calculated using non-missing values for the given age category as denominator.
1.Percentages are based on the number of male patients in the treatment group.
2.Percentages are based on the number of female patients in the treatment group.
Source: Table 15.1.4, Appendix 8: Additional documents.

There were a total of 1106 patients in the age category of 9 to 18 years. Out of these, overall, 664 (60.7%) patients were in puberty, of which 370 (66.5%) patients were in the Genotropin group, 150 (62.2%) were in the Other daily hGH group, and 144 (48.5%) were in the Ngenla group. A total of 294 (26.6%) patients were in prepuberty, out of which overall, 130 (23.2%) were in the Genotropin group, 62 (25.1%) were in the Other daily hGH group, and 102 (34.1%) were in the Ngenla group (Table 8).

Overall, majority of the patients from 9–18 years category were in pubic hair stage 1 (n=396, 36.1%), of which 199 (35.7%) patients were in the Genotropin group, 69 (28.5%) were in the

Other daily hGH group, and 128 (43.0%) were in the Ngenla group. Overall, majority of the male patients were in genital stage 1 (n=254, 32.6%), followed by unknown stage (n=206, 26.4%). Majority of the male patients from Genotropin group were in stage 1 (n=125, 30.9%), from the Other daily hGH group were in unknown stage (n=54, 31.6%), and from the Ngenla group were in stage 1 (n=88, 43.1%) (Table 8).

The mean (SD) left testis volume for overall patients was 7.1 (5.92). The mean (SD) left testis volume for patients in Genotropin group was 7.5 (5.81), for Other daily hGH group was 6.8 (5.85), and for Ngenla group was 6.4 (6.16). The mean (SD) left testis volume among pubertal patients (n=350, 44.6%) overall was 9.6 (6.02). The mean (SD) left testis volume among pubertal patients in the Genotropin group (n=213, 52.6%) was 9.5 (5.81), in the Other daily hGH group (n=71, 40.6%) was 9.5 (6.27), and in the Ngenla group (n=66, 32.2%) was 10.1 (6.49). The mean (SD) left testis volume among non-pubertal patients (n=224, 28.5%) overall was 3.1 (2.60). The mean (SD) left testis volume among non-pubertal patients in the Genotropin group (n=93, 23.0%) was 2.8 (1.47), in the Other daily hGH group (n=57, 32.6%) was 3.5 (2.85), and in the Ngenla group (n=74, 36.1%) was 3.1 (3.38) (Table 8).

The mean (SD) right testis volume for overall patients was 7.1 (5.90). The mean (SD) left testis volume for patients in Genotropin group was 7.5 (5.87), for Other daily hGH group was 7.0 (5.81), and for Ngenla group was 6.2 (6.00). The mean (SD) right testis volume among pubertal patients overall was 9.7 (6.00). The mean (SD) right testis volume among pubertal patients in the Genotropin group was 9.6 (5.84), in the Other daily hGH group was 9.6 (6.23), and in the Ngenla group was 9.8 (6.33). The mean (SD) right testis volume among non-pubertal patients overall was 3.1 (2.58). The mean (SD) right testis volume among non-pubertal patients in the Genotropin group was 2.8 (1.46), in the Other daily hGH group was 3.6 (2.81), and in the Ngenla group was 3.0 (3.35) (Table 8).

Overall, majority of the female patients were in breast stage 1 (n=84, 26.5%), followed by stage 2 (n=74, 23.3%). Majority of the female patients from Genotropin group were in stage 1 (n=41, 27.0%), from the Other daily hGH group were in stage 2 (n=18, 25.4%), and from the Ngenla group were in stage 1 (n=30, 31.9%). Overall, majority of the female pubertal patients were in breast stage 2 (n=66, 20.6%). Majority of the female patients from Genotropin group were in stage 2 (n=35, 22.6%), from the Other daily hGH group were in stage 2 (n=17, 23.6%), and from the Ngenla group were in unknown stage (n=17, 18.1%). Overall, majority of the female non-pubertal patients were in breast stage 1 (n=74, 23.1%), of which 35 (22.6%) were from Genotropin group, 20 (27.8%) were from the Other daily hGH group, and 44 (46.8%) were from the Ngenla group (Table 8). Majority of the female patients (n=267, 84.2%) were not in menarche. Details of their pubertal characteristics are given in Table 8.

Table 8 Pubertal Characteristics in 9-18 (year) Age Category at Baseline by Treatment Groups

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
No. of patients in 9–18 years of age							1106
Patient in puberty, n (%)							
Yes	370 (66.5)	11 (55.0)	68 (67.3)	71 (59.2)	150 (62.2)	144 (48.5)	664 (60.7)
No	186 (33.5)	9 (45.0)	33 (32.7)	49 (40.8)	91 (37.8)	153 (51.5)	430 (39.3)
Missing	4	0	3	3	6	2	12
Patient in prepuberty (derived), n (%)	130 (23.2)	5 (25.0)	23 (22.1)	34 (27.6)	62 (25.1)	102 (34.1)	294 (26.6)
Tanner breast stage<B2 and puberty induced =“"N"" (for females)	37 (6.6)	2 (10.0)	3 (2.9)	8 (6.5)	13 (5.3)	30 (10.0)	80 (7.2)
Maximum testis volume (left/right) <4 mL and puberty induced =“"N"" (for males)	98 (17.5)	3 (15.0)	20 (19.2)	29 (23.6)	52 (21.1)	73 (24.4)	223 (20.2)
Puberty induced, n (%)							
Yes	79 (14.2)	0	8 (7.9)	6 (5.0)	14 (5.8)	31 (10.5)	124 (11.4)
No	476 (85.8)	20 (100)	93 (92.1)	114 (95.0)	227 (94.2)	265 (89.5)	968 (88.6)
Missing	5	0	3	3	6	3	14
Pubic hair stage, n (%)							

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
1	199 (35.7)	7 (35.0)	27 (26.5)	35 (29.2)	69 (28.5)	128 (43.0)	396 (36.1)
2	84 (15.1)	3 (15.0)	13 (12.7)	25 (20.8)	41 (16.9)	35 (11.7)	160 (14.6)
3	74 (13.3)	1 (5.0)	15 (14.7)	21 (17.5)	37 (15.3)	22 (7.4)	133 (12.1)
4	71 (12.7)	1 (5.0)	14 (13.7)	13 (10.8)	28 (11.6)	12 (4.0)	111 (10.1)
5	24 (4.3)	2 (10.0)	7 (6.9)	7 (5.8)	16 (6.6)	14 (4.7)	54 (4.9)
Unknown	105 (18.9)	6 (30.0)	26 (25.5)	19 (15.8)	51 (21.1)	87 (29.2)	243 (22.2)
Missing	3	0	2	3	5	1	9
Testis volume (left) (mL)[1]							
n	306	8	56	64	128	140	574
Mean (SD)	7.5 (5.81)	7.3 (5.39)	7.2 (5.98)	6.5 (5.86)	6.8 (5.85)	6.4 (6.16)	7.1 (5.92)
Median	6.0	5.0	4.5	4.0	4.0	3.0	5.0
Q1; Q3	3.0; 10.0	3.0; 12.5	3.0; 10.0	3.0; 10.0	3.0; 10.0	2.0; 8.0	3.0; 10.0
Min; Max	0.0; 45.0	2.0; 15.0	0.0; 25.0	0.0; 25.0	0.0; 25.0	1.0; 25.0	0.0; 45.0
Missing	99	5	20	22	47	65	211
Testis volume by Pubertal Status (left) (mL), n (%)[1]							
Pubertal patients	213 (52.6)	4 (30.8)	31 (40.8)	36 (41.9)	71 (40.6)	66 (32.2)	350 (44.6)
n	213	4	31	36	71	66	350
Mean (SD)	9.5 (5.81)	10.0 (5.83)	9.9 (6.38)	9.2 (6.38)	9.5 (6.27)	10.1 (6.49)	9.6 (6.02)
Median	8.0	10.5	8.0	7.0	7.0	8.0	8.0
Q1; Q3	5.0; 12.0	5.0; 15.0	5.0; 15.0	4.0; 12.0	4.0; 15.0	5.0; 12.0	5.0; 12.0
Min; Max	1.0; 45.0	4.0; 15.0	2.0; 25.0	2.0; 25.0	2.0; 25.0	2.0; 25.0	1.0; 45.0

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Missing	56	3	15	10	28	28	112
Not pubertal patients	93 (23.0)	4 (30.8)	25 (32.9)	28 (32.6)	57 (32.6)	74 (36.1)	224 (28.5)
n	93	4	25	28	57	74	224
Mean (SD)	2.8 (1.47)	4.5 (3.70)	3.8 (3.18)	3.1 (2.42)	3.5 (2.85)	3.1 (3.38)	3.1 (2.60)
Median	3.0	3.0	3.0	3.0	3.0	2.0	3.0
Q1; Q3	2.0; 3.0	2.5; 6.5	3.0; 3.0	2.0; 3.0	2.0; 3.0	2.0; 3.0	2.0; 3.0
Min; Max	0.0; 9.0	2.0; 10.0	0.0; 15.0	0.0; 12.0	0.0; 15.0	1.0; 24.0	0.0; 24.0
Missing	42	2	3	9	14	35	91
Testis volume (right) (mL) [1]							
n	306	8	55	64	127	140	573
Mean (SD)	7.5 (5.87)	7.8 (6.69)	7.4 (5.94)	6.5 (5.65)	7.0 (5.81)	6.2 (6.00)	7.1 (5.90)
Median	6.0	5.0	5.0	4.0	4.0	3.0	5.0
Q1; Q3	3.0; 10.0	2.5; 12.5	3.0; 10.0	3.0; 10.0	3.0; 10.0	2.0; 8.0	3.0; 10.0
Min; Max	0.0; 40.0	2.0; 20.0	0.0; 25.0	0.0; 25.0	0.0; 25.0	0.0; 25.0	0.0; 40.0
Missing	99	5	21	22	48	65	212
Testis volume by Pubertal Status (right) (mL), n (%)[1]							
Pubertal patients	213 (52.6)	4 (30.8)	31 (40.8)	36 (41.9)	71 (40.6)	66 (32.2)	350 (44.6)
n	213	4	31	36	71	66	350
Mean (SD)	9.6 (5.84)	11.3 (7.54)	9.9 (6.32)	9.1 (6.16)	9.6 (6.23)	9.8 (6.33)	9.7 (6.00)
Median	8.0	10.5	8.0	6.5	8.0	8.0	8.0
Q1; Q3	5.0; 12.0	5.0; 17.5	5.0; 15.0	4.0; 12.0	4.0; 15.0	5.0; 12.0	5.0; 12.0

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Min; Max	1.0; 40.0	4.0; 20.0	2.0; 25.0	2.0; 25.0	2.0; 25.0	0.0; 25.0	0.0; 40.0
Missing	56	3	15	10	28	28	112
Not pubertal patients	93 (23.0)	4 (30.8)	24 (31.6)	28 (32.6)	56 (32.0)	74 (36.1)	223 (28.4)
n	93	4	24	28	56	74	223
Mean (SD)	2.8 (1.46)	4.3 (3.86)	4.1 (3.30)	3.1 (2.16)	3.6 (2.81)	3.0 (3.35)	3.1 (2.58)
Median	3.0	2.5	3.0	3.0	3.0	2.0	3.0
Q1; Q3	2.0; 3.0	2.0; 6.5	3.0; 3.0	2.0; 3.0	2.0; 3.0	2.0; 3.0	2.0; 3.0
Min; Max	0.0; 9.0	2.0; 10.0	0.0; 15.0	0.0; 10.0	0.0; 15.0	1.0; 24.0	0.0; 24.0
Missing	42	2	4	9	15	35	92
Genital stage (male), n (%)[1]							
1	125 (30.9)	2 (15.4)	15 (20.0)	24 (28.9)	41 (24.0)	88 (43.1)	254 (32.6)
2	53 (13.1)	3 (23.1)	10 (13.3)	18 (21.7)	31 (18.1)	22 (10.8)	106 (13.6)
3	66 (16.3)	0	9 (12.0)	7 (8.4)	16 (9.4)	20 (9.8)	102 (13.1)
4	42 (10.4)	2 (15.4)	10 (13.3)	7 (8.4)	19 (11.1)	10 (4.9)	71 (9.1)
5	22 (5.4)	0	5 (6.7)	5 (6.0)	10 (5.8)	9 (4.4)	41 (5.3)
Unknown	97 (24.0)	6 (46.2)	26 (34.7)	22 (26.5)	54 (31.6)	55 (27.0)	206 (26.4)
Missing	0	0	1	3	4	1	5
Breast stage (female), n (%)[2]							
1	41 (27.0)	2 (28.6)	3 (11.1)	8 (21.6)	13 (18.3)	30 (31.9)	84 (26.5)
2	39 (25.7)	2 (28.6)	5 (18.5)	11 (29.7)	18 (25.4)	17 (18.1)	74 (23.3)
3	27 (17.8)	1 (14.3)	4 (14.8)	6 (16.2)	11 (15.5)	11 (11.7)	49 (15.5)

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
4	24 (15.8)	0	1 (3.7)	5 (13.5)	6 (8.5)	5 (5.3)	35 (11.0)
5	5 (3.3)	1 (14.3)	4 (14.8)	1 (2.7)	6 (8.5)	3 (3.2)	14 (4.4)
Unknown	16 (10.5)	1 (14.3)	10 (37.0)	6 (16.2)	17 (23.9)	28 (29.8)	61 (19.2)
Missing	3	0	1	0	1	0	4
Breast stage (female) by Pubertal Status, n (%)[2]							
Pubertal patients	101 (65.2)	4 (57.1)	22 (78.6)	25 (67.6)	51 (70.8)	50 (53.2)	202 (62.9)
1	6 (3.9)	0	1 (3.6)	1 (2.7)	2 (2.8)	2 (2.1)	10 (3.1)
2	35 (22.6)	2 (28.6)	5 (17.9)	10 (27.0)	17 (23.6)	14 (14.9)	66 (20.6)
3	22 (14.2)	0	3 (10.7)	5 (13.5)	8 (11.1)	10 (10.6)	40 (12.5)
4	23 (14.8)	0	1 (3.6)	5 (13.5)	6 (8.3)	4 (4.3)	33 (10.3)
5	5 (3.2)	1 (14.3)	4 (14.3)	1 (2.7)	6 (8.3)	3 (3.2)	14 (4.4)
Unknown	10 (6.5)	1 (14.3)	8 (28.6)	3 (8.1)	12 (16.7)	17 (18.1)	39 (12.1)
Not pubertal patients	51 (32.9)	3 (42.9)	5 (17.9)	12 (32.4)	20 (27.8)	44 (46.8)	115 (35.8)
1	35 (22.6)	2 (28.6)	2 (7.1)	7 (18.9)	11 (15.3)	28 (29.8)	74 (23.1)
2	4 (2.6)	0	0	1 (2.7)	1 (1.4)	3 (3.2)	8 (2.5)
3	5 (3.2)	1 (14.3)	1 (3.6)	1 (2.7)	3 (4.2)	1 (1.1)	9 (2.8)
4	1 (0.6)	0	0	0	0	1 (1.1)	2 (0.6)
5	0	0	0	0	0	0	0
Unknown	6 (3.9)	0	2 (7.1)	3 (8.1)	5 (6.9)	11 (11.7)	22 (6.9)
Menarche, n (%)[2]							
Yes	24 (15.8)	2 (28.6)	5 (18.5)	7 (18.9)	14 (19.7)	12 (12.8)	50 (15.8)

Pubertal Status	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
No	128 (84.2)	5 (71.4)	22 (81.5)	30 (81.1)	57 (80.3)	82 (87.2)	267 (84.2)
Missing	3	0	1	0	1	0	4

hGH: human Growth Hormone; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard Deviation.
Percentages are calculated using non-missing values for the given age category as denominator.
1.Percentages are based on the number of male patients in the treatment group.
2.Percentages are based on the number of female patients in the treatment group.
Source: Table 15.1.4, Appendix 8: Additional documents.

There were 5 patients in the age category of ≥19 years and were reported as being in puberty at enrollment. Two patients (40.0%) were in pubic hair stage 4, and 1 each in stage 2, stage 5, and unknown stage. The only male patient was in genital stage 4, while 3 female patients were in breast stage 5 and 1 was in unknown stage. All 4 female patients had onset of menarche. The full table for the ≥19 years age group is available in Source Table 15.1.4 in Appendix 8).

10.2.2. Birth History by Treatment Groups

The mean (SD) birth weight for patients overall was 2.9 (0.69) kg. For patients in the Genotropin group the mean (SD) birth weight was 2.9 (0.70) kg, for patients in the Other daily hGH group it was 2.9 (0.71) kg, and for Ngenla group it was 2.9 (0.67) kg. Data were not available for 160 patients: 74 patients in the Genotropin group, 58 in the Other daily hGH group, and 28 in the Ngenla group (Table 9).

The mean (SD) birth weight SDS for patients overall was -1.0 (1.81). For patients in the Genotropin group the mean (SD) birth weight SDS was -1.1 (1.81), for patients in the Other daily hGH group it was -1.1 (1.87), and for Ngenla group it was -1.0 (1.79). Most patients (n=1096, 80.8%) had birth weight SDS >-2. Among the Genotropin group, the Other daily hGH group, and Ngenla group, 510 (79.4%) patients, 242 (80.4%) patients, and 344 (83.3%) patients had birth weight SDS >-2, respectively (Table 9).

Data for birth length were available for 973 patients, of which 437 were in the Genotropin group, 194 were in the Other daily hGH group, and 342 in the Ngenla group. The mean (SD) birth length for the overall patients was 47.8 (3.81) cm. For patients in the Genotropin group the mean (SD) birth length was 47.7 (4.19) cm, for patients in the Other daily hGH group it was 47.6 (3.84) cm, and for Ngenla group it was 48.2 (3.23) cm (Table 9).

The mean (SD) birth length SDS for patients overall was -1.0 (2.01). For patients in the Genotropin group the mean (SD) birth length SDS was -1.0 (2.21), for patients in the Other daily hGH group it was -1.1 (2.02), and for Ngenla group it was -0.8 (1.71). Most patients (n=770, 79.1%) had birth length SDS >-2. Among the Genotropin group, the Other daily hGH group, and the Ngenla group, 343 (78.5%), 146 (75.3%), and 281 (82.2%) patients had birth length SDS >-2, respectively (Table 9).

Data for birth head circumference were missing for the majority (1096 out of 1516) of patients. The mean (SD) birth head circumference for the remaining overall patients was 33.5 (2.53) cm. For patients in the Genotropin group the mean (SD) birth head circumference was 33.4 (2.72) cm, for patients in the Other daily hGH group it was 33.4 (2.54) cm, and for Ngenla group it was 33.7 (2.27) cm (Table 9).

The mean (SD) gestational age of patients overall was 38.1 (2.96) weeks. Among patients in the Genotropin group, the mean (SD) gestational age was 38.1 (2.78) weeks, for patients in the Other daily hGH group it was 37.9 (3.17) weeks, and in the Ngenla group it was 38.2 (3.06) weeks. Data for gestational age were missing for overall 254 patients (of which 130 were in the Genotropin group, 73 were in the Other daily hGH group, and 51 in the Ngenla group) (Table 9).

For most patients, the delivery method was either normal (n=689, 45.4%) or unknown (n=477, 31.5%) overall. For the Genotropin group, delivery method was normal in nearly half of patients (n=327, 45.7%). For the Other daily hGH group patients, the most common method of delivery was normal (n=154, 42.9%). For the Ngenla group, the most common method of delivery was normal (n=208, 47.2%) (Table 9).

Overall, no instrument was used for delivery for most patients (n=782, 51.6%) followed by unknown instrument used (n=694, 45.8%). In the Genotropin group, a similar number of patients reported use of no instruments (n=344, 48.0%) or unknown instruments (n=354, 49.4%) for delivery. In the Other daily hGH group, approximately half of the patients (n=177, 49.3%) reported use of no instruments for delivery. Similarly, in the Ngenla group, no instrument was used for delivery for over half of the patients (n=261, 59.2%) (Table 9).

Data on Apgar scores (1, 5, and 10 minutes) were missing for majority of the patients (n=1150, 1148, and 1385, respectively) (Source Table 15.1.5, Appendix 8.1).

Table 9 Birth History by Treatment Groups

History of Birth	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Birth weight (kg)							
n	642	22	119	160	301	413	1356
Mean (SD)	2.9 (0.70)	3.1 (0.65)	2.9 (0.79)	2.9 (0.67)	2.9 (0.71)	2.9 (0.67)	2.9 (0.69)
Median	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Q1; Q3	2.5; 3.3	2.7; 3.5	2.5; 3.5	2.6; 3.3	2.6; 3.4	2.6; 3.4	2.6; 3.3
Min; Max	0.5; 7.5	1.8; 4.3	0.4; 4.4	0.9; 4.3	0.4; 4.4	0.5; 4.4	0.4; 7.5
Missing	74	6	31	21	58	28	160

History of Birth	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Birth weight SDS							
n	642	22	119	160	301	413	1356
Mean (SD)	-1.1 (1.81)	-0.6 (1.48)	-1.1 (2.10)	-1.1 (1.74)	-1.1 (1.87)	-1.0 (1.79)	-1.0 (1.81)
Median	-0.7	-0.7	-0.7	-0.7	-0.7	-0.6	-0.7
Q1; Q3	-1.7; 0.0	-1.4; 0.6	-1.7; 0.3	-1.7; -0.0	-1.7; 0.1	-1.5; 0.1	-1.7; 0.1
Min; Max	-9.6; 6.4	-3.8; 1.8	-10.0; 1.9	-7.4; 1.8	-10.0; 1.9	-9.5; 2.0	-10.0; 6.4
Missing	74	6	31	21	58	28	160
SDS ≤-2%	132 (20.6)	3 (13.6)	27 (22.7)	29 (18.1)	59 (19.6)	69 (16.7)	260 (19.2)
SDS >-2%	510 (79.4)	19 (86.4)	92 (77.3)	131 (81.9)	242 (80.4)	344 (83.3)	1096 (80.8)
Birth length (cm)							
n	437	4	72	118	194	342	973
Mean (SD)	47.7 (4.19)	46.6 (0.48)	47.8 (3.99)	47.5 (3.82)	47.6 (3.84)	48.2 (3.23)	47.8 (3.81)
Median	48.3	46.8	48.3	48.0	48.2	48.9	48.3
Q1; Q3	46.5; 50.0	46.3; 47.0	45.6; 50.8	46.0; 50.0	46.0; 50.0	47.0; 50.0	46.5; 50.0
Min; Max	25.4; 56.0	46.0; 47.0	35.0; 53.8	32.5; 54.0	32.5; 54.0	31.0; 59.0	25.4; 59.0
Missing	279	24	78	63	165	99	543
Birth length SDS							
n	437	4	72	118	194	342	973
Mean (SD)	-1.0 (2.21)	-1.5 (0.11)	-1.0 (2.08)	-1.2 (2.02)	-1.1 (2.02)	-0.8 (1.71)	-1.0 (2.01)
Median	-0.7	-1.5	-0.5	-0.7	-0.7	-0.5	-0.6
Q1; Q3	-1.7; 0.1	-1.6; -1.5	-2.1; 0.5	-1.8; 0.1	-2.0; 0.1	-1.5; 0.1	-1.5; 0.1
Min; Max	-12.9; 3.2	-1.7; -1.4	-7.6; 2.5	-8.9; 2.2	-8.9; 2.5	-10.0; 4.8	-12.9; 4.8

History of Birth	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Missing	279	24	78	63	165	99	543
SDS ≤-2%	94 (21.5)	0	19 (26.4)	29 (24.6)	48 (24.7)	61 (17.8)	203 (20.9)
SDS >-2%	343 (78.5)	4 (100)	53 (73.6)	89 (75.4)	146 (75.3)	281 (82.2)	770 (79.1)
Birth head circumference (cm)							
n	171	2	36	67	105	144	420
Mean (SD)	33.4 (2.72)	33.5 (0.07)	33.8 (2.39)	33.2 (2.65)	33.4 (2.54)	33.7 (2.27)	33.5 (2.53)
Median	33.5	33.5	34.0	33.5	34.0	34.0	34.0
Q1; Q3	32.5; 35.0	33.4; 33.5	32.9; 35.0	32.0; 35.0	32.0; 35.0	33.0; 35.0	32.5; 35.0
Min; Max	22.0; 39.0	33.4; 33.5	26.0; 38.0	24.0; 39.0	24.0; 39.0	23.5; 39.0	22.0; 39.0
Missing	545	26	114	114	254	297	1096
Gestational age (weeks)							
n	586	21	117	148	286	390	1262
Mean (SD)	38.1 (2.78)	38.3 (2.11)	37.7 (3.32)	38.1 (3.17)	37.9 (3.17)	38.2 (3.06)	38.1 (2.96)
Median	39.0	38.0	39.0	39.0	39.0	39.0	39.0
Q1; Q3	37.0; 40.0	38.0; 39.0	37.0; 40.0	37.0; 40.0	37.0; 40.0	37.0; 40.0	37.0; 40.0
Min; Max	24.0; 42.0	32.0; 42.0	27.0; 42.0	24.0; 42.0	24.0; 42.0	24.0; 42.0	24.0; 42.0
Missing	130	7	33	33	73	51	254
Delivery method of gestational age, n (%)							
Normal	327 (45.7)	15 (53.6)	55 (36.7)	84 (46.4)	154 (42.9)	208 (47.2)	689 (45.4)
Breech	4 (0.6)	0	0	0	0	1 (0.2)	5 (0.3)

History of Birth	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
C-section	153 (21.4)	5 (17.9)	38 (25.3)	45 (24.9)	88 (24.5)	90 (20.4)	331 (21.8)
Other	3 (0.4)	0	2 (1.3)	1 (0.6)	3 (0.8)	3 (0.7)	9 (0.6)
Unknown	226 (31.6)	8 (28.6)	54 (36.0)	50 (27.6)	112 (31.2)	139 (31.5)	477 (31.5)
Instrument, n (%)[1]							
None	344 (48.0)	15 (53.6)	65 (43.3)	97 (53.6)	177 (49.3)	261 (59.2)	782 (51.6)
Vacuum-extractor	7 (1.0)	0	3 (2.0)	5 (2.8)	8 (2.2)	4 (0.9)	19 (1.3)
Forceps	8 (1.1)	0	2 (1.3)	5 (2.8)	7 (1.9)	0	15 (1.0)
Unknown	354 (49.4)	13 (46.4)	79 (52.7)	72 (39.8)	164 (45.7)	176 (39.9)	694 (45.8)
Apgar Score							
1 minute							
n	138	4	31	63	98	130	366
Mean (SD)	8.2 (2.01)	8.0 (1.41)	7.2 (2.34)	8.3 (2.08)	7.9 (2.19)	7.8 (2.57)	8.0 (2.27)
Median	9.0	8.5	8.0	9.0	9.0	9.0	9.0
Q1; Q3	8.0; 9.0	7.0; 9.0	6.0; 9.0	8.0; 9.0	7.0; 9.0	7.0; 9.0	8.0; 9.0
Min; Max	0.0; 10.0	6.0; 9.0	1.0; 10.0	1.0; 10.0	1.0; 10.0	0.0; 10.0	0.0; 10.0
Missing	578	24	119	118	261	311	1150
5 minutes							
n	138	4	28	65	97	133	368
Mean (SD)	9.2 (1.35)	9.3 (0.96)	8.5 (1.97)	9.4 (1.26)	9.1 (1.53)	9.1 (1.39)	9.1 (1.41)
Median	10.0	9.5	9.0	10.0	10.0	10.0	10.0
Q1; Q3	9.0; 10.0	8.5; 10.0	8.0; 10.0	9.0; 10.0	9.0; 10.0	9.0; 10.0	9.0; 10.0
Min; Max	3.0; 10.0	8.0; 10.0	1.0; 10.0	2.0; 10.0	1.0; 10.0	3.0; 10.0	1.0; 10.0
Missing	578	24	122	116	262	308	1148

History of Birth	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
10 minutes							
n	31	1	13	23	37	63	131
Mean (SD)	9.0 (2.09)	8.0 (-)	8.1 (2.93)	9.5 (0.95)	9.0 (1.98)	9.4 (1.00)	9.2 (1.62)
Median	10.0	8.0	9.0	10.0	10.0	10.0	10.0
Q1; Q3	9.0; 10.0	8.0; 8.0	8.0; 10.0	9.0; 10.0	9.0; 10.0	9.0; 10.0	9.0; 10.0
Min; Max	0.0; 10.0	8.0; 8.0	0.0; 10.0	6.0; 10.0	0.0; 10.0	5.0; 10.0	0.0; 10.0
Missing	685	27	137	158	322	378	1385

Apgar: Appearance, Pulse, Grimace, Activity and Respiration; hGH: Human Growth Hormone; Min: Minimum; Max: Maximum; SDS: Standard Deviation Score; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; WHO: World Health Organization.
Percentages are calculated using non-missing values as denominator.
[1] The summed percentage can be more than 100% as more than one option can be selected.
Reference population from Growth Analyzer for Birth Length and Birth Weight: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined).
Birth length and Birth length SDS have been removed for patients '26027016' and '26027140' due to data issues.
Source: Table 15.1.5, Appendix 8: Additional documents.

10.2.3. Family History

Overall, 69 patients were reported as being twins. Among patients overall, 61.2% (n=921) reported no history of GHD in the family while data were unknown for 27.7% (n=417) patients (Table 10).

The mean (SD) father's (biological) height was 173.3 (7.62) cm overall. Among patients in the Genotropin group, the mean (SD) father's height was 172.8 (7.53) cm, for patients in the Other daily hGH group it was 175.0 (8.00) cm, and for Ngenla group it was 172.7 (7.29) cm (Table 10).

The mean (SD) (biological) mother's height was 159.5 (7.19) cm overall. Among patients in the Genotropin group, the mean (SD) mother's height was 159.0 (7.24) cm, for patients in the Other daily hGH group it was 160.4 (7.46) cm, and for Ngenla group it was 159.6 (6.85) cm (Table 10).

For more than half of patients overall (n=872, 59.6%), father's puberty timing (growth spurt) was unknown and for 456 (31.2%) it was normal. The timing of father's puberty was reported as normal by less than half patients in the Genotropin group (n=248, 35.9%), in the Other daily hGH group (n=107, 31.0%), and in the Ngenla group (n=101, 23.7%) (Table 10).

The mother's age at menarche was between 12 to 14 years for 44.7% (n=309), 42.0% (n=145), and 33.6% (n=143) patients in the Genotropin group, Other daily hGH group, Ngenla group, respectively.

Most of the patients (n=1009, 67.9%) had at least one sibling. The mean (SD) siblings' height was 113.3 (49.77) cm overall. Among patients in the Genotropin group, the mean (SD) siblings' height was 116.1 (48.28) cm, for patients in the Other daily hGH group it was 123.1 (50.48) cm, and for Ngenla group it was 82.1 (43.59) cm. Most of the siblings' data for growth issues were missing (n=1197) (Table 10).

Table 10 Family History by Treatment Groups

Family History	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Twin, n (%)							
Yes	45 (6.4)	2 (7.4)	7 (4.8)	3 (1.7)	12 (3.4)	12 (2.7)	69 (4.6)
No	659 (93.6)	25 (92.6)	140 (95.2)	175 (98.3)	340 (96.6)	427 (97.3)	1426 (95.4)
Missing	12	1	3	3	7	2	21
History of GHD in the family, n (%)							
Yes	90 (12.6)	2 (7.1)	15 (10.2)	22 (12.2)	39 (11.0)	38 (8.7)	167 (11.1)
No	376 (52.8)	15 (53.6)	90 (61.2)	123 (68.3)	228 (64.2)	317 (72.4)	921 (61.2)
Unknown	246 (34.6)	11 (39.3)	42 (28.6)	35 (19.4)	88 (24.8)	83 (18.9)	417 (27.7)
Missing	4	0	3	1	4	3	11
Father's (biological) height (cm)							
n	612	22	118	152	292	396	1300
Mean (SD)	172.8 (7.53)	172.8 (6.20)	175.9 (7.89)	174.7 (8.26)	175.0 (8.00)	172.7 (7.29)	173.3 (7.62)
Median	172.7	174.5	175.3	175.0	175.0	172.0	173.0
Q1; Q3	168.0; 177.8	169.0; 177.8	170.2; 181.0	168.0; 180.0	169.0; 180.3	168.0; 177.4	168.0; 178.0
Min; Max	146.0; 195.6	160.0; 180.3	156.0; 195.0	156.5; 198.0	156.0; 198.0	154.2; 198.1	146.0; 198.1
Missing	104	6	32	29	67	45	216
Father's (biological)							

Family History	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
height SDS (cm)							
n	612	22	118	152	292	396	1300
Mean (SD)	0.1 (1.41)	0.2 (1.43)	0.6 (1.61)	0.4 (1.62)	0.5 (1.60)	0.1 (1.37)	0.2 (1.45)
Median	-0.0	-0.2	0.5	0.2	0.3	-0.1	0.0
Q1; Q3	-0.9; 1.0	-0.9; 1.9	-0.8; 1.6	-0.9; 1.6	-0.9; 1.6	-0.9; 1.0	-0.9; 1.2
Min; Max	-4.2; 5.0	-2.3; 2.4	-2.8; 4.9	-2.7; 4.6	-2.8; 4.9	-3.1; 5.3	-4.2; 5.3
Missing	104	6	32	29	67	45	216
Mother's (biological) height (cm)							
n	619	22	119	151	292	402	1313
Mean (SD)	159.0 (7.24)	158.4 (10.77)	161.4 (7.48)	160.0 (6.79)	160.4 (7.46)	159.6 (6.85)	159.5 (7.19)
Median	158.0	154.9	160.0	160.0	160.0	159.0	159.0
Q1; Q3	154.0; 163.8	152.0; 162.6	157.0; 167.0	156.0; 164.0	155.2; 165.0	155.0; 164.0	154.9; 164.0
Min; Max	139.6; 180.3	142.2; 179.1	140.0; 183.0	134.6; 180.0	134.6; 183.0	140.0; 182.0	134.6; 183.0
Missing	97	6	31	30	67	39	203
Mother's (biological) height SDS (cm)							
n	619	22	119	151	292	402	1313
Mean (SD)	-1.9 (1.32)	-1.8 (1.85)	-1.5 (1.47)	-1.7 (1.32)	-1.6 (1.42)	-1.7 (1.25)	-1.8 (1.33)
Median	-2.0	-2.3	-1.6	-1.9	-1.9	-1.8	-1.9
Q1; Q3	-2.8; -0.9	-3.3; -0.9	-2.6; -0.5	-2.6; -0.7	-2.6; -0.6	-2.7; -0.9	-2.7; -0.9
Min; Max	-5.0; 2.3	-3.9; 2.2	-4.4; 2.6	-5.8; 2.6	-5.8; 2.6	-4.9; 2.3	-5.8; 2.6
Missing	97	6	31	30	67	39	203
Father's puberty timing							

Family History	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
(growth spurt), n (%)							
Early	9 (1.3)	1 (3.7)	0	2 (1.2)	3 (0.9)	1 (0.2)	13 (0.9)
Normal	248 (35.9)	9 (33.3)	40 (27.6)	58 (33.5)	107 (31.0)	101 (23.7)	456 (31.2)
Late	59 (8.5)	3 (11.1)	15 (10.3)	13 (7.5)	31 (9.0)	31 (7.3)	121 (8.3)
Unknown	375 (54.3)	14 (51.9)	90 (62.1)	100 (57.8)	204 (59.1)	293 (68.8)	872 (59.6)
Missing	25	1	5	8	14	15	54
Mother's puberty timing (age of menarche), n (%)							
<12 years	72 (10.4)	2 (7.4)	12 (8.3)	13 (7.5)	27 (7.8)	44 (10.3)	143 (9.8)
12-14 years	309 (44.7)	12 (44.4)	51 (35.2)	82 (47.4)	145 (42.0)	143 (33.6)	597 (40.8)
>14 years	77 (11.1)	3 (11.1)	18 (12.4)	10 (5.8)	31 (9.0)	40 (9.4)	148 (10.1)
Unknown	233 (33.7)	10 (37.0)	64 (44.1)	68 (39.3)	142 (41.2)	199 (46.7)	574 (39.3)
Missing	25	1	5	8	14	15	54
Siblings, n (%)							
Yes–- At least one	459 (65.7)	20 (74.1)	107 (73.8)	118 (67.0)	245 (70.4)	305 (69.6)	1009 (67.9)
No	240 (34.3)	7 (25.9)	38 (26.2)	58 (33.0)	103 (29.6)	133 (30.4)	476 (32.1)
Missing	17	1	5	5	11	3	31
Sibling weight (kg)							
n	50	1	11	14	26	17	93
n (siblings)	60	3	18	17	38	18	116
Mean (SD)	29.0 (23.01)	36.6 (19.57)	26.1 (19.21)	34.4 (24.39)	30.7 (21.61)	15.3 (18.44)	27.4 (22.36)
Median	26.0	28.1	22.7	41.1	32.4	3.3	24.3

Family History	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Q1; Q3	3.8; 49.6	22.7; 59.0	7.4; 41.4	3.4; 49.9	7.4; 45.4	3.1; 28.7	3.4; 46.4
Min; Max	1.7; 86.2	22.7; 59.0	3.0; 56.7	1.0; 78.0	1.0; 78.0	2.6; 53.9	1.0; 86.2
Missing/ Unknown	666	27	139	167	333	424	1423
Number of siblings, n (%)							
1	244 (53.4)	11 (57.9)	50 (47.6)	81 (68.6)	142 (58.7)	191 (63.0)	577 (57.6)
2	153 (33.5)	6 (31.6)	35 (33.3)	22 (18.6)	63 (26.0)	81 (26.7)	297 (29.6)
≥3	60 (13.1)	2 (10.5)	20 (19.0)	15 (12.7)	37 (15.3)	31 (10.2)	128 (12.8)
Sibling (s') height (cm)							
n	48	1	9	12	22	16	86
n (siblings)	57	3	17	15	35	16	108
Mean (SD)	116.1 (48.28)	144.8 (19.81)	130.7 (48.05)	110.2 (56.08)	123.1 (50.48)	82.1 (43.59)	113.3 (49.77)
Median	129.5	134.6	149.9	147.3	147.3	49.5	127.4
Q1; Q3	53.9; 158.8	132.1; 167.6	99.1; 162.6	47.3; 154.4	55.0; 157.5	47.8; 124.9	49.8; 157.0
Min; Max	26.2; 178.3	132.1; 167.6	48.0; 193.0	33.0; 176.3	33.0; 193.0	46.0; 160.8	26.2; 193.0
Missing/ Unknown	668	27	141	169	337	425	1430
At least one Sibling with growth issues, n (%)[1]							
Yes	48 (10.5)	0	12 (11.2)	13 (11.0)	25 (10.2)	15 (4.9)	88 (8.7)
No	90 (19.6)	4 (20.0)	28 (26.2)	29 (24.6)	61 (24.9)	80 (26.2)	231 (22.9)
Missing	578	24	110	139	273	346	1197

Family History	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Sibling (s') hGH diagnosis details, n (%)[1]							
Growth Hormone Deficiency	35 (7.6)	0	5 (4.7)	11 (9.3)	16 (6.5)	14 (4.6)	65 (6.4)
Turner syndrome	0	0	0	0	0	0	0
SGA/IUGR	5 (1.1)	0	2 (1.9)	1 (0.8)	3 (1.2)	1 (0.3)	9 (0.9)
Idiopathic Short Stature	1 (0.2)	0	2 (1.9)	1 (0.8)	3 (1.2)	0	4 (0.4)
Other	9 (2.0)	0	3 (2.8)	2 (1.7)	5 (2.0)	2 (0.7)	16 (1.6)

GHD: Growth Hormone Deficiency; hGH: Human Growth Hormone; IUGR: Intrauterine Growth Restriction; Min: Minimum; Max: Maximum; SDS: Standard Deviation Score; SD: Standard Deviation; SGA: Small for Gestational Age; Q1: First quartile; Q3: Third quartile; WHO: World Health Organization.
Percentages are calculated using non-missing values as denominator.
[1] Percentages are calculated using the number of patients with at least one sibling.
A patient can have one or more siblings with growth hormone issues.
The summary of sibling's weight and height is based on the number of siblings with available results.
Reference population from Growth Analyzer for Father's Height and Mother's Height: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined).SDS was calculated assuming the age of 20 years.
Source: Table 15.1.6, Appendix 8: Additional documents.

10.2.4. hGH Diagnosis

Among all patients, 1118 (74.5%) of patients had a primary hGH diagnosis of idiopathic GHD. Among patients in the Genotropin, the Other daily hGH group, and the Ngenla group, 541 (76.5%), 224 (63.1%), and 353 (80.6%) patients, respectively, had primary hGH diagnosis of idiopathic GHD. Among all patients with a secondary diagnosis, 27 (21.3%) patients had a secondary hGH diagnosis of idiopathic GHD and 2 (12.5%) patients had a third hGH diagnosis.

Among all patients, 67 (4.5%) of patients had a primary hGH diagnosis of small for gestational age/intrauterine growth restriction (SGA/IUGR). Among patients in the Genotropin, the Other daily hGH group, and the Ngenla group, 34 (4.8%), 27 (7.6%), and 6 (1.4%) patients, respectively, had primary hGH diagnosis of SGA/IUGR. Among all patients with a secondary diagnosis, 29 (22.8%) patients had a secondary hGH diagnosis of SGA/IUGR and 1 (6.3%) patient had a third hGH diagnosis (Table 11).

Among all patients, 29 (1.9%) of patients had a primary hGH diagnosis of Prader-Labhart-Willi/Prader-Willi Syndrome. Among patients in the Genotropin and the Other daily hGH group, 23 (3.3%) and 6 (1.7%) patients, respectively, had primary hGH diagnosis of Prader-Labhart-Willi/Prader-Willi Syndrome. None of the patients from the Ngenla group had a primary hGH diagnosis of Prader-Labhart-Willi/Prader-Willi Syndrome. Among all patients

with a secondary diagnosis, only 1 (0.8%) patient had a secondary hGH diagnosis of Prader-Labhart-Willi/Prader-Willi Syndrome and 1 (6.3%) patient had a third hGH diagnosis (Table 11).

Among all patients, 23 (1.5%) of patients had a primary hGH diagnosis of ISS. Among patients in the Genotropin, the Other daily hGH group, and the Ngenla group, 15 (2.1%), 6 (1.7%), and 2 (0.5%) patients had primary hGH diagnosis of ISS, respectively. Among all patients with a secondary diagnosis, only 7 (5.5%) patients had a secondary hGH diagnosis of ISS and 1 (6.3%) patient had a third hGH diagnosis (Table 11).

The mean (SD) age at the time of primary diagnosis was 7.9 (4.10) years for all patients. For patients in the Genotropin group, the mean (SD) age was 8.5 (4.00) years, in the Other daily hGH group the mean (SD) age was 7.2 (4.34) years, and in the Ngenla group it was 7.5 (3.96) years (Table 11).

The mean (SD) age at the time of secondary diagnosis was 6.3 (4.40) years for all patients. For patients in the Genotropin group, the mean (SD) age was 7.4 (4.01) years, in the Other daily hGH group the mean (SD) age was 5.6 (4.50) years, and in the Ngenla group it was 5.1 (4.66) years (Table 11).

The mean (SD) age at the time of third diagnosis was 5.2 (4.28) years for all patients. For patients in the Genotropin group, the mean (SD) age was 3.0 (3.61) years, in the Other daily hGH group the mean (SD) age was 5.9 (4.63) years, and in the Ngenla group it was 5.0 (-) years (Table 11).

Only 1 patient had data for a change in diagnosis (Table 11) (Source Table 16.2.5.5, Appendix 8).

Table 11 Human Growth Hormone Diagnosis by Treatment Groups

hGH Diagnosis	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Primary hGH diagnosis, n (%)							
Idiopathic GHD	541 (76.5)	19 (67.9)	90 (60.8)	115 (64.2)	224 (63.1)	353 (80.6)	1118 (74.5)
Turner Syndrome	8 (1.1)	1 (3.6)	1 (0.7)	5 (2.8)	7 (2.0)	0	15 (1.0)
SGA/IUGR	34 (4.8)	0	11 (7.4)	16 (8.9)	27 (7.6)	6 (1.4)	67 (4.5)
ISS	15 (2.1)	1 (3.6)	2 (1.4)	3 (1.7)	6 (1.7)	2 (0.5)	23 (1.5)
Disturbed GH Secretory Pattern/Neurosecretory dysfunction	3 (0.4)	1 (3.6)	4 (2.7)	1 (0.6)	6 (1.7)	6 (1.4)	15 (1.0)

hGH Diagnosis	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Prader-Labhart-Willi / Prader-Willi Syndrome	23 (3.3)	1 (3.6)	1 (0.7)	4 (2.2)	6 (1.7)	0	29 (1.9)
Familial Short Stature	2 (0.3)	0	3 (2.0)	0	3 (0.8)	1 (0.2)	6 (0.4)
Medulloblastoma	4 (0.6)	0	1 (0.7)	1 (0.6)	2 (0.6)	0	6 (0.4)
Empty sella syndrome/Pituitary aplasia	3 (0.4)	0	3 (2.0)	3 (1.7)	6 (1.7)	7 (1.6)	16 (1.1)
Septo-Optic Dysplasia/Optic Nerve Hypoplasia	2 (0.3)	0	3 (2.0)	3 (1.7)	6 (1.7)	9 (2.1)	17 (1.1)
Silver-Russell / Russell-Silver Syndrome	3 (0.4)	0	0	1 (0.6)	1 (0.3)	0	4 (0.3)
Renal disease	1 (0.1)	0	0	0	0	0	1 (0.1)
Noonan syndrome	5 (0.7)	1 (3.6)	3 (2.0)	0	4 (1.1)	0	9 (0.6)
Tumor of the pituitary/hypothalamic area	8 (1.1)	0	3 (2.0)	2 (1.1)	5 (1.4)	1 (0.2)	14 (0.9)
Skeletal dysplasias	0	1 (3.6)	0	1 (0.6)	2 (0.6)	1 (0.2)	3 (0.2)
Astrocytoma	1 (0.1)	0	0	0	0	0	1 (0.1)
Neurofibromatosis / von Recklinghausen syndrome	1 (0.1)	0	0	0	0	0	1 (0.1)
Bio-inactive GH syndromes / Kowarski Syndrome	2 (0.3)	0	2 (1.4)	3 (1.7)	5 (1.4)	3 (0.7)	10 (0.7)
Histiocytosis	2 (0.3)	0	1 (0.7)	0	1 (0.3)	1 (0.2)	4 (0.3)
Other	49 (6.9)	3 (10.7)	20 (13.5)	21 (11.7)	44 (12.4)	48 (11.0)	141 (9.4)
Missing	9	0	2	2	4	3	16
Secondary hGH diagnosis, n (%)							

hGH Diagnosis	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Idiopathic GHD	12 (22.6)	1 (50.0)	5 (19.2)	6 (22.2)	12 (21.8)	3 (15.8)	27 (21.3)
Turner syndrome	0	0	1 (3.8)	0	1 (1.8)	0	1 (0.8)
SGA/IUGR	12 (22.6)	0	4 (15.4)	5 (18.5)	9 (16.4)	8 (42.1)	29 (22.8)
ISS	2 (3.8)	0	4 (15.4)	1 (3.7)	5 (9.1)	0	7 (5.5)
Disturbed GH Secretory Pattern/Neurosecretory dysfunction	0	0	0	1 (3.7)	1 (1.8)	1 (5.3)	2 (1.6)
Prader-Labhart-Willi / Prader-Willi Syndrome	0	0	1 (3.8)	0	1 (1.8)	0	1 (0.8)
Prader-Labhart-Willi syndrome (with chromosomal aberration)	0	0	1 (3.8)	0	1 (1.8)	0	1 (0.8)
Familial Short Stature	0	0	1 (3.8)	0	1 (1.8)	0	1 (0.8)
FSS, onset of puberty unknown	1 (1.9)	0	0	0	0	0	1 (0.8)
Empty sella syndrome/Pituitary aplasia	4 (7.5)	0	0	6 (22.2)	6 (10.9)	0	10 (7.9)
Septo-Optic Dysplasia/Optic Nerve Hypoplasia	0	0	1 (3.8)	1 (3.7)	2 (3.6)	0	2 (1.6)
Silver-Russell / Russell-Silver Syndrome	1 (1.9)	0	0	0	0	0	1 (0.8)
Renal disease	2 (3.8)	0	0	1 (3.7)	1 (1.8)	0	3 (2.4)
Renal hypoplasia/dysplasia/aplasia including multicystic dysplasia	0	0	0	0	0	1 (5.3)	1 (0.8)
Noonan syndrome	3 (5.7)	0	0	1 (3.7)	1 (1.8)	0	4 (3.1)

hGH Diagnosis	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Craniopharyngioma	4 (7.5)	0	0	0	0	0	4 (3.1)
Skeletal dysplasias	0	0	0	0	0	1 (5.3)	1 (0.8)
Osteogenesis imperfecta (specify)	0	0	0	0	0	1 (5.3)	1 (0.8)
Astrocytoma	0	0	1 (3.8)	0	1 (1.8)	0	1 (0.8)
Neurofibromatosis / von Recklinghausen syndrome	1 (1.9)	0	0	0	0	0	1 (0.8)
Bio-inactive GH syndromes / Kowarski Syndrome	0	0	1 (3.8)	0	1 (1.8)	0	1 (0.8)
Other	11 (20.8)	1 (50.0)	6 (23.1)	5 (18.5)	12 (21.8)	4 (21.1)	27 (21.3)
Missing	663	26	124	154	304	422	1389
Third hGH diagnosis, n (%)							
Idiopathic GHD	0	0	0	2 (33.3)	2 (20.0)	0	2 (12.5)
SGA/IUGR	1 (33.3)	0	0	0	0	0	1 (6.3)
ISS	0	0	0	1 (16.7)	1 (10.0)	0	1 (6.3)
Prader-Labhart-Willi / Prader-Willi Syndrome	0	0	0	0	0	1 (33.3)	1 (6.3)
Empty sella syndrome/Pituitary aplasia	1 (33.3)	0	0	0	0	0	1 (6.3)
Septo-Optic Dysplasia/Optic Nerve Hypoplasia	1 (33.3)	0	0	0	0	0	1 (6.3)
Other	0	0	4 (100)	3 (50.0)	7 (70.0)	2 (66.7)	9 (56.3)
Missing	713	28	146	175	349	438	1500
Age at the time of primary diagnosis (years)							

hGH Diagnosis	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
N	655	24	125	156	305	416	1376
Mean (SD)	8.5 (4.00)	7.3 (4.07)	7.0 (4.32)	7.3 (4.43)	7.2 (4.34)	7.5 (3.96)	7.9 (4.10)
Median	9.0	6.0	7.0	8.0	7.0	7.0	8.0
Q1; Q3	5.0; 12.0	4.0; 10.5	4.0; 10.0	4.0; 11.0	4.0; 11.0	4.5; 11.0	5.0; 11.0
Min; Max	0.0; 18.0	0.0; 15.0	0.0; 15.0	0.0; 17.0	0.0; 17.0	0.0; 17.0	0.0; 18.0
Missing	61	4	25	25	54	25	140
Age at the time of secondary diagnosis (years)							
N	48	2	21	25	48	18	114
Mean (SD)	7.4 (4.01)	3.5 (0.71)	5.0 (4.36)	6.3 (4.77)	5.6 (4.50)	5.1 (4.66)	6.3 (4.40)
Median	7.0	3.5	5.0	5.0	5.0	4.0	6.0
Q1; Q3	5.0; 11.0	3.0; 4.0	1.0; 8.0	3.0; 11.0	1.0; 9.0	1.0; 7.0	3.0; 10.0
Min; Max	0.0; 16.0	3.0; 4.0	0.0; 14.0	0.0; 15.0	0.0; 15.0	0.0; 15.0	0.0; 16.0
Missing	668	26	129	156	311	423	1402
Age at the time of third diagnosis (years)							
N	3	0	4	6	10	1	14
Mean (SD)	3.0 (3.61)	- (-)	6.5 (4.65)	5.5 (5.01)	5.9 (4.63)	5.0 (-)	5.2 (4.28)
Median	2.0	-	6.5	4.5	5.0	5.0	5.0
Q1; Q3	0.0; 7.0	-;-	3.0; 10.0	4.0; 5.0	4.0; 8.0	5.0; 5.0	2.0; 7.0
Min; Max	0.0; 7.0	-;-	1.0; 12.0	0.0; 15.0	0.0; 15.0	5.0; 5.0	0.0; 15.0
Missing	713	28	146	175	349	440	1502
Change in diagnosis, n (%)							
Yes	1 (100)	0	0	0	0	0	1 (100)
No	0	0	0	0	0	0	0

hGH Diagnosis	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Missing	715	28	150	181	359	441	1515
Previous diagnosis, n (%)							
Other	1 (100)	0	0	0	0	0	1 (100)
Missing	715	28	150	181	359	441	1515
Changed diagnosis, n (%)							
Other	1 (100)	0	0	0	0	0	1 (100)
Missing	715	28	150	181	359	441	1515

FSS: Familial short stature; GHD: Growth Hormone Deficiency; hGH: Human Growth Hormone; ISS: Idiopathic short stature; IUGR: Intrauterine Growth Restriction; Max: Maximum ; Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard Deviation; SGA, Small for gestational age.
Percentages are calculated using non-missing values as denominator.
Source: Table 15.1.7, Appendix 8: Additional documents.

10.2.5. Laboratory Assessments

Among all patients, the mean (SD) baseline blood glucose was 4.8 (0.71) mmol/L. The baseline mean (SD) blood glucose was similar in the Genotropin, the Other daily hGH group, and the Ngenla group (4.8 [0.63], 4.8 [0.60] and 4.8 [0.88] mmol/L, respectively). Blood glucose data at baseline were missing for 1025 patients. At Month 12, the overall mean (SD) change from baseline in blood glucose was 0.3 (0.96) mmol/L. The overall change was similar in the Genotropin and the Other daily hGH group (0.3 [0.94] mmol/L and 0.3 [1.15] mmol/L, respectively), and was highest in the Ngenla group (1.9 [-] mmol/L). Data were missing for 1474 patients (Table 12).

Among all patients, the mean (SD) baseline HbA1c was 5.4 (2.69)% and was similar in the Genotropin, Other daily hGH group, and the Ngenla group (5.5 [2.85]%, 5.1 [1.01]%, and 5.7 [3.41]%, respectively). HbA1c data at baseline were missing for 1177 patients. There was no appreciable change from baseline in mean HbA1c at Months 12 and 24; however, longitudinal data were only available for 11 patients at Month 12 and 0 patients at Month 24 (Table 12).

Insulin data at baseline were missing for 1357 patients. Among 159 patients with data, the mean (SD) value was 47.8 (51.54) pmol/L. The mean (SD) insulin in the Other daily hGH and the Ngenla group was slightly less than the baseline (38.2 [40.98] and 36.7 [49.90] pmol/L, respectively) and was highest in the Genotropin group (63.8 [55.41] pmol/L). At Month 12, the overall mean (SD) change from baseline in insulin was -8.1 (26.07) pmol/L and was similar in the Genotropin group (-8.7 [36.84] pmol/L) and greater than the Other daily hGH group (-6.9 [-] pmol/L). Patient details for Ngenla group were not available for Month 12. Data were missing for 1513 patients. No data were available at Month 24 (Table 12).

Among all patients, the median (min, max) thyroid stimulating hormone (TSH) at baseline was 2.0 (0.0, 931.0) µIU/mL (the normal range for many assays is 0.4-4.0 µIU/mL). The TSH data at baseline were missing for 788 patients. At Month 12, the overall median (min, max) change from baseline in TSH was -0.2 (-88.4, 1.5) µIU/mL and was similar in the Genotropin group (-0.2 [-88.4, 0.5] µIU/mL) and lower than the Other daily hGH group (-0.6 [-3.0, 0.7] µIU/mL). No data were available at Month 24 (Table 12).

Among all patients, the median (min, max) baseline free thyroxine was 13.8 (0.0, 23169.6) pmol/L (the normal range for many assays is 10-26 pmol/L). The baseline median (min, max) free thyroxine was similar in the Genotropin group, the Other daily hGH group and the Ngenla group (13.3 [0.0, 23169.6] pmol/L, 14.2 [1.1, 1493.2] pmol/L, and 14.0 [1.2, 25.6] pmol/L, respectively). The free thyroxine data at baseline were missing for 887 patients. At Month 12, the overall median (min, max) change from baseline in free thyroxine from 23 patients with longitudinal data was -0.8 (-1527.9, 3.8) pmol/L. The change was similar in the Genotropin group and the Ngenla group (-1.2 [-1527.9, 3.8] pmol/L, -0.8 [-0.8, -0.8] pmol/L and greater than the Other daily hGH group (-0.0 [-10.3, 3.2] pmol/L). Data were missing for 1493 patients. No data were available at Month 24 (Table 12).

Total thyroxine data at baseline were missing for 1457 patients. Among 59 patients with data, the mean (SD) value was 67.1 (53.76) nmol/L (the normal range for many assays is 83-172 nmol/L). The baseline mean (SD) total thyroxine was lower than the Genotropin group and the Other daily hGH group (73.7 [48.80] nmol/L and 78.3 [55.52] nmol/L, respectively). The mean (SD) total thyroxine was the lowest in the Ngenla group (3.2 [7.67] nmol/L). Only 1 patient in the Other daily hGH group had longitudinal data for total thyroxine at Month 12 and the overall mean (SD) change from baseline for total thyroxine was 6.4 (-) nmol/L. No data were available for Genotropin and the Ngenla group. Data were missing for 1515 patients. No data were available at Month 24 (Table 12) only.

Alkaline phosphatase data at baseline were missing for 1228 patients. Among 288 patients with data, the mean (SD) values was 264.6 (120.15) U/L. The baseline mean (SD) alkaline phosphatase was similar to the Genotropin group and the Other daily hGH group (293.2 [129.49] U/L and 257.5 [100.11] U/L, respectively). The baseline mean (SD) alkaline phosphatase was lowest in the Ngenla group (220.7 [108.64] U/L). At Month 12, among 35 patients with longitudinal data, the overall mean (SD) change from baseline in alkaline phosphatase was -19.9 (97.09) U/L. The change was similar to the Genotropin group (-20.6 [99.17] U/L) and higher than the Other daily hGH group (-8.5 [74.25] U/L). No appreciable data was available for the Ngenla group. Data were missing for 1481 patients (Table 12).

Calcium data at baseline were missing for 1147 patients. Among 369 patients with data, the mean (SD) value was 3.1 (11.12) mmol/L. The baseline mean (SD) calcium was similar to the Genotropin group and the Ngenla group (2.4 [0.58] mmol/L and 2.8 [2.63] mmol/L, respectively). The baseline mean (SD) calcium was highest in the Other daily hGH group (4.5 [20.39] mmol/L). At Month 12, among 37 patients with longitudinal data, no appreciable changes were observed. Data were missing for 1479 patients (Table 12).

Cholesterol data at baseline were missing for 1133 patients. Among 383 patients with data, the mean (SD) values was 7.4 (23.32) mmol/L. The baseline mean (SD) cholesterol was higher than the Genotropin group and the Other daily hGH group (4.3 [0.77] mmol/L and 4.3 [0.80] mmol/L, respectively). The baseline mean (SD) cholesterol was highest in the Ngenla

group (13.6 [39.39] mmol/L). At Month 12, among 37 patients with longitudinal data, the overall mean (SD) change from baseline in cholesterol was 4.3 (26.93) mmol/L. The change was similar to the Genotropin group (4.7 [28.08] mmol/L) and higher than the Other daily hGH group (-1.0 [0.49] mmol/L). No appreciable data was available for the Ngenla group. Data were missing for 1479 patients (Table 12).

Estradiol data at baseline were missing for 1406 patients. Among 110 patients with data, the mean (SD) value was 79.9 (86.54) pmol/L. The baseline mean (SD) estradiol was similar to the Genotropin group and the Ngenla group (71.3 [74.69] pmol/L and 67.6 [66.02] pmol/L, respectively). The mean (SD) estradiol was highest in the Other daily hGH group (113.1 [120.82] pmol/L). At Month 12, 10 patients in the Genotropin group had longitudinal data for estradiol and the overall mean (SD) change from baseline was -14.5 (21.21) pmol/L. No data were available for the Other daily hGH group and the Ngenla group. Data were missing for 1506 patients. No data were available at Month 24 (Table 12).

Follicle-stimulating hormone (FSH) data at baseline were missing for 1215 patients. Among 301 patients with data, the median (min, max) value was 2.2 (0.0, 20680.0) mIU/mL. The baseline median (min, max) FSH was lower than the Genotropin group (2.5 [0.0, 600.0] mIU/mL) and higher than the Other daily hGH group and the Ngenla group (1.8 [0.0, 20680.0] mIU/mL and 1.8 [0.0, 15.7] mIU/mL, respectively). At Month 12, 32 patients had longitudinal data for FSH and the overall median (min, max) change from baseline was -0.1 (-5.6, 9.6) mIU/mL and was similar in the Genotropin group (-0.1 [-5.6, 9.6] mIU/mL). The change was highest in the Other daily hGH group (1.2 [1.2, 1.2] mIU/mL). No appreciable data were available for the Ngenla group. Data were missing for 1484 patients. No data were available at Month 24 (Table 12).

High-density lipoprotein (HDL) cholesterol data at baseline were missing for 1239 patients. Among 277 patients with data, the mean (SD) value was 2.2 (5.82) mmol/L. The baseline mean (SD) HDL cholesterol was higher than the Genotropin group and the Other daily hGH group (1.5 [0.35] mmol/L and 1.4 [0.30] mmol/L, respectively). The mean (SD) HDL cholesterol was highest in the Ngenla group (3.5 [9.88] mmol/L). At Month 12, only 3 patients had longitudinal data for HDL cholesterol and the overall mean (SD) change from baseline was -0.2 (0.15) mmol/L and was similar in the Genotropin group and the Other daily hGH group (-0.2 [0.21] mmol/L and -0.2 [-] mmol/L, respectively). No appreciable data were available for the Ngenla group. Data were missing for 1513 patients (Table 12).

Hemoglobin data at baseline were missing for 1092 patients. Among 424 patients with data, the mean (SD) value was 126.6 (28.85) g/L. The baseline mean (SD) hemoglobin was similar to the Genotropin group and the Other daily hGH group (128.5 [27.65] g/L and 129.8 [24.34] g/L, respectively). The mean (SD) hemoglobin was lowest in the Ngenla group (121.2 [32.98] g/L). At Month 12, 38 patients had longitudinal data for hemoglobin and the overall mean (SD) change from baseline was -1.2 (27.20) g/L. The change from baseline in the Genotropin group and the Other daily hGH group were 1.4 [23.30] g/L and -24.0 [48.85] g/L, respectively. No appreciable data were available for the Ngenla group. Data were missing for 1478 patients (Table 12).

IGF-I data at baseline were missing for 673 patients. Among 843 patients with data, the mean (SD) value was 2415.1 (27902.64) nmol/L. The mean (SD) IGF-I was similar in the Genotropin group (2399.6 [26090.97] nmol/L), highest in the Other daily hGH group (5357.9

[43732.19] nmol/L) and lowest in the Ngenla group (37.8 [52.37] nmol/L). At Month 12, 62 patients had longitudinal data for IGF-I. The overall mean (SD) change from baseline was 15.4 (74.37) nmol/L. The mean change from baseline in the Genotropin group was 19.3 [82.07] nmol/L in the Other daily hGH group and the Ngenla group were 3.5 [51.07] nmol/L and 7.1 [11.84] nmol/L, respectively. Data were missing for 1454 patients. At Month 24, only 1 patient in the Other daily hGH group had longitudinal data for IGF-I (135.2 nmol/L). No data were available for the Genotropin group and the Ngenla group. Data were missing for 1515 patients. (Table 12).

Insulin-like growth factor-binding protein 3 (IGFBP-3) data at baseline were missing for 1206 patients. Among 310 patients with data, the mean (SD) value was 189822.6 (1047463.66) mg/L. The baseline mean (SD) IGFBP-3 was similar in the Genotropin group (191221.6 [1066200.69] mg/L). The mean (SD) IGFBP-3 was highest in the Other daily hGH group (359728.1 [1414634.97] mg/L) and lowest in the Ngenla group (553.1 [1372.13] mg/L). At Month 12, 7 patients had longitudinal data for IGFBP-3 and the overall mean (SD) change from baseline was 1.7 (2.33) mg/L and was similar in the Ngenla group (2.0 [-] mg/L), lower than the Genotropin group (3.1 [2.84] mg/L) and higher than the Other daily hGH group (0.1 [1.30] mg/L). Data were missing for 1509 patients. At Month 24, only 1 patient in the Other daily hGH group had longitudinal data for IGFBP-3 (-0.5 [-] mg/L). No data were available for the Genotropin group and the Ngenla group. Data were missing for 1515 patients. (Table 12).

Low-density lipoprotein (LDL) cholesterol data at baseline were missing for 1279 patients. Among 237 patients with data, the mean (SD) value was 8.0 (22.66) mmol/L. The baseline mean (SD) LDL cholesterol in the Other daily hGH group was 7.5 [21.08] mmol/L, which was higher than the Genotropin group (5.5 [16.17] mmol/L) and lower than the Ngenla group (11.9 [30.25] mmol/L). At Month 12, 33 patients had longitudinal data for LDL cholesterol and the overall mean (SD) change from baseline was -0.0 (0.71) mmol/L and was similar in the Genotropin group (-0.0 [0.71] mmol/L) and higher than the Other daily hGH group (-0.8 [-] mmol/L). No appreciable data were available for the Ngenla group. Data were missing for 1483 patients (Table 12).

Luteinizing hormone (LH) data at baseline were missing for 1205 patients. Among 311 patients with data, the mean (SD) value was 2.5 (13.65) mIU/mL. The Genotropin group baseline mean was 3.5 [19.39] mIU/mL, which was higher than the Other daily hGH group and the Ngenla group (1.4 [2.40] mIU/mL and 1.6 [2.80] mIU/mL, respectively). At Month 12, 32 patients had longitudinal data for LH and the overall mean (SD) change from baseline was -0.0 (2.04) mIU/mL and was similar in the Genotropin group (-0.1 [2.06] mIU/mL). The change was highest in the Other daily hGH group (0.7 [-] mIU/mL). No appreciable data were available for the Ngenla group. Data were missing for 1484 patients. No data were available at Month 24 (Table 12).

Phosphate data at baseline were missing for 1275 patients. Among 241 patients with data, the mean (SD) value was 2.7 (19.44) mmol/L. The baseline mean (SD) phosphate in the Genotropin group was 4.3 [28.90] mmol/L, which was higher than the Other daily hGH group and the Ngenla group (1.6 [0.56] mmol/L and 1.4 [0.60] mmol/L, respectively). At Month 12, 33 patients had longitudinal data for phosphate and the overall mean (SD) change from baseline was -0.0 (0.85) mmol/L and was similar in the Genotropin group (-0.0 [0.88]

mmol/L). No appreciable data were available for the Other daily hGH group and the Ngenla group. Data were missing for 1483 patients (Table 12).

Testosterone data at baseline were missing for 1303 patients. Among 213 patients with data, the mean (SD) value was 12.8 (72.30) nmol/L. The baseline mean (SD) testosterone in the Ngenla group was 14.4 [85.01] nmol/L, which was higher than the Genotropin group (3.9 [6.40] nmol/L) and lower than the Other daily hGH group (31.8 [122.01] nmol/L). At Month 12, 35 patients had longitudinal data for testosterone and the overall mean (SD) change from baseline was -0.0 (4.20) nmol/L. No appreciable data were available for the Ngenla group. Data were missing for 1481 patients. No data were available at Month 24 (Table 12).

Triglycerides data at baseline were missing for 1193 patients. Among 323 patients with data, the mean (SD) value was 2.4 (13.01) mmol/L. The baseline mean (SD) triglycerides in the Genotropin group and the Other daily hGH group were 1.4 [5.62] mmol/L and 1.0 [0.76] mmol/L, respectively, and was highest in the Ngenla group (4.4 [20.89] mmol/L). At Month 12, only 4 patients had longitudinal data for triglycerides and the overall mean (SD) change from baseline was -0.3 (0.50) mmol/L. Data were missing for 1512 patients (Table 12).

Table 12 Laboratory Test Results by Treatment Groups

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
ALS (U/L)	Baseline	n	6		0		2		2		4		7		17	
		Mean (SD)	27.0 (19.77)		- (-)		18.0 (7.07)		21.0 (4.24)		19.5 (5.07)		28.6 (12.75)		25.9 (14.20)	
		Median	19.0		-		18.0		21.0		20.5		34.0		23.0	
		Q1; Q3	14.0; 49.0		-;-		13.0; 23.0		18.0; 24.0		15.5; 23.5		14.0; 40.0		14.0; 37.0	
		Min; Max	6.7; 54.0		-;-		13.0; 23.0		18.0; 24.0		13.0; 24.0		11.0; 42.0		6.7; 54.0	
		Missing	710		28		148		179		355		434		1499	
	Month 12	n	1	0	0	0	1	1	1	0	2	1	0	0	3	1
		Mean (SD)	17.0 (-)	- (-)	- (-)	- (-)	14.0 (-)	1.0 (-)	18.0 (-)	- (-)	16.0 (2.83)	1.0 (-)	- (-)	- (-)	16.3 (2.08)	1.0 (-)
		Median	17.0	-	-	-	14.0	1.0	18.0	-	16.0	1.0	-	-	17.0	1.0
		Q1; Q3	17.0; 17.0	-;-	-;-	-;-	14.0; 14.0	1.0; 1.0	18.0; 18.0	-;-	14.0; 18.0	1.0; 1.0	-;-	-;-	14.0; 18.0	1.0; 1.0
		Min; Max	17.0; 17.0	-;-	-;-	-;-	14.0; 14.0	1.0; 1.0	18.0; 18.0	-;-	14.0; 18.0	1.0; 1.0	-;-	-;-	14.0; 18.0	1.0; 1.0
		Missing	715	716	28	28	149	149	180	181	357	358	441	441	1513	1515

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Alkaline phosphatase (U/L	Baseline	n	134		3		22		54		79		75		288	
		Mean (SD)	293.2 (129.49)		248.0 (94.43)		262.5 (87.43)		256.0 (106.61)		257.5 (100.11)		220.7 (108.64)		264.6 (120.15)	
		Median	279.5		196.0		252.5		241.5		242.0		213.0		244.0	
		Q1; Q3	209.0; 356.0		191.0; 357.0		188.0; 323.0		188.0; 303.0		188.0; 323.0		168.0; 275.0		190.5; 332.5	
		Min; Max	2.0; 773.0		191.0; 357.0		146.0; 449.0		2.4; 557.0		2.4; 557.0		3.2; 679.0		2.0; 773.0	
		Missing	582		25		128		127		280		366		1228	
	Month 12	n	68	33	0	0	5	0	4	2	9	2	5	0	82	35
		Mean (SD)	315.3 (90.54)	-20.6 (99.17)	- (-)	- (-)	263.2 (53.49)	- (-)	261.0 (98.97)	-8.5 (74.25)	262.2 (71.45)	-8.5 (74.25)	337.2 (126.48)	- (-)	310.8 (91.64)	-19.9 (97.09)
		Median	295.5	-19.0	-	-	253.0	-	277.5	-8.5	259.0	-8.5	258.0	-	295.0	-19.0
		Q1; Q3	261.0; 364.0	-84.0; 29.0	-;-	-;-	219.0; 311.0	-;-	193.0; 329.0	-61.0; 44.0	219.0; 311.0	-61.0; 44.0	251.0; 450.0	-;-	253.0; 362.0	-84.0; 42.0

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Min; Max	96.0; 565.0	-207.0; 263.0	-;-	-;-	207.0; 326.0	-;-	127.0; 362.0	-61.0; 44.0	127.0; 362.0	-61.0; 44.0	229.0; 498.0	-;-	96.0; 565.0	-207.0; 263.0
		Missing	648	683	28	28	145	150	177	179	350	357	436	441	1434	1481
Apolipoprotein B (mg/dL)	Baseline	n	8		0		3		7		10		6		24	
		Mean (SD)	0.7 (0.13)		- (-)		34.9 (31.91)		55.2 (46.73)		49.2 (42.17)		80.8 (43.36)		40.9 (45.94)	
		Median	0.8		-		40.0		57.0		51.5		85.5		20.5	
		Q1; Q3	0.6; 0.8		-;-		0.8; 64.0		0.9; 87.0		0.9; 64.0		79.0; 105.0		0.8; 80.0	
		Min; Max	0.6; 0.9		-;-		0.8; 64.0		0.8; 133.0		0.8; 133.0		0.8; 129.0		0.6; 133.0	
		Missing	708		28		147		174		349		435		1492	
Blood glucose (mmol/L)	Baseline	n	222		6		35		74		115		154		491	
		Mean (SD)	4.8 (0.63)		5.4 (0.82)		4.8 (0.68)		4.8 (0.52)		4.8 (0.60)		4.8 (0.88)		4.8 (0.71)	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Median	4.8		5.4		4.7		4.8		4.8		4.7		4.8	
		Q1; Q3	4.4; 5.1		4.8; 6.2		4.3; 5.1		4.6; 5.1		4.5; 5.1		4.4; 5.1		4.4; 5.1	
		Min; Max	2.9; 6.9		4.1; 6.2		3.6; 6.5		3.2; 7.5		3.2; 7.5		3.1; 9.7		2.9; 9.7	
		Missing	494		22		115		107		244		287		1025	
	Month 12	n	73	38	0	0	6	0	5	3	11	3	2	1	86	42
		Mean (SD)	5.1 (0.76)	0.3 (0.94)	- (-)	- (-)	5.2 (0.61)	- (-)	4.7 (0.92)	0.3 (1.15)	4.9 (0.77)	0.3 (1.15)	5.2 (0.42)	1.9 (-)	5.1 (0.75)	0.3 (0.96)
		Median	5.1	0.2	-	-	5.1	-	4.9	0.2	5.0	0.2	5.2	1.9	5.1	0.2
		Q1; Q3	4.6; 5.5	-0.2; 0.8	-;-	-;-	4.7; 5.3	-;-	3.8; 5.3	-0.8; 1.5	4.6; 5.3	-0.8; 1.5	4.9; 5.5	1.9; 1.9	4.6; 5.5	-0.2; 0.8
		Min; Max	3.6; 7.6	-1.9; 3.2	-;-	-;-	4.6; 6.3	-;-	3.6; 5.7	-0.8; 1.5	3.6; 6.3	-0.8; 1.5	4.9; 5.5	1.9; 1.9	3.6; 7.6	-1.9; 3.2
		Missing	643	678	28	28	144	150	176	178	348	356	439	440	1430	1474
Bone-specific alkaline phosphatase (IU/L)	Baseline	n	3		0		4		6		10		10		23	
		Mean (SD)	258.3 (68.06)		- (-)		192.1 (95.00)		89.7 (52.67)		130.6 (85.72)		90.7 (73.17)		129.9 (92.55)	
		Median	292.0		-		168.6		81.2		104.3		68.6		105.1	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Q1; Q3	180.0; 303.0		-;-		118.2; 266.0		57.1; 94.3		73.9; 188.0		51.9; 107.3		63.6; 200.0	
		Min; Max	180.0; 303.0		-;-		114.3; 317.0		36.1; 188.0		36.1; 317.0		1.4; 227.0		1.4; 317.0	
		Missing	713		28		146		175		349		431		1493	
Calcium (mmol/L)	Baseline	n	160		5		32		71		108		101		369	
		Mean (SD)	2.4 (0.58)		2.4 (0.08)		2.3 (0.32)		5.7 (25.13)		4.5 (20.39)		2.8 (2.63)		3.1 (11.12)	
		Median	2.4		2.4		2.4		2.4		2.4		2.4		2.4	
		Q1; Q3	2.3; 2.5		2.4; 2.5		2.3; 2.5		2.4; 2.5		2.4; 2.5		2.4; 2.5		2.3; 2.5	
		Min; Max	1.8; 9.6		2.3; 2.5		1.2; 2.7		0.0; 214.0		0.0; 214.0		1.3; 26.7		0.0; 214.0	
		Missing	556		23		118		110		251		340		1147	
	Month 12	n	69	34	0	0	5	0	5	2	10	2	6	1	85	37
		Mean (SD)	2.3 (0.10)	-0.0 (0.09)	- (-)	- (-)	2.3 (0.07)	- (-)	2.4 (0.04)	-0.1 (0.07)	2.3 (0.07)	-0.1 (0.07)	7.7 (9.46)	0.0 (-)	2.7 (2.70)	-0.0 (0.09)
		Median	2.3	0.0	-	-	2.3	-	2.4	-0.1	2.3	-0.1	2.5	0.0	2.3	0.0
		Q1; Q3	2.2; 2.3	-0.1; 0.1	-;-	-;-	2.3; 2.3	-;-	2.4; 2.4	-0.1; 0.0	2.3; 2.4	-0.1; 0.0	2.5; 10.3	0.0; 0.0	2.2; 2.4	-0.1; 0.1
		Min; Max	2.1; 2.6	-0.2; 0.1	-;-	-;-	2.2; 2.4	-;-	2.3; 2.4	-0.1; 0.0	2.2; 2.4	-0.1; 0.0	2.4; 25.9	0.0; 0.0	2.1; 25.9	-0.2; 0.1

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	647	682	28	28	145	150	176	179	349	357	435	440	1431	1479
Cholesterol (mmol/L)	Baseline	n	168		5		20		60		85		130		383	
		Mean (SD)	4.3 (0.77)		4.4 (0.90)		4.1 (0.76)		4.3 (0.82)		4.3 (0.80)		13.6 (39.39)		7.4 (23.32)	
		Median	4.3		4.4		4.3		4.2		4.3		4.4		4.3	
		Q1; Q3	3.8; 4.7		3.9; 4.6		3.7; 4.4		3.8; 4.9		3.8; 4.8		3.8; 5.0		3.8; 4.8	
		Min; Max	0.0; 6.5		3.4; 5.8		2.8; 5.7		2.6; 6.4		2.6; 6.4		0.0; 216.0		0.0; 216.0	
		Missing	548		23		130		121		274		311		1133	
	Month 12	n	69	34	0	0	4	0	3	2	7	2	2	1	78	37
		Mean (SD)	8.7 (28.80)	4.7 (28.08)	- (-)	- (-)	3.8 (0.62)	- (-)	3.6 (0.78)	-1.0 (0.49)	3.7 (0.64)	-1.0 (0.49)	3.8 (0.49)	0.0 (-)	8.1 (27.11)	4.3 (26.93)
		Median	3.9	-0.2	-	-	3.8	-	4.0	-1.0	3.9	-1.0	3.8	0.0	3.9	-0.2
		Q1; Q3	3.4; 4.3	-0.4; 0.2	-;-	-;-	3.4; 4.3	-;-	2.7; 4.1	-1.3; -0.6	3.1; 4.1	-1.3; -0.6	3.4; 4.1	0.0; 0.0	3.4; 4.3	-0.4; 0.1
		Min; Max	0.0; 180.0	-1.1; 163.6	-;-	-;-	3.1; 4.6	-;-	2.7; 4.1	-1.3; -0.6	2.7; 4.6	-1.3; -0.6	3.4; 4.1	0.0; 0.0	0.0; 180.0	-1.3; 163.6
		Missing	647	682	28	28	146	150	178	179	352	357	439	440	1438	1479

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Estradiol (pmol/L)	Baseline	n	57		2		8		15		25		28		110	
		Mean (SD)	71.3 (74.69)		18.4 (25.95)		136.9 (126.73)		113.1 (123.86)		113.1 (120.82)		67.6 (66.02)		79.9 (86.54)	
		Median	55.1		18.4		93.7		73.4		69.8		45.9		53.2	
		Q1; Q3	18.4; 88.1		0.0; 36.7		40.7; 225.5		37.0; 165.2		37.0; 165.2		27.9; 88.1		18.4; 99.5	
		Min; Max	0.0; 373.0		0.0; 36.7		18.4; 357.0		7.0; 500.0		0.0; 500.0		0.0; 268.0		0.0; 500.0	
		Missing	659		26		142		166		334		413		1406	
	Month 12	n	53	10	1	0	1	0	2	0	4	0	1	0	58	10
		Mean (SD)	11.2 (34.23)	-14.5 (21.21)	124.8 (-)	- (-)	0.4 (-)	- (-)	7.4 (10.39)	- (-)	35.0 (60.27)	- (-)	0.9 (-)	- (-)	12.7 (36.04)	-14.5 (21.21)
		Median	1.2	-16.5	124.8	-	0.4	-	7.4	-	7.6	-	0.9	-	1.2	-16.5
		Q1; Q3	0.0; 5.0	-18.4; -11.4	124.8; 124.8	-;-	0.4; 0.4	-;-	0.0; 14.7	-;-	0.2; 69.8	-;-	0.9; 0.9	-;-	0.0; 6.1	-18.4; -11.4
		Min; Max	0.0; 183.5	-59.1; 28.5	124.8; 124.8	-;-	0.4; 0.4	-;-	0.0; 14.7	-;-	0.0; 124.8	-;-	0.9; 0.9	-;-	0.0; 183.5	-59.1; 28.5
		Missing	663	706	27	28	149	150	179	181	355	359	440	441	1458	1506
	Month 24	n	0	0	1	0	0	0	0	0	1	0	0	0	1	0
		Mean (SD)	- (-)	- (-)	223.9 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	223.9 (-)	- (-)	- (-)	- (-)	223.9 (-)	- (-)

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Median	-	-	223.9	-	-	-	-	-	223.9	-	-	-	223.9	-
		Q1; Q3	-;-	-;-	223.9; 223.9	-;-	-;-	-;-	-;-	-;-	223.9; 223.9	-;-	-;-	-;-	223.9; 223.9	-;-
		Min; Max	-;-	-;-	223.9; 223.9	-;-	-;-	-;-	-;-	-;-	223.9; 223.9	-;-	-;-	-;-	223.9; 223.9	-;-
		Missing	716	716	27	28	150	150	181	181	358	359	441	441	1515	1516
FSH (mIU/mL)	Baseline	n	150		4		25		40		69		82		301	
		Mean (SD)	7.2 (48.84)		9.2 (16.21)		830.9 (4135.22)		2.3 (2.33)		302.9 (2489.19)		2.7 (2.63)		73.8 (1192.18)	
		Median	2.5		1.5		1.8		1.7		1.8		1.8		2.2	
		Q1; Q3	1.4; 4.2		0.5; 18.0		1.0; 6.3		0.7; 3.0		0.8; 3.5		0.8; 3.5		1.0; 3.8	
		Min; Max	0.0; 600.0		0.4; 33.5		0.0; 20680.0		0.1; 10.2		0.0; 20680.0		0.0; 15.7		0.0; 20680.0	
		Missing	566		24		125		141		290		359		1215	
	Month 12	n	67	31	1	0	4	0	3	1	8	1	1	0	76	32
		Mean (SD)	3.6 (2.35)	0.0 (2.94)	8.6 (-)	- (-)	2.2 (1.55)	- (-)	1.7 (1.57)	1.2 (-)	2.8 (2.70)	1.2 (-)	4.9 (-)	- (-)	3.5 (2.37)	0.0 (2.90)
		Median	3.1	-0.1	8.6	-	1.8	-	1.4	1.2	1.8	1.2	4.9	-	3.1	-0.1
		Q1; Q3	2.2; 4.3	-1.4; 1.0	8.6; 8.6	-;-	1.2; 3.2	-;-	0.3; 3.4	1.2; 1.2	1.1; 3.9	1.2; 1.2	4.9; 4.9	-;-	1.9; 4.4	-1.3; 1.1

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Min; Max	0.6; 12.0	-5.6; 9.6	8.6; 8.6	-;-	0.8; 4.4	-;-	0.3; 3.4	1.2; 1.2	0.3; 8.6	1.2; 1.2	4.9; 4.9	-;-	0.3; 12.0	-5.6; 9.6
		Missing	649	685	27	28	146	150	178	180	351	358	440	441	1440	1484
	Month 24	n	0	0	1	0	0	0	0	0	1	0	0	0	1	0
		Mean (SD)	- (-)	- (-)	4.4 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	4.4 (-)	- (-)	- (-)	- (-)	4.4 (-)	- (-)
		Median	-	-	4.4	-	-	-	-	-	4.4	-	-	-	4.4	-
		Q1; Q3	-;-	-;-	4.4; 4.4	-;-	-;-	-;-	-;-	-;-	4.4; 4.4	-;-	-;-	-;-	4.4; 4.4	-;-
		Min; Max	-;-	-;-	4.4; 4.4	-;-	-;-	-;-	-;-	-;-	4.4; 4.4	-;-	-;-	-;-	4.4; 4.4	-;-
		Missing	716	716	27	28	150	150	181	181	358	359	441	441	1515	1516
Free thyroxine (pmol/L)	Baseline	n	315		8		49		86		143		171		629	
		Mean (SD)	349.8 (2141.05)		14.7 (2.07)		15.3 (4.41)		32.8 (160.16)		25.8 (124.25)		14.1 (3.09)		184.9 (1524.11)	
		Median	13.3		13.9		15.2		14.1		14.2		14.0		13.8	
		Q1; Q3	11.6; 15.8		12.9; 16.9		12.9; 17.6		12.1; 15.8		12.7; 16.7		12.0; 16.0		12.0; 16.0	
		Min; Max	0.0; 23169.6		12.9; 17.4		1.1; 28.3		1.1; 1493.2		1.1; 1493.2		1.2; 25.6		0.0; 23169.6	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	401		20		101		95		216		270		887	
	Month 12	n	47	13	3	2	5	2	9	5	17	9	1	1	65	23
		Mean (SD)	1355.2 (6432.95)	-207.9 (511.74)	9879.0 (17083.71)	1.0 (3.18)	15.0 (2.81)	0.9 (0.35)	14.3 (3.75)	-2.3 (4.86)	1755.3 (7176.85)	-0.9 (4.00)	15.8 (-)	-0.8 (-)	1439.2 (6533.31)	-117.9 (392.25)
		Median	14.2	-1.2	16.1	1.0	13.9	0.9	15.4	-1.3	15.4	0.0	15.8	-0.8	15.1	-0.8
		Q1; Q3	12.9; 15.4	-2.5; 0.2	15.4; 29605.6	-1.3; 3.2	13.3; 15.2	0.6; 1.1	12.9; 16.6	-2.6; 0.0	13.3; 16.6	-1.3; 1.1	15.8; 15.8	-0.8; -0.8	12.9; 15.4	-2.5; 1.1
		Min; Max	1.0; 32180.0	-1527.9; 3.8	15.4; 29605.6	-1.3; 3.2	12.9; 19.8	0.6; 1.1	5.6; 18.7	-10.3; 2.6	5.6; 29605.6	-10.3; 3.2	15.8; 15.8	-0.8; -0.8	1.0; 32180.0	-1527.9; 3.8
		Missing	669	703	25	26	145	148	172	176	342	350	440	440	1451	1493
	Month 24	n	2	0	0	0	1	0	2	0	3	0	0	0	5	0
		Mean (SD)	14.2 (1.77)	- (-)	- (-)	- (-)	16.7 (-)	- (-)	14.2 (1.77)	- (-)	15.0 (1.93)	- (-)	- (-)	- (-)	14.7 (1.69)	- (-)
		Median	14.2	-	-	-	16.7	-	14.2	-	15.4	-	-	-	15.4	-
		Q1; Q3	12.9; 15.4	-;-	-;-	-;-	16.7; 16.7	-;-	12.9; 15.4	-;-	12.9; 16.7	-;-	-;-	-;-	12.9; 15.4	-;-
		Min; Max	12.9; 15.4	-;-	-;-	-;-	16.7; 16.7	-;-	12.9; 15.4	-;-	12.9; 16.7	-;-	-;-	-;-	12.9; 16.7	-;-
		Missing	714	716	28	28	149	150	179	181	356	359	441	441	1511	1516
GH (µg/L)	Baseline	n	27		3		2		10		15		24		66	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Mean (SD)	240.0 (1081.06)		52.8 (85.68)		11.8 (14.47)		13.6 (26.26)		21.2 (42.14)		8.6 (28.82)		106.1 (693.38)	
		Median	1.6		6.7		11.8		1.1		1.5		0.8		1.4	
		Q1; Q3	0.4; 87.0		0.1; 151.7		1.5; 22.0		0.5; 22.0		0.5; 22.0		0.2; 4.2		0.2; 6.7	
		Min; Max	0.0; 5640.0		0.1; 151.7		1.5; 22.0		0.1; 84.0		0.1; 151.7		0.1; 142.0		0.0; 5640.0	
		Missing	689		25		148		171		344		417		1450	
HDL cholesterol (mmol/L)	Baseline	n	112		4		19		48		71		94		277	
		Mean (SD)	1.5 (0.35)		1.5 (0.57)		1.4 (0.31)		1.5 (0.28)		1.4 (0.30)		3.5 (9.88)		2.2 (5.82)	
		Median	1.4		1.3		1.4		1.4		1.4		1.5		1.4	
		Q1; Q3	1.2; 1.6		1.1; 1.9		1.2; 1.7		1.3; 1.7		1.2; 1.7		1.2; 1.8		1.2; 1.7	
		Min; Max	0.7; 3.2		1.0; 2.3		0.9; 2.0		1.0; 2.1		0.9; 2.3		0.5; 57.0		0.5; 57.0	
		Missing	604		24		131		133		288		347		1239	
	Month 12	n	3	2	0	0	1	0	2	1	3	1	1	0	7	3
		Mean (SD)	1.5 (0.30)	-0.2 (0.21)	- (-)	- (-)	1.6 (-)	- (-)	1.1 (0.21)	-0.2 (-)	1.2 (0.35)	-0.2 (-)	2.0 (-)	- (-)	1.5 (0.38)	-0.2 (0.15)

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Median	1.5	-0.2	-	-	1.6	-	1.1	-0.2	1.2	-0.2	2.0	-	1.5	-0.2
		Q1; Q3	1.2; 1.8	-0.3; 0.0	-;-	-;-	1.6; 1.6	-;-	0.9; 1.2	-0.2; -0.2	0.9; 1.6	-0.2; -0.2	2.0; 2.0	-;-	1.2; 1.8	-0.3; 0.0
		Min; Max	1.2; 1.8	-0.3; 0.0	-;-	-;-	1.6; 1.6	-;-	0.9; 1.2	-0.2; -0.2	0.9; 1.6	-0.2; -0.2	2.0; 2.0	-;-	0.9; 2.0	-0.3; 0.0
		Missing	713	714	28	28	149	150	179	180	356	358	440	441	1509	1513
HbA1c (%)	Baseline	n	157		4		37		48		89		93		339	
		Mean (SD)	5.5 (2.85)		4.2 (2.79)		5.2 (0.66)		5.1 (1.00)		5.1 (1.01)		5.7 (3.41)		5.4 (2.69)	
		Median	5.4		5.6		5.3		5.3		5.3		5.4		5.4	
		Q1; Q3	5.2; 5.5		2.8; 5.7		5.2; 5.6		5.1; 5.5		5.1; 5.6		5.2; 5.6		5.2; 5.6	
		Min; Max	0.1; 40.0		0.1; 5.7		2.6; 5.8		0.1; 6.1		0.1; 6.1		2.6; 38.0		0.1; 40.0	
		Missing	559		24		113		133		270		348		1177	
	Month 12	n	46	10	2	1	7	0	4	0	13	1	5	0	64	11
		Mean (SD)	5.4 (0.22)	-0.0 (0.21)	5.4 (0.35)	-0.1 (-)	5.2 (0.32)	- (-)	5.3 (0.08)	- (-)	5.3 (0.26)	-0.1 (-)	5.4 (0.26)	- (-)	5.4 (0.23)	-0.0 (0.20)
		Median	5.4	0.0	5.4	-0.1	5.3	-	5.3	-	5.3	-0.1	5.4	-	5.4	0.0
		Q1; Q3	5.2; 5.5	-0.1; 0.1	5.1; 5.6	-0.1; -0.1	5.0; 5.6	-;-	5.3; 5.4	-;-	5.2; 5.4	-0.1; -0.1	5.3; 5.5	-;-	5.2; 5.5	-0.1; 0.1
		Min; Max	4.9; 5.9	-0.4; 0.3	5.1; 5.6	-0.1; -0.1	4.7; 5.6	-;-	5.2; 5.4	-;-	4.7; 5.6	-0.1; -0.1	5.1; 5.8	-;-	4.7; 5.9	-0.4; 0.3

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	670	706	26	27	143	150	177	181	346	358	436	441	1452	1505
	Month 24	n	0	0	2	0	1	0	1	0	4	0	0	0	4	0
		Mean (SD)	- (-)	- (-)	5.5 (0.14)	- (-)	6.0 (-)	- (-)	5.4 (-)	- (-)	5.6 (0.28)	- (-)	- (-)	- (-)	5.6 (0.28)	- (-)
		Median	-	-	5.5	-	6.0	-	5.4	-	5.5	-	-	-	5.5	-
		Q1; Q3	-;-	-;-	5.4; 5.6	-;-	6.0; 6.0	-;-	5.4; 5.4	-;-	5.4; 5.8	-;-	-;-	-;-	5.4; 5.8	-;-
		Min; Max	-;-	-;-	5.4; 5.6	-;-	6.0; 6.0	-;-	5.4; 5.4	-;-	5.4; 6.0	-;-	-;-	-;-	5.4; 6.0	-;-
		Missing	716	716	26	28	149	150	180	181	355	359	441	441	1512	1516
Hemoglobin (g/L)	Baseline	n	197		4		26		68		98		129		424	
		Mean (SD)	128.5 (27.65)		124.3 (10.31)		131.0 (9.83)		129.7 (28.54)		129.8 (24.34)		121.2 (32.98)		126.6 (28.85)	
		Median	134.0		123.0		131.0		132.5		131.0		129.0		132.0	
		Q1; Q3	127.0; 142.0		118.0; 130.5		126.0; 138.0		126.0; 139.0		126.0; 138.0		121.0; 138.0		124.0; 139.5	
		Min; Max	0.0; 168.0		113.0; 138.0		105.0; 154.0		12.5; 233.0		12.5; 233.0		1.3; 155.0		0.0; 233.0	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	519		24		124		113		261		312		1092	
	Month 12	n	72	34	0	0	5	1	5	3	10	4	6	0	88	38
		Mean (SD)	140.5 (44.30)	1.4 (23.30)	- (-)	- (-)	131.0 (14.51)	-7.0 (-)	114.4 (39.00)	-29.6 (58.21)	122.7 (29.08)	-24.0 (48.85)	114.2 (49.28)	- (-)	136.7 (43.57)	-1.2 (27.20)
		Median	141.0	5.0	-	-	129.0	-7.0	130.0	3.0	129.5	-2.0	132.5	-	137.0	4.5
		Q1; Q3	130.5; 149.0	-1.0; 11.0	-;-	-;-	124.0; 135.0	-7.0; -7.0	125.0; 134.0	-96.8; 5.0	124.0; 135.0	-51.9; 4.0	128.0; 137.0	-;-	129.0; 148.0	-1.0; 11.0
		Min; Max	13.1; 454.0	-122.9; 25.0	-;-	-;-	114.0; 153.0	-7.0; -7.0	45.2; 138.0	-96.8; 5.0	45.2; 153.0	-96.8; 5.0	14.0; 141.0	-;-	13.1; 454.0	-122.9; 25.0
		Missing	644	682	28	28	145	149	176	178	349	355	435	441	1428	1478
IGF-I (nmol/L)	Baseline	n	389		10		80		114		204		250		843	
		Mean (SD)	2399.6 (26090.97)		31.7 (19.41)		3194.3 (28169.52)		7343.4 (53583.33)		5357.9 (43732.19)		37.8 (52.37)		2415.1 (27902.64)	
		Median	36.9		39.2		34.5		31.4		33.9		25.7		32.7	
		Q1; Q3	19.7; 54.4		22.5; 45.7		17.0; 54.9		16.7; 54.9		17.0; 54.1		11.4; 49.1		15.9; 53.0	
		Min; Max	0.0; 372000.0		0.0; 54.1		0.0; 252000.0		0.1; 469000.0		0.0; 469000.0		0.0; 427.0		0.0; 469000.0	
		Missing	327		18		70		67		155		191		673	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Month 12	n	117	46	4	3	11	3	10	7	25	13	8	3	150	62
		Mean (SD)	59.2 (57.00)	19.3 (82.07)	38.8 (8.26)	0.0 (3.57)	47.0 (35.78)	-0.2 (123.15)	48.9 (20.77)	6.6 (11.55)	46.4 (26.76)	3.5 (51.07)	40.2 (11.03)	7.1 (11.84)	56.1 (51.84)	15.4 (74.37)
		Median	52.7	5.6	40.8	0.8	35.7	5.6	47.8	4.9	41.2	3.9	39.2	3.6	50.3	4.8
		Q1; Q3	38.7; 66.8	-1.0; 20.2	33.8; 43.9	-3.9; 3.1	13.5; 67.2	-126.2; 119.9	34.8; 63.0	-3.4; 8.9	34.8; 61.0	-3.4; 7.9	31.8; 49.8	-2.6; 20.3	36.6; 65.2	-2.6; 17.8
		Min; Max	0.3; 619.0	-41.0; 552.7	27.1; 46.5	-3.9; 3.1	0.7; 121.0	-126.2; 119.9	16.3; 82.3	-5.8; 29.6	0.7; 121.0	-126.2; 119.9	24.3; 55.5	-2.6; 20.3	0.3; 619.0	-126.2; 552.7
		Missing	599	670	24	25	139	147	171	174	334	346	433	438	1366	1454
	Month 24	n	2	0	2	0	2	1	2	0	6	1	0	0	8	1
		Mean (SD)	66.1 (35.50)	- (-)	28.9 (40.38)	- (-)	98.2 (53.95)	135.2 (-)	64.0 (38.18)	- (-)	63.7 (46.48)	135.2 (-)	- (-)	- (-)	64.3 (41.53)	135.2 (-)
		Median	66.1	-	28.9	-	98.2	135.2	64.0	-	58.7	135.2	-	-	58.7	135.2
		Q1; Q3	41.0; 91.2	-;-	0.3; 57.4	-;-	60.0; 136.3	135.2; 135.2	37.0; 91.0	-;-	37.0; 91.0	135.2; 135.2	-;-	-;-	39.0; 91.1	135.2; 135.2
		Min; Max	41.0; 91.2	-;-	0.3; 57.4	-;-	60.0; 136.3	135.2; 135.2	37.0; 91.0	-;-	0.3; 136.3	135.2; 135.2	-;-	-;-	0.3; 136.3	135.2; 135.2

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	714	716	26	28	148	149	179	181	353	358	441	441	1508	1515
IGFBP-3 (mg/L)	Baseline	n	125		6		32		59		97		88		310	
		Mean (SD)	191221.6 (1066200.69)		15.7 (25.32)		758803.4 (2051401.33)		179861.4 (963804.32)		359728.1 (1414634.97)		553.1 (1372.13)		189822.6 (1047463.66)	
		Median	5.7		6.2		6.5		5.8		6.1		4.8		5.8	
		Q1; Q3	4.5; 7.2		6.0; 8.6		3.9; 2262.5		3.5; 8.8		3.8; 60.0		3.3; 9.3		3.8; 8.0	
		Min; Max	0.0; 6810000.0		0.0; 67.0		0.0; 7180000.0		0.0; 5400000.0		0.0; 7180000.0		0.0; 5528.0		0.0; 7180000.0	
		Missing	591		22		118		122		262		353		1206	
	Month 12	n	19	3	2	1	4	2	4	0	10	3	1	1	30	7
		Mean (SD)	6.6 (1.90)	3.1 (2.84)	5.9 (0.64)	0.2 (-)	7.6 (2.00)	0.1 (1.84)	7.6 (1.37)	- (-)	7.2 (1.60)	0.1 (1.30)	3.6 (-)	2.0 (-)	6.7 (1.86)	1.7 (2.33)
		Median	7.3	3.6	5.9	0.2	7.5	0.1	7.7	-	7.2	0.2	3.6	2.0	7.2	1.4
		Q1; Q3	5.3; 8.0	0.0; 5.6	5.4; 6.3	0.2; 0.2	6.2; 9.1	-1.2; 1.4	6.6; 8.5	-;-	5.8; 7.9	-1.2; 1.4	3.6; 3.6	2.0; 2.0	5.4; 7.9	0.0; 3.6
		Min; Max	2.1; 9.8	0.0; 5.6	5.4; 6.3	0.2; 0.2	5.4; 10.2	-1.2; 1.4	5.8; 9.1	-;-	5.4; 10.2	-1.2; 1.4	3.6; 3.6	2.0; 2.0	2.1; 10.2	-1.2; 5.6
		Missing	697	713	26	27	146	148	177	181	349	356	440	440	1486	1509

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Month 24	n	0	0	2	0	1	1	1	0	4	1	0	0	4	1
		Mean (SD)	- (-)	- (-)	7.3 (3.61)	- (-)	10.9 (-)	-0.5 (-)	8.4 (-)	- (-)	8.5 (2.70)	-0.5 (-)	- (-)	- (-)	8.5 (2.70)	-0.5 (-)
		Median	-	-	7.3	-	10.9	-0.5	8.4	-	9.1	-0.5	-	-	9.1	-0.5
		Q1; Q3	-;-	-;-	4.7; 9.8	-;-	10.9; 10.9	-0.5; -0.5	8.4; 8.4	-;-	6.6; 10.4	-0.5; -0.5	-;-	-;-	6.6; 10.4	-0.5; -0.5
		Min; Max	-;-	-;-	4.7; 9.8	-;-	10.9; 10.9	-0.5; -0.5	8.4; 8.4	-;-	4.7; 10.9	-0.5; -0.5	-;-	-;-	4.7; 10.9	-0.5; -0.5
		Missing	716	716	26	28	149	149	180	181	355	358	441	441	1512	1515
Insulin (pmol/L)	Baseline	n	63		0		7		33		40		56		159	
		Mean (SD)	63.8 (55.41)		- (-)		35.9 (58.32)		38.7 (37.52)		38.2 (40.98)		36.7 (49.90)		47.8 (51.54)	
		Median	56.4		-		19.4		20.8		20.3		11.8		27.1	
		Q1; Q3	19.8; 88.9		-;-		7.4; 20.8		6.6; 56.9		6.8; 55.8		4.4; 58.2		7.8; 69.4	
		Min; Max	4.6; 213.9		-;-		6.6; 167.4		3.0; 129.2		3.0; 167.4		0.0; 183.3		0.0; 213.9	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	653		28		143		148		319		385		1357	
	Month 12	n	3	2	0	0	2	0	1	1	3	1	1	0	7	3
		Mean (SD)	44.3 (16.71)	-8.7 (36.84)	- (-)	- (-)	44.5 (13.79)	- (-)	13.9 (-)	-6.9 (-)	34.3 (20.15)	-6.9 (-)	6.1 (-)	- (-)	34.5 (20.27)	-8.1 (26.07)
		Median	34.7	-8.7	-	-	44.5	-	13.9	-6.9	34.7	-6.9	6.1	-	34.7	-6.9
		Q1; Q3	34.6; 63.6	-34.7; 17.4	-;-	-;-	34.7; 54.2	-;-	13.9; 13.9	-6.9; -6.9	13.9; 54.2	-6.9; -6.9	6.1; 6.1	-;-	13.9; 54.2	-34.7; 17.4
		Min; Max	34.6; 63.6	-34.7; 17.4	-;-	-;-	34.7; 54.2	-;-	13.9; 13.9	-6.9; -6.9	13.9; 54.2	-6.9; -6.9	6.1; 6.1	-;-	6.1; 63.6	-34.7; 17.4
		Missing	713	714	28	28	148	150	180	180	356	358	440	441	1509	1513
LDLc (mmol/L)	Baseline	n	110		3		9		39		51		76		237	
		Mean (SD)	5.5 (16.17)		2.4 (0.72)		2.1 (0.79)		9.2 (23.93)		7.5 (21.08)		11.9 (30.25)		8.0 (22.66)	
		Median	2.4		2.0		2.3		2.4		2.3		2.6		2.4	
		Q1; Q3	2.0; 2.8		1.9; 3.2		1.5; 2.7		2.0; 3.0		2.0; 2.8		2.0; 3.1		2.0; 2.9	
		Min; Max	1.2; 93.0		1.9; 3.2		0.6; 3.0		1.3; 106.0		0.6; 106.0		0.6; 137.0		0.6; 137.0	
		Missing	606		25		141		142		308		365		1279	
	Month 12	n	63	32	0	0	3	0	1	1	4	1	1	0	68	33

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Mean (SD)	3.3 (7.80)	-0.0 (0.71)	- (-)	- (-)	2.2 (0.59)	- (-)	1.6 (-)	-0.8 (-)	2.0 (0.56)	-0.8 (-)	1.4 (-)	- (-)	3.2 (7.51)	-0.0 (0.71)
		Median	2.3	0.0	-	-	2.4	-	1.6	-0.8	2.0	-0.8	1.4	-	2.3	0.0
		Q1; Q3	1.9; 2.7	-0.2; 0.2	-;-	-;-	1.5; 2.6	-;-	1.6; 1.6	-0.8; -0.8	1.6; 2.5	-0.8; -0.8	1.4; 1.4	-;-	1.9; 2.6	-0.2; 0.2
		Min; Max	0.4; 64.0	-3.3; 1.0	-;-	-;-	1.5; 2.6	-;-	1.6; 1.6	-0.8; -0.8	1.5; 2.6	-0.8; -0.8	1.4; 1.4	-;-	0.4; 64.0	-3.3; 1.0
		Missing	653	684	28	28	147	150	180	180	355	358	440	441	1448	1483
LH (mIU/ml)	Baseline	n	151		4		27		41		72		88		311	
		Mean (SD)	3.5 (19.39)		1.0 (1.77)		2.1 (3.47)		1.1 (1.31)		1.4 (2.40)		1.6 (2.80)		2.5 (13.65)	
		Median	0.9		0.1		0.7		0.3		0.6		0.4		0.7	
		Q1; Q3	0.3; 2.1		0.1; 1.9		0.3; 2.0		0.2; 1.8		0.2; 1.8		0.1; 2.3		0.2; 2.1	
		Min; Max	0.0; 230.0		0.0; 3.6		0.0; 13.0		0.0; 5.8		0.0; 13.0		0.0; 21.1		0.0; 230.0	
		Missing	565		24		123		140		287		353		1205	
	Month 12	n	67	31	1	0	4	0	3	1	8	1	1	0	76	32
		Mean (SD)	2.0 (1.53)	-0.1 (2.06)	1.3 (-)	- (-)	1.1 (1.50)	- (-)	0.8 (0.25)	0.7 (-)	1.0 (1.01)	0.7 (-)	5.2 (-)	- (-)	1.9 (1.54)	-0.0 (2.04)
		Median	1.6	0.0	1.3	-	0.3	-	0.8	0.7	0.7	0.7	5.2	-	1.5	0.0

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Q1; Q3	0.7; 3.1	-0.9; 0.8	1.3; 1.3	-;-	0.3; 1.8	-;-	0.5; 1.0	0.7; 0.7	0.3; 1.2	0.7; 0.7	5.2; 5.2	-;-	0.5; 3.0	-0.9; 0.8
		Min; Max	0.1; 6.0	-5.9; 5.5	1.3; 1.3	-;-	0.3; 3.3	-;-	0.5; 1.0	0.7; 0.7	0.3; 3.3	0.7; 0.7	5.2; 5.2	-;-	0.1; 6.0	-5.9; 5.5
		Missing	649	685	27	28	146	150	178	180	351	358	440	441	1440	1484
	Month 24	n	0	0	1	0	0	0	0	0	1	0	0	0	1	0
		Mean (SD)	- (-)	- (-)	0.5 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	0.5 (-)	- (-)	- (-)	- (-)	0.5 (-)	- (-)
		Median	-	-	0.5	-	-	-	-	-	0.5	-	-	-	0.5	-
		Q1; Q3	-;-	-;-	0.5; 0.5	-;-	-;-	-;-	-;-	-;-	0.5; 0.5	-;-	-;-	-;-	0.5; 0.5	-;-
		Min; Max	-;-	-;-	0.5; 0.5	-;-	-;-	-;-	-;-	-;-	0.5; 0.5	-;-	-;-	-;-	0.5; 0.5	-;-
		Missing	716	716	27	28	150	150	181	181	358	359	441	441	1515	1516
Lp (a) (mg/dL)	Baseline	n	8		0		1		1		2		3		13	
		Mean (SD)	68.0 (79.16)		- (-)		7.0 (-)		7.0 (-)		7.0 (0.00)		12.3 (8.04)		45.7 (67.27)	
		Median	25.7		-		7.0		7.0		7.0		10.9		10.9	
		Q1; Q3	7.0; 140.1		-;-		7.0; 7.0		7.0; 7.0		7.0; 7.0		5.0; 20.9		7.0; 35.1	
		Min; Max	7.0; 191.2		-;-		7.0; 7.0		7.0; 7.0		7.0; 7.0		5.0; 20.9		5.0; 191.2	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	708		28		149		180		357		438		1503	
Osteocalcin (ng/ml)	Baseline	n	0		0		2		7		9		6		15	
		Mean (SD)	- (-)		- (-)		112.5 (17.68)		86.5 (46.49)		92.3 (42.33)		102.3 (45.69)		96.3 (42.37)	
		Median	-		-		112.5		85.1		93.8		96.4		95.0	
		Q1; Q3	-;-		-;-		100.0; 125.0		54.2; 96.4		61.1; 100.0		79.3; 133.0		61.1; 125.0	
		Min; Max	-;-		-;-		100.0; 125.0		35.8; 179.0		35.8; 179.0		37.7; 171.0		35.8; 179.0	
		Missing	716		28		148		174		350		435		1501	
Parathyroid hormone (pmol/L)	Baseline	n	18		0		4		11		15		16		49	
		Mean (SD)	3.2 (1.64)		- (-)		3.7 (0.40)		3.5 (1.59)		3.5 (1.36)		14.8 (32.97)		7.1 (19.24)	
		Median	3.0		-		3.8		3.4		3.6		4.0		3.4	
		Q1; Q3	2.3; 3.7		-;-		3.4; 4.0		2.3; 4.2		2.5; 4.0		2.8; 6.5		2.8; 4.2	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Min; Max	1.3; 8.5		-;-		3.1; 4.0		1.6; 6.9		1.6; 6.9		1.3; 131.8		1.3; 131.8	
		Missing	698		28		146		170		344		425		1467	
	Month 12	n	0	0	0	0	1	0	1	0	2	0	0	0	2	0
		Mean (SD)	- (-)	- (-)	- (-)	- (-)	27.0 (-)	- (-)	3.8 (-)	- (-)	15.4 (16.40)	- (-)	- (-)	- (-)	15.4 (16.40)	- (-)
		Median	-	-	-	-	27.0	-	3.8	-	15.4	-	-	-	15.4	-
		Q1; Q3	-;-	-;-	-;-	-;-	27.0; 27.0	-;-	3.8; 3.8	-;-	3.8; 27.0	-;-	-;-	-;-	3.8; 27.0	-;-
		Min; Max	-;-	-;-	-;-	-;-	27.0; 27.0	-;-	3.8; 3.8	-;-	3.8; 27.0	-;-	-;-	-;-	3.8; 27.0	-;-
		Missing	716	716	28	28	149	150	180	181	357	359	441	441	1514	1516
Phosphate (mmol/L)	Baseline	n	109		0		13		43		56		76		241	
		Mean (SD)	4.3 (28.90)		- (-)		1.6 (0.36)		1.6 (0.61)		1.6 (0.56)		1.4 (0.60)		2.7 (19.44)	
		Median	1.3		-		1.5		1.4		1.4		1.3		1.3	
		Q1; Q3	1.2; 1.5		-;-		1.3; 1.6		1.2; 1.8		1.3; 1.8		1.2; 1.5		1.2; 1.5	
		Min; Max	0.6; 303.0		-;-		1.1; 2.4		0.9; 4.7		0.9; 4.7		1.0; 6.1		0.6; 303.0	
		Missing	607		28		137		138		303		365		1275	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Month 12	n	65	31	0	0	4	0	2	1	6	1	2	1	73	33
		Mean (SD)	1.3 (0.69)	-0.0 (0.88)	- (-)	- (-)	1.2 (0.17)	- (-)	1.3 (0.35)	0.0 (-)	1.2 (0.21)	0.0 (-)	1.4 (0.07)	0.0 (-)	1.3 (0.65)	-0.0 (0.85)
		Median	1.2	0.0	-	-	1.3	-	1.3	0.0	1.3	0.0	1.4	0.0	1.2	0.0
		Q1; Q3	1.1; 1.3	-0.2; 0.0	-;-	-;-	1.1; 1.4	-;-	1.0; 1.5	0.0; 0.0	1.0; 1.4	0.0; 0.0	1.3; 1.4	0.0; 0.0	1.1; 1.3	-0.1; 0.0
		Min; Max	0.8; 5.4	-3.3; 3.3	-;-	-;-	1.0; 1.4	-;-	1.0; 1.5	0.0; 0.0	1.0; 1.5	0.0; 0.0	1.3; 1.4	0.0; 0.0	0.8; 5.4	-3.3; 3.3
		Missing	651	685	28	28	146	150	179	180	353	358	439	440	1443	1483
Procollagen-1 C-terminal propeptide (ng/ml)	Baseline	n	0		0		2		5		7		3		10	
		Mean (SD)	- (-)		- (-)		1.7 (0.03)		1.5 (0.38)		1.6 (0.33)		1.4 (0.63)		1.5 (0.41)	
		Median	-		-		1.7		1.6		1.6		1.0		1.6	
		Q1; Q3	-;-		-;-		1.7; 1.8		1.2; 1.6		1.2; 1.8		1.0; 2.1		1.1; 1.8	
		Min; Max	-;-		-;-		1.7; 1.8		1.1; 2.1		1.1; 2.1		1.0; 2.1		1.0; 2.1	
		Missing	716		28		148		176		352		438		1506	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Prolactin (µg/L)	Baseline	n	21		1		8		12		21		18		60	
		Mean (SD)	56.4 (98.43)		9.4 (-)		2207.5 (6219.51)		29.4 (46.83)		858.2 (3836.19)		36.8 (56.23)		331.2 (2268.26)	
		Median	13.0		9.4		6.2		12.1		9.7		11.3		11.9	
		Q1; Q3	8.7; 34.1		9.4; 9.4		5.7; 15.4		7.8; 30.4		6.0; 20.3		7.7; 31.8		6.4; 30.4	
		Min; Max	0.0; 330.0		9.4; 9.4		5.6; 17600.0		0.2; 171.8		0.2; 17600.0		0.8; 180.0		0.0; 17600.0	
		Missing	695		27		142		169		338		423		1456	
	Month 12	n	1	0	0	0	0	0	0	0	0	0	0	0	1	0
		Mean (SD)	0.0 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	0.0 (-)	- (-)
		Median	0.0	-	-	-	-	-	-	-	-	-	-	-	0.0	-
		Q1; Q3	0.0; 0.0	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	0.0; 0.0	-;-
		Min; Max	0.0; 0.0	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	-;-	0.0; 0.0	-;-
		Missing	715	716	28	28	150	150	181	181	359	359	441	441	1515	1516
TSH (µIU/mL)	Baseline	n	344		13		55		109		177		207		728	
		Mean (SD)	6.4 (52.93)		2.2 (1.13)		2.2 (1.58)		2.2 (1.16)		2.2 (1.30)		2.3 (1.40)		4.2 (36.43)	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Median	1.9		1.8		2.0		2.1		2.1		2.0		2.0	
		Q1; Q3	1.3; 2.9		1.5; 2.3		1.0; 2.8		1.4; 3.0		1.4; 2.8		1.3; 3.0		1.3; 2.9	
		Min; Max	0.0; 931.0		1.0; 5.1		0.0; 7.8		0.0; 5.4		0.0; 7.8		0.0; 9.1		0.0; 931.0	
		Missing	372		15		95		72		182		234		788	
	Month 12	n	49	12	4	3	6	0	10	5	20	8	5	1	74	21
		Mean (SD)	1.8 (0.92)	-7.8 (25.41)	1.8 (0.64)	-0.7 (1.18)	1.3 (0.44)	- (-)	1.6 (0.78)	-1.0 (1.41)	1.5 (0.67)	-0.9 (1.24)	1.8 (0.84)	1.5 (-)	1.7 (0.85)	-4.7 (19.21)
		Median	1.7	-0.2	1.9	-0.1	1.4	-	1.9	-0.9	1.6	-0.6	1.8	1.5	1.7	-0.2
		Q1; Q3	1.1; 2.2	-0.8; 0.2	1.3; 2.3	-2.1; 0.0	0.8; 1.7	-;-	0.9; 2.3	-1.6; -0.2	1.0; 2.1	-1.9; -0.1	1.3; 2.4	1.5; 1.5	1.1; 2.2	-0.9; 0.1
		Min; Max	0.0; 4.3	-88.4; 0.5	1.0; 2.4	-2.1; 0.0	0.7; 1.7	-;-	0.2; 2.5	-3.0; 0.7	0.2; 2.5	-3.0; 0.7	0.8; 2.9	1.5; 1.5	0.0; 4.3	-88.4; 1.5

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	667	704	24	25	144	150	171	176	339	351	436	440	1442	1495
	Month 24	n	2	0	2	0	2	0	2	0	6	0	0	0	8	0
		Mean (SD)	1.1 (0.42)	- (-)	1.6 (0.49)	- (-)	2.0 (0.85)	- (-)	1.0 (0.64)	- (-)	1.5 (0.70)	- (-)	- (-)	- (-)	1.4 (0.64)	- (-)
		Median	1.1	-	1.6	-	2.0	-	1.0	-	1.4	-	-	-	1.4	-
		Q1; Q3	0.8; 1.4	-;-	1.2; 1.9	-;-	1.4; 2.6	-;-	0.5; 1.4	-;-	1.2; 1.9	-;-	-;-	-;-	1.0; 1.7	-;-
		Min; Max	0.8; 1.4	-;-	1.2; 1.9	-;-	1.4; 2.6	-;-	0.5; 1.4	-;-	0.5; 2.6	-;-	-;-	-;-	0.5; 2.6	-;-
		Missing	714	716	26	28	148	150	179	181	353	359	441	441	1508	1516
Testosterone (nmol/L)	Baseline	n	114		3		16		31		50		49		213	
		Mean (SD)	3.9 (6.40)		2.6 (2.14)		2.4 (3.90)		49.8 (153.05)		31.8 (122.01)		14.4 (85.01)		12.8 (72.30)	
		Median	0.8		3.3		1.5		0.6		1.1		0.4		0.7	
		Q1; Q3	0.3; 3.6		0.2; 4.3		0.3; 2.5		0.1; 10.9		0.2; 4.3		0.2; 2.7		0.2; 3.6	
		Min; Max	0.0; 28.5		0.2; 4.3		0.1; 16.1		0.0; 718.0		0.0; 718.0		0.0; 596.7		0.0; 718.0	
		Missing	602		25		134		150		309		392		1303	
	Month 12	n	68	33	0	0	2	0	3	2	5	2	4	0	77	35

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Mean (SD)	3.5 (5.45)	-0.0 (4.33)	- (-)	- (-)	15.1 (21.14)	- (-)	0.4 (0.42)	0.2 (0.21)	6.3 (13.26)	0.2 (0.21)	0.9 (1.62)	- (-)	3.5 (6.03)	-0.0 (4.20)
		Median	1.0	0.0	-	-	15.1	-	0.3	0.2	0.3	0.2	0.1	-	1.0	0.0
		Q1; Q3	0.4; 4.4	-0.7; 0.9	-;-	-;-	0.1; 30.0	-;-	0.1; 0.9	0.0; 0.3	0.1; 0.9	0.0; 0.3	0.0; 1.8	-;-	0.2; 3.3	-0.7; 0.9
		Min; Max	0.0; 29.5	-12.7; 10.3	-;-	-;-	0.1; 30.0	-;-	0.1; 0.9	0.0; 0.3	0.1; 30.0	0.0; 0.3	0.0; 3.3	-;-	0.0; 30.0	-12.7; 10.3
		Missing	648	683	28	28	148	150	178	179	354	357	437	441	1439	1481
	Month 24	n	1	0	0	0	1	0	0	0	1	0	0	0	2	0
		Mean (SD)	21.1 (-)	- (-)	- (-)	- (-)	13.1 (-)	- (-)	- (-)	- (-)	13.1 (-)	- (-)	- (-)	- (-)	17.1 (5.66)	- (-)
		Median	21.1	-	-	-	13.1	-	-	-	13.1	-	-	-	17.1	-
		Q1; Q3	21.1; 21.1	-;-	-;-	-;-	13.1; 13.1	-;-	-;-	-;-	13.1; 13.1	-;-	-;-	-;-	13.1; 21.1	-;-
		Min; Max	21.1; 21.1	-;-	-;-	-;-	13.1; 13.1	-;-	-;-	-;-	13.1; 13.1	-;-	-;-	-;-	13.1; 21.1	-;-
		Missing	715	716	28	28	149	150	181	181	358	359	441	441	1514	1516
Total Thyroxine (nmol/L)	Baseline	n	29		2		12		9		23		7		59	
		Mean (SD)	73.7 (48.80)		89.5 (6.36)		83.4 (66.78)		69.0 (46.62)		78.3 (55.52)		3.2 (7.67)		67.1 (53.76)	
		Median	95.5		89.5		79.8		90.1		85.0		0.0		83.7	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Q1; Q3	16.5; 111.9		85.0; 94.0		33.8; 112.0		16.3; 104.3		16.3; 105.6		0.0; 1.6		11.5; 105.6	
		Min; Max	0.0; 142.1		85.0; 94.0		0.0; 209.8		4.7; 122.3		0.0; 209.8		0.0; 20.5		0.0; 209.8	
		Missing	687		26		138		172		336		434		1457	
	Month 12	n	4	0	2	1	2	0	0	0	4	1	0	0	8	1
		Mean (SD)	116.5 (9.89)	- (-)	109.4 (25.46)	6.4 (-)	94.7 (0.92)	- (-)	- (-)	- (-)	102.0 (16.99)	6.4 (-)	- (-)	- (-)	109.3 (15.02)	6.4 (-)
		Median	112.0	-	109.4	6.4	94.7	-	-	-	94.7	6.4	-	-	111.4	6.4
		Q1; Q3	111.4; 121.7	-;-	91.4; 127.4	6.4; 6.4	94.0; 95.3	-;-	-;-	-;-	92.7; 111.4	6.4; 6.4	-;-	-;-	94.7; 119.7	6.4; 6.4
		Min; Max	110.7; 131.3	-;-	91.4; 127.4	6.4; 6.4	94.0; 95.3	-;-	-;-	-;-	91.4; 127.4	6.4; 6.4	-;-	-;-	91.4; 131.3	6.4; 6.4

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Missing	712	716	26	27	148	150	181	181	355	358	441	441	1508	1515
	Month 24	n	0	0	2	0	1	0	0	0	3	0	0	0	3	0
		Mean (SD)	- (-)	- (-)	121.0 (9.05)	- (-)	95.3 (-)	- (-)	- (-)	- (-)	112.4 (16.16)	- (-)	- (-)	- (-)	112.4 (16.16)	- (-)
		Median	-	-	121.0	-	95.3	-	-	-	114.6	-	-	-	114.6	-
		Q1; Q3	-;-	-;-	114.6; 127.4	-;-	95.3; 95.3	-;-	-;-	-;-	95.3; 127.4	-;-	-;-	-;-	95.3; 127.4	-;-
		Min; Max	-;-	-;-	114.6; 127.4	-;-	95.3; 95.3	-;-	-;-	-;-	95.3; 127.4	-;-	-;-	-;-	95.3; 127.4	-;-
		Missing	716	716	26	28	149	150	181	181	356	359	441	441	1513	1516
Triglycerides (mmol/L)	Baseline	n	127		5		20		56		81		115		323	
		Mean (SD)	1.4 (5.62)		1.5 (1.43)		1.3 (1.05)		0.9 (0.51)		1.0 (0.76)		4.4 (20.89)		2.4 (13.01)	
		Median	0.8		1.0		1.0		0.9		0.9		0.8		0.8	
		Q1; Q3	0.6; 1.1		0.6; 1.3		0.6; 1.7		0.5; 1.0		0.6; 1.2		0.5; 1.1		0.6; 1.1	
		Min; Max	0.0; 64.0		0.6; 4.0		0.4; 5.1		0.3; 2.8		0.3; 5.1		0.2; 201.0		0.0; 201.0	
		Missing	589		23		130		125		278		326		1193	

Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Month 12	n	5	2	0	0	1	0	2	1	3	1	1	1	9	4
		Mean (SD)	0.8 (0.17)	-0.1 (0.14)	- (-)	- (-)	0.8 (-)	- (-)	0.9 (0.78)	-1.0 (-)	0.8 (0.55)	-1.0 (-)	0.6 (-)	0.1 (-)	0.8 (0.31)	-0.3 (0.50)
		Median	0.8	-0.1	-	-	0.8	-	0.9	-1.0	0.8	-1.0	0.6	0.1	0.8	-0.1
		Q1; Q3	0.8; 1.0	-0.2; 0.0	-;-	-;-	0.8; 0.8	-;-	0.3; 1.4	-1.0; -1.0	0.3; 1.4	-1.0; -1.0	0.6; 0.6	0.1; 0.1	0.6; 1.0	-0.6; 0.1
		Min; Max	0.6; 1.0	-0.2; 0.0	-;-	-;-	0.8; 0.8	-;-	0.3; 1.4	-1.0; -1.0	0.3; 1.4	-1.0; -1.0	0.6; 0.6	0.1; 0.1	0.3; 1.4	-1.0; 0.1
		Missing	711	714	28	28	149	150	179	180	356	358	440	440	1507	1512

hGH: Human Growth Hormone; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard deviation; TSH: thyroid stimulating hormone.
The baseline is the results measured at baseline visit prior to informed consent.
For 'Blood Glucose', outlier values were removed for 16 patients where the values were less than 1 mmol/L or greater than 14 mmol/L.
For 'TSH', outlier values were removed for 4 patients where the values exceeded 1000 µIU/mL.
Source: Table 15.3.17.1, Appendix 8: Additional documents

10.3. Outcome Data

There were 1559 patients enrolled in the study. A total of 1516 patients were included in the FAS with 716 patients in the Genotropin group, 359 patients in the Other daily hGH group, and 441 patients enrolled in the Ngenla group (Table 5).

10.4. Main Results

10.4.1. Primary Safety Results

Primary AESIs are presented in Section 10.6.1.

10.4.2. Primary Effectiveness Results

Primary effectiveness results available include annual HV, HVSDS, change in height SDS, and change in annual BMI SDS. Data for BMD and amount of dose adjustment necessary for targeted increase or decrease in IGF-1 response are sparse and presented in Appendix 8: Additional documents.

Among all patients, the mean (SD) height at baseline was 136.5 (21.17) cm and was similar in the Genotropin, Other daily hGH group, and the Ngenla group (139.5 [20.04], 136.2 [22.72], and 131.7 [20.76] cm, respectively). Data for baseline height were missing for 92 patients. At Month 12, the overall mean (SD) HV was 7.3 (1.86) and was similar in the Genotropin and the Ngenla group (7.5 [1.88] and 7.6 [1.84], respectively). The overall mean (SD) HV was higher than the Other daily hGH group (6.5 [1.61]). Data were missing for 1307 patients. At Month 24, the overall mean (SD) HV was 6.4 (1.55) and was greater in the Genotropin group (7.7 [1.47]) than in the Other daily hGH group (5.9 [1.28]). There were no patient details available for the Ngenla group at Month 24 and data were missing for 1500 patients (Table 13).

Among patients with idiopathic GHD (N=1118), the overall mean (SD) height at baseline was 137.6 (20.10) and was less than Genotropin group (140.6 [18.88]), similar to Other daily hGH group (138.3 [21.61]), and more than Ngenla group (132.6 [20.03]). Data for baseline annual HV were missing for 67 patients. At Month 12, the overall mean (SD) annual HV was 7.3 (1.80) and was similar to Genotropin group and Ngenla group (7.5 [1.79] and 7.2 [1.77], respectively) and more than Other daily hGH group (6.6 [1.70]). Data were missing for 932 patients. At Month 24, the overall mean (SD) annual HV was 6.6 (1.63), which was less than Genotropin (8.1 [1.21]) and more than the Other daily hGH group (5.9 [1.35]). Patient details were not available for the Ngenla group at Month 24. Data were missing for 1105 patients (Table 14).

Among patients with Turner syndrome (N=15), the overall mean (SD) height at baseline was 128.2 (17.18) and was less than Genotropin group (135.6 [13.74]), and more than Other daily hGH group (119.9 [17.79]). Baseline patient details were not available for the Ngenla group. At Months 12 and 24, no patient details were available, and data were missing for 15 patients during both time points (Table 14).

Among patients with SGA/IUGR (N=67), the overall mean (SD) height at baseline was 125.8 (19.22) and was similar to the Genotropin group and the Other daily hGH group (128.8 [19.88] and 123.4 [19.70], respectively), and more than the Ngenla group (119.8 [11.44]). Data for baseline annual HV were missing for 3 patients. At Month 12, the mean (SD)

annual HV was 5.1 (0.77) in the Other daily hGH group (5.1 [0.77]). Patient details were not available for the Genotropin group and the Ngenla group at Month 12 and data were missing for 64 patients. At Month 24, no patient details were available; data were missing for all 67 patients (Table 14).

Among patients with ISS (N=23), the overall mean (SD) height at baseline was 137.6 (17.36) and was less than the Genotropin group (140.1 [13.77]), similar to the Other daily hGH group (137.1 [24.77]) and more than the Ngenla group (122.9 [12.94]). Data for baseline height were missing for 2 patients. At Months 12 and 24, no patient details were available; data were missing for all 23 patients during both time points (Table 14).

Among patients with Prader-Labhart-Willi/Prader-Willi Syndrome (N=29), the overall mean (SD) height at baseline was 132.7 (29.04) and was similar to Genotropin group (130.6 [31.39]) and less than the Other daily hGH group (139.0 [21.60]). Baseline patient details were not available for the Ngenla group. Data for baseline height were missing for 5 patients. At Month 12, the mean (SD) annual HV was 6.6 (0.17) in the Genotropin group. Patient details were not available for the Other daily hGH group and the Ngenla group at Month 12 and data were missing for 27 patients. At Month 24, no patient details were available; data were missing for all 29 patients (Table 14).

Table 13 Primary Effectiveness Outcome, Annual HV – Full Analysis Set

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
Baseline Height	n	670	26	144	173	343	411	1424
	Mean (SD)	139.5 (20.04)	140.6 (21.12)	137.7 (22.99)	134.2 (22.66)	136.2 (22.72)	131.7 (20.76)	136.5 (21.17)
	Median	142.0	144.1	140.5	136.4	139.0	133.4	138.7
	Q1; Q3	128.4 ; 154.6	124.3 ; 158.9	122.1 ; 155.3	117.5 ; 152.7	119.5 ; 153.9	116.8 ; 146.7	122.1 ; 152.4
	Min; Max	53.5 ; 182.1	93.4 ; 170.1	80.9 ; 179.0	68.0 ; 180.3	68.0 ; 180.3	78.6 ; 182.5	53.5 ; 182.5
	Missing	46	2	6	8	16	30	92
Month 12 HV	n	154	7	21	18	46	9	209
	Mean (SD)	7.5 (1.88)	5.6 (0.95)	6.7 (1.53)	6.7 (1.84)	6.5 (1.61)	7.6 (1.84)	7.3 (1.86)
	Median	7.4	5.7	6.8	6.5	6.3	7.7	7.2
	Q1; Q3	6.1 ; 8.6	4.8 ; 6.2	6.0 ; 7.9	5.3 ; 7.8	5.3 ; 7.6	6.5 ; 8.9	6.0 ; 8.4
	Min; Max	4.2 ; 14.0	4.1 ; 6.9	2.6 ; 9.6	3.7 ; 10.2	2.6 ; 10.2	4.5 ; 10.3	2.6 ; 14.0
	Missing	562	21	129	163	313	432	1307
Month 24 HV	n	5	3	4	4	11	0	16
	Mean (SD)	7.7 (1.47)	5.3 (0.98)	5.7 (1.23)	6.4 (1.59)	5.9 (1.28)	- (-)	6.4 (1.55)

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
	Median	7.1	4.9	5.6	6.4	5.1	-	6.3
	Q1; Q3	7.0 ; 9.1	4.6 ; 6.4	4.8 ; 6.7	5.1 ; 7.8	4.9 ; 7.2	- ; -	5.0 ; 7.4
	Min; Max	5.8 ; 9.2	4.6 ; 6.4	4.4 ; 7.2	5.0 ; 8.0	4.4 ; 8.0	- ; -	4.4 ; 9.2
	Missing	711	25	146	177	348	441	1500

hGH: Human Growth Hormone; HV: Height Velocity; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard Deviation.
Height Velocity is calculated as ((Height at a given time point – Height at a previous time point)/(Follow-up measurement date – previous measurement date))*365.25.
Source: Table 15.2.1.1, Appendix 8: Additional documents

Table 14 Primary Effectiveness Outcome - Annual HV by Primary Diagnosis (Full Analysis Set)

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points/Primary Diagnosis Categories		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
Idiopathic GHD (N=1118)								
Baseline Height	n	509	17	88	109	214	328	1051
	Mean (SD)	140.6 (18.88)	141.5 (22.13)	139.1 (21.32)	137.2 (21.89)	138.3 (21.61)	132.6 (20.03)	137.6 (20.10)
	Median	142.8	144.2	142.4	138.8	141.1	135.7	139.3
	Q1; Q3	129.5; 154.7	124.5; 158.9	127.2; 154.4	124.5; 153.6	125.7; 154.8	117.6; 146.8	125.0; 152.5
	Min; Max	74.6; 182.1	93.4; 170.1	85.0; 176.7	68.0; 180.3	68.0; 180.3	78.6; 176.0	68.0; 182.1
	Missing	32	2	2	6	10	25	67
Month 12 HV	n	145	4	16	14	34	7	186
	Mean (SD)	7.5 (1.79)	5.4 (0.99)	6.6 (1.71)	6.9 (1.80)	6.6 (1.70)	7.2 (1.77)	7.3 (1.80)
	Median	7.5	5.7	6.9	6.7	6.5	7.7	7.3
	Q1; Q3	6.1; 8.6	4.7; 6.2	5.6; 8.0	5.3; 7.8	5.3; 7.8	5.7; 8.9	6.0; 8.6
	Min; Max	4.2; 12.7	4.1; 6.2	2.6; 9.6	3.7; 10.2	2.6; 10.2	4.5; 9.6	2.6; 12.7
	Missing	396	15	74	101	190	346	932
Month 24 HV	n	4	1	4	4	9	0	13
	Mean (SD)	8.1 (1.21)	4.9 (-)	5.7 (1.23)	6.4 (1.59)	5.9 (1.35)	- (-)	6.6 (1.63)
	Median	8.1	4.9	5.6	6.4	5.1	-	7.0

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points/Primary Diagnosis Categories		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
	Q1; Q3	7.1; 9.2	4.9; 4.9	4.8; 6.7	5.1; 7.8	5.0; 7.2	-; -	5.1; 7.7
	Min; Max	7.0; 9.2	4.9; 4.9	4.4; 7.2	5.0; 8.0	4.4; 8.0	-; -	4.4; 9.2
	Missing	537	18	86	111	215	353	1105
Turner syndrome (N=15)								
Baseline Height	n	8	1	1	5	7	0	15
	Mean (SD)	135.6 (13.74)	122.5 (-)	100.0 (-)	123.4 (18.94)	119.9 (17.79)	- (-)	128.2 (17.18)
	Median	135.3	122.5	100.0	119.5	119.5	-	123.4
	Q1; Q3	122.3; 147.3	122.5; 122.5	100.0; 100.0	112.0; 123.4	106.7; 123.4	-; -	119.5; 141.4
	Min; Max	120.0; 154.9	122.5; 122.5	100.0; 100.0	106.7; 155.2	100.0; 155.2	-; -	100.0; 155.2
	Missing	0	0	0	0	0	0	0
Month 12 HV	n	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	8	1	1	5	7	0	15

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points/Primary Diagnosis Categories		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
Month 24 HV	n	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	8	1	1	5	7	0	15
SGA/IUGR (N=67)								
Baseline Height	n	32	0	10	16	26	6	64
	Mean (SD)	128.8 (19.88)	- (-)	124.0 (18.78)	123.1 (20.85)	123.4 (19.70)	119.8 (11.44)	125.8 (19.22)
	Median	129.8	-	124.6	119.8	124.6	121.5	124.9
	Q1; Q3	116.0; 142.9	-; -	106.3; 138.7	107.8; 139.5	107.6; 138.7	112.5; 125.2	110.5; 140.0
	Min; Max	86.6; 163.5	-; -	102.3; 157.8	94.0; 161.0	94.0; 161.0	102.2; 135.6	86.6; 163.5
	Missing	2	0	1	0	1	0	3
Month 12 HV	n	0	0	1	2	3	0	3
	Mean (SD)	- (-)	- (-)	6.0 (-)	4.7 (0.22)	5.1 (0.77)	- (-)	5.1 (0.77)
	Median	-	-	6.0	4.7	4.8	-	4.8
	Q1; Q3	-; -	-; -	6.0; 6.0	4.5; 4.8	4.5; 6.0	-; -	4.5; 6.0

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points/Primary Diagnosis Categories		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
	Min; Max	-; -	-; -	6.0; 6.0	4.5; 4.8	4.5; 6.0	-; -	4.5; 6.0
	Missing	34	0	10	14	24	6	64
Month 24 HV	n	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	34	0	11	16	27	6	67
ISS (N=23)								
Baseline Height	n	13	1	2	3	6	2	21
	Mean (SD)	140.1 (13.77)	152.8 (-)	137.1 (0.21)	131.8 (37.01)	137.1 (24.77)	122.9 (12.94)	137.6 (17.36)
	Median	138.7	152.8	137.1	145.2	141.2	122.9	137.5
	Q1; Q3	131.9; 149.3	152.8; 152.8	136.9; 137.2	90.0; 160.3	136.9; 152.8	113.7; 132.0	131.9; 149.3
	Min; Max	116.5; 167.0	152.8; 152.8	136.9; 137.2	90.0; 160.3	90.0; 160.3	113.7; 132.0	90.0; 167.0
	Missing	2	0	0	0	0	0	2
Month 12 HV	n	0	0	0	0	0	0	0

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points/Primary Diagnosis Categories		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	15	1	2	3	6	2	23
Month 24 HV	n	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	15	1	2	3	6	2	23
Prader-Labhart-Willi / Prader-Willi Syndrome (N=29)								
Baseline Height	n	18	1	1	4	6	0	24
	Mean (SD)	130.6 (31.39)	163.1 (-)	99.7 (-)	142.8 (7.02)	139.0 (21.60)	- (-)	132.7 (29.04)
	Median	139.5	163.1	99.7	143.0	143.0	-	141.4
	Q1; Q3	104.5; 158.7	163.1; 163.1	99.7; 99.7	136.8; 148.9	136.3; 149.0	-; -	105.9; 158.5
	Min; Max	82.5; 173.5	163.1; 163.1	99.7; 99.7	136.3; 149.0	99.7; 163.1	-; -	82.5; 173.5

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points/Primary Diagnosis Categories		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
	Missing	5	0	0	0	0	0	5
Month 12 HV	n	2	0	0	0	0	0	2
	Mean (SD)	6.6 (0.17)	- (-)	- (-)	- (-)	- (-)	- (-)	6.6 (0.17)
	Median	6.6	-	-	-	-	-	6.6
	Q1; Q3	6.5; 6.8	-; -	-; -	-; -	-; -	-; -	6.5; 6.8
	Min; Max	6.5; 6.8	-; -	-; -	-; -	-; -	-; -	6.5; 6.8
	Missing	21	1	1	4	6	0	27
Month 24 HV	n	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	23	1	1	4	6	0	29
Other (N=248)								
Baseline Height	n	81	6	41	34	81	72	234
	Mean (SD)	139.3 (24.64)	135.3 (20.72)	139.3 (25.96)	130.7 (25.36)	135.4 (25.43)	129.4 (24.13)	134.9 (24.99)

			Other daily hGH					
		Genotropin (N=716)	**Humatrope (N=28)**	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points/Primary Diagnosis Categories		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
	Median	144.8	135.2	146.5	135.7	140.9	127.8	136.8
	Q1; Q3	128.0; 158.8	124.3; 149.2	117.5; 160.8	108.6; 153.9	112.9; 155.5	111.0; 147.2	118.0; 155.5
	Min; Max	53.5; 177.3	104.0; 163.7	80.9; 179.0	87.4; 169.0	80.9; 179.0	84.8; 182.5	53.5; 182.5
	Missing	5	0	2	2	4	5	14
Month 12 HV	n	6	3	4	2	9	2	17
	Mean (SD)	9.0 (3.45)	5.8 (1.06)	7.0 (0.81)	7.0 (2.54)	6.6 (1.30)	8.8 (2.11)	7.7 (2.50)
	Median	7.8	5.7	6.9	7.0	6.4	8.8	7.3
	Q1; Q3	6.2; 12.4	4.8; 6.9	6.3; 7.7	5.2; 8.8	5.7; 7.4	7.3; 10.3	6.2; 8.3
	Min; Max	5.5; 14.0	4.8; 6.9	6.3; 8.0	5.2; 8.8	4.8; 8.8	7.3; 10.3	4.8; 14.0
	Missing	80	3	39	34	76	75	231
Month 24 HV	n	1	2	0	0	2	0	3
	Mean (SD)	5.8 (-)	5.5 (1.27)	- (-)	- (-)	5.5 (1.27)	- (-)	5.6 (0.92)
	Median	5.8	5.5	-	-	5.5	-	5.8
	Q1; Q3	5.8; 5.8	4.6; 6.4	-; -	-; -	4.6; 6.4	-; -	4.6; 6.4
	Min; Max	5.8; 5.8	4.6; 6.4	-; -	-; -	4.6; 6.4	-; -	4.6; 6.4
	Missing	85	4	43	36	83	77	245

hGH: Human Growth Hormone; HV: Height Velocity; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.
Height Velocity is calculated as ((Height at a given time point – Height at a previous time point)/(Follow-up measurement date – previous measurement date))*365.25.

Note: Other Diagnosis includes Disturbed GH Secretory Pattern/Neurosecretory dysfunction, Familial Short Stature, Medulloblastoma, Empty sella syndrome/Pituitary aplasia, Septo-Optic Dysplasia/Optic Nerve Hypoplasia, Silver-Russell / Russell-Silver Syndrome, Renal disease, Noonan syndrome, Tumor of the pituitary/hypothalamic area, Skeletal dysplasias, Astrocytoma, Neurofibromatosis / von Recklinghausen syndrome, Bio-inactive GH syndromes / Kowarski Syndrome, Histiocytosis and Other.
Source: Table 15.2.1.1.12, Appendix 8: Additional documents

Among all patients, the overall mean (SD) height SDS at baseline was -1.3 (1.20) and was similar in the Genotropin, Other daily hGH group, and the Ngenla group (-1.2 [1.14], -1.2 [1.16], and -1.5 [1.29], respectively). Data for baseline height SDS were missing for 92 patients. At Month 12, the overall mean (SD) HVSDS was 1.1 (2.54). The HVSDS in the Genotropin group was 1.3 (2.52), the Other daily hGH group was 0.6 2.45), and the Ngenla group was 1.5 [3.14]. Data were missing for 1308 patients. At Month 24, the overall mean (SD) HVSDS was 0.6 (2.62). The highest mean (SD) HVSDS was seen in the Genotropin group (2.5 [2.02]) and the least mean (SD) HVSDS was seen in the Other daily hGH group (-0.3 [2.43]). There were no patient details available for the Ngenla group at Month 24. Data were missing for 1500 patients (Table 15).

Table 15 Primary Effectiveness Outcome, HVSDS – Full Analysis Set

		Genotropin (N=716)	**Other daily hGH**					
			Humatrope (N=28)	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**	**Ngenla (N=441)**	**Overall (N=1516)**
Time Points		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
Baseline height SDS	n	670	26	144	173	343	411	1424
	Mean (SD)	-1.2 (1.14)	-1.1 (1.12)	-1.0 (1.14)	-1.3 (1.18)	-1.2 (1.16)	-1.5 (1.29)	-1.3 (1.20)
	Median	-1.2	-0.9	-1.1	-1.3	-1.1	-1.6	-1.3
	Q1; Q3	-1.9 ; -0.6	-1.6 ; -0.4	-1.6 ; -0.4	-2.0 ; -0.6	-1.9 ; -0.5	-2.2 ; -0.7	-2.0 ; -0.6
	Min; Max	-5.2 ; 4.5	-4.1 ; 1.1	-4.5 ; 2.8	-7.9 ; 1.7	-7.9 ; 2.8	-10.4 ; 2.3	-10.4 ; 4.5
	Missing	46	2	6	8	16	30	92
Month 12 HVSDS	n	154	6	21	18	45	9	208
	Mean (SD)	1.3 (2.52)	-0.0 (1.82)	0.4 (2.49)	1.1 (2.62)	0.6 (2.45)	1.5 (3.14)	1.1 (2.54)
	Median	0.9	-0.1	0.1	0.3	0.1	1.9	0.9
	Q1; Q3	-0.4 ; 2.7	-1.7 ; 1.8	-0.8 ; 1.9	-0.8 ; 2.7	-1.0 ; 2.0	-0.9 ; 3.0	-0.5 ; 2.5
	Min; Max	-3.8 ; 11.4	-2.1 ; 2.0	-4.9 ; 6.2	-2.4 ; 8.5	-4.9 ; 8.5	-3.2 ; 6.9	-4.9 ; 11.4
	Missing	562	22	129	163	314	432	1308

		Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
			Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Time Points		Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value	Observed Value
Month 24 HVSDS	n	5	3	4	4	11	0	16
	Mean (SD)	2.5 (2.02)	-0.6 (2.40)	-0.9 (2.79)	0.4 (2.65)	-0.3 (2.43)	- (-)	0.6 (2.62)
	Median	2.4	0.5	-0.9	0.3	0.5	-	1.0
	Q1; Q3	2.4 ; 2.8	-3.3 ; 1.1	-3.3 ; 1.5	-1.5 ; 2.3	-3.1 ; 1.3	- ; -	-1.5 ; 2.4
	Min; Max	-0.4 ; 5.3	-3.3 ; 1.1	-3.4 ; 1.8	-2.6 ; 3.7	-3.4 ; 3.7	- ; -	-3.4 ; 5.3
	Missing	711	25	146	177	348	441	1500

HVSDS: Height Velocity Standard Deviation Score; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard Deviation; SDS: Standard Deviation Score; WHO: World Health Organization.
HVSDS is calculated as ((Height velocity at a given time point – Mean)/Standard Deviation); where mean and standard deviation is using Tanner, Davis 1985 reference.
Reference population from Growth Analyzer for Height SDS: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined).
Source: Table 15.2.1.2, Appendix 8: Additional documents.

Among all patients, the overall mean (SD) height SDS at baseline was -1.3 (1.20) and was similar to the Genotropin group, the Other daily hGH group, and the Ngenla group (-1.2 [1.14], -1.2 [1.16], -1.5 [1.29], respectively). Data for baseline height SDS were missing for 92 patients. At Month 12, the overall mean (SD) change from baseline in height SDS was 1.0 (0.29) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (1.0 [0.28] and 1.0 [0.32], 1.2 [0.31], respectively). Data were missing for 1307 patients. At Month 24, the overall mean (SD) change from baseline in height SDS was 2.0 (0.41) and was similar to Genotropin and the Other daily hGH group (2.2 [0.26], 1.8 [0.42], respectively). There were no patient details available for the Ngenla group at Month 24. Data were missing for 1500 patients (Table 16).

Among patients in puberty (N=677), the overall mean (SD) height SDS at baseline was -1.0 (1.17) and was similar to the Genotropin group and the Other daily hGH group (-1.0 [1.09] and -0.9 [1.07], respectively), and less than the Ngenla group (-1.2 [1.44]). Data for baseline height SDS were missing for 40 patients. At Month 12, the overall mean (SD) change from baseline in height SDS was 1.0 (0.28) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (1.0 [0.26], 0.9 [0.35], 1.1 [0.27], respectively). Data were missing for 557 patients. At Month 24, the overall mean (SD) change from baseline in height SDS was 1.7 (0.41) and was similar in the Other daily hGH group (1.7 [0.41]). There were no patient details available for the Genotropin group and the Ngenla group at Month 24. Data were missing for 671 patients (Table 17).

Among patients not in puberty (N=825), the overall mean (SD) height SDS at baseline was -1.5 (1.19) and was similar to the Genotropin group, the Other daily hGH group, and the Ngenla group (-1.4 [1.15], -1.4 [1.19], -1.6 [1.21], respectively). Data for baseline height SDS were missing for 49 patients. At Month 12, the overall mean (SD) change from baseline in height SDS was 1.1 (0.29) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (1.1 [0.28], 1.1 [0.28], 1.3 [0.36] and respectively). Data were missing for 738 patients. At Month 24, the overall mean (SD) change from baseline in height SDS was 2.1 (0.35) and was similar in the Genotropin and the Other daily hGH group (2.2 [0.26] and 2.0 [0.41], respectively). There were no patient details available for the Ngenla group at Month 24. Data were missing for 815 patients (Table 17).

Among patients with idiopathic GHD (N=1118), the overall mean (SD) height SDS at baseline was -1.3 (1.13) and was similar to the Genotropin group and the Other daily hGH group (-1.2 [1.08], -1.2 [1.20], respectively), and less than the Ngenla group (-1.5 [1.12]). Data for baseline height SDS were missing for 67 patients. At Month 12, the overall mean (SD) change from baseline in height SDS was 1.0 (0.27) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (1.0 [0.26], 1.0 [0.29], 1.1 [0.32], respectively). Data were missing for 932 patients. At Month 24, the overall mean (SD) change from baseline in height SDS was 2.0 (0.42) and was less than the Genotropin group (2.3 [0.25]) and more than the Other daily hGH group (1.8 [0.40]). There were no patient details available for the Ngenla group at Month 24. Data were missing for 1105 patients (Table 18).

Among patients with Turner syndrome (N=15), the overall mean (SD) height SDS at baseline was -1.9 (0.93) and was more than Genotropin group (-1.6 [1.06]) and less than the Other daily hGH group (-2.1 [0.74]). There were no baseline patient details available for the Ngenla group. Data for baseline height SDS were missing for 0 patients. At Months 12 and 24, no patient details were available; data were missing for all 15 patients during both time points (Table 18).

Among patients with SGA/IUGR (N=67), the overall mean (SD) height SDS at baseline was -1.7 (0.93) and was similar to Genotropin group and the Other daily hGH group (-1.8 [0.93], -1.6 [1.00], respectively), and more than Ngenla group (-1.4 [0.63]). Data for baseline height SDS were missing for 3 patients. At Month 12, the overall mean (SD) change from baseline in height SDS was 0.8 (0.12) and was similar to the Other daily hGH group (0.8 [0.12]). There were no patient details available for the Genotropin group and the Ngenla group at Month 12. Data were missing for 64 patients. At Month 24, no patient details were available; data were missing for all 67 patients (Table 18).

Among patients with ISS (N=23), the overall mean (SD) height SDS at baseline was -1.6 (1.31) and was more than Genotropin group (-1.3 [1.50]), similar to the Other daily hGH group (-1.7 [0.85]), and less than Ngenla group (-2.8 [0.12]). Data for baseline height SDS were missing for 2 patients. At Months 12 and 24, no patient details were available; data were missing for all 23 patients during both time points (Table 18).

Among patients with Prader-Labhart-Willi/Prader-Willi Syndrome (N=29), the overall mean (SD) height SDS at baseline was -0.5 (1.24) and was similar to Genotropin group (-0.4 [1.26]) and less than the Other daily hGH group (-0.8 [1.27]). Baseline patient details were not available for the Ngenla group. Data for baseline height SDS were missing for 5

patients. At Month 12, the overall mean (SD) change from baseline in height SDS was 1.4 (0.02) and was similar to the Genotropin group (1.4 [0.02]). Patient details were not available for the Other daily hGH group and the Ngenla group at Month 12 and data were missing for 27 patients. At Month 24, there were no patient details available; data were missing for all 29 patients (Table 18).

Among patients with other diagnosis (N=248), the overall mean (SD) height SDS at baseline was -1.1 (1.50) and was similar to Genotropin group and the Other daily hGH group (-1.0 [1.34], -1.0 [1.10], respectively), and less than Ngenla group (-1.5 [1.95]). Data for baseline height SDS were missing for 14 patients. At Month 12, the overall mean (SD) change from baseline in height SDS was 1.3 (0.37) and was similar to the Genotropin group, the Other daily hGH group and the Ngenla group (1.3 [0.41], 1.3 [0.39], 1.4 [0.27], respectively). Data were missing for 231 patients. At Month 24, the overall mean (SD) change from baseline in height SDS was 1.9 (0.47) and was similar in the Genotropin group and the Other daily hGH group (2.0 [-], 1.9 [0.66], respectively). There were no patient details available for the Ngenla group at Month 24. Data were missing for 245 patients (Table 18).

Table 16 Primary Effectiveness Outcome, Change in Height SDS – Full Analysis Set

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline	n	670		26		144		173		343		411		1424	
	Mean (SD)	-1.2 (1.14)		-1.1 (1.12)		-1.0 (1.14)		-1.3 (1.18)		-1.2 (1.16)		-1.5 (1.29)		-1.3 (1.20)	
	Median	-1.2		-0.9		-1.1		-1.3		-1.1		-1.6		-1.3	
	Q1; Q3	-1.9 ; -0.6		-1.6 ; -0.4		-1.6 ; -0.4		-2.0 ; -0.6		-1.9 ; -0.5		-2.2 ; -0.7		-2.0 ; -0.6	
	Min; Max	-5.2 ; 4.5		-4.1 ; 1.1		-4.5 ; 2.8		-7.9 ; 1.7		-7.9 ; 2.8		-10.4 ; 2.3		-10.4 ; 4.5	
	Missing	46		2		6		8		16		30		92	
Month 12	n	175	154	7	7	23	21	19	18	49	46	9	9	233	209
	Mean (SD)	-0.1 (1.09)	1.0 (0.28)	0.6 (0.59)	0.9 (0.21)	0.3 (1.06)	1.1 (0.36)	0.4 (0.91)	1.1 (0.32)	0.4 (0.93)	1.0 (0.32)	-0.7 (0.60)	1.2 (0.31)	0.0 (1.07)	1.0 (0.29)
	Median	-0.2	1.0	0.4	0.8	0.3	1.0	0.3	1.0	0.4	1.0	-0.6	1.2	-0.1	1.0

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Q1; Q3	-0.8 ; 0.5	0.8 ; 1.2	0.4 ; 1.0	0.8 ; 1.1	-0.5 ; 0.9	0.8 ; 1.4	-0.3 ; 0.8	0.8 ; 1.3	-0.3 ; 0.8	0.8 ; 1.3	-1.0 ; -0.4	1.0 ; 1.4	-0.8 ; 0.6	0.8 ; 1.2
	Min; Max	-2.2 ; 3.4	0.5 ; 2.2	-0.4 ; 1.4	0.7 ; 1.3	-1.6 ; 2.9	0.3 ; 1.8	-1.0 ; 2.6	0.5 ; 1.9	-1.6 ; 2.9	0.3 ; 1.9	-1.6 ; 0.4	0.7 ; 1.5	-2.2 ; 3.4	0.3 ; 2.2
	Missing	541	562	21	21	127	129	162	163	310	313	432	432	1283	1307
Month 24	n	5	5	3	3	4	4	4	4	11	11	0	0	16	16
	Mean (SD)	0.9 (0.60)	2.2 (0.26)	1.7 (0.33)	1.8 (0.53)	1.0 (0.88)	1.8 (0.41)	1.9 (0.88)	1.9 (0.47)	1.5 (0.83)	1.8 (0.42)	- (-)	- (-)	1.3 (0.80)	2.0 (0.41)
	Median	1.2	2.2	1.6	1.5	1.0	1.8	1.8	1.8	1.5	1.7	-	-	1.4	2.0
	Q1; Q3	0.6 ; 1.3	2.0 ; 2.5	1.5 ; 2.1	1.5 ; 2.4	0.3 ; 1.7	1.5 ; 2.1	1.3 ; 2.6	1.5 ; 2.2	1.2 ; 2.1	1.5 ; 2.4	- ;-	- ;-	0.9 ; 1.8	1.5 ; 2.4
	Min; Max	-0.0 ; 1.4	2.0 ; 2.5	1.5 ; 2.1	1.5 ; 2.4	0.1 ; 2.0	1.4 ; 2.4	1.2 ; 3.1	1.4 ; 2.4	0.1 ; 3.1	1.4 ; 2.4	- ;-	- ;-	-0.0 ; 3.1	1.4 ; 2.5
	Missing	711	711	25	25	146	146	177	177	348	348	441	441	1500	1500

hGH: Human Growth Hormone; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard Deviation; SDS: Standard Deviation Score; WHO: World Health Organization.
Reference population from Growth Analyzer for Height: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined).
Source: Table 15.2.1.3, Appendix 8: Additional documents

Table 17 Primary Effectiveness Outcome - Change in Height SDS by Puberty Status (Full Analysis Set)

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points/ Puberty Status Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Patient in puberty (N=677)															
Baseline	n	357		11		70		68		149		131		637	
	Mean (SD)	-1.0 (1.09)		-0.7 (1.03)		-0.7 (1.00)		-1.1 (1.13)		-0.9 (1.07)		-1.2 (1.44)		-1.0 (1.17)	
	Median	-1.1		-0.8		-0.8		-1.0		-0.9		-1.3		-1.0	
	Q1; Q3	-1.8; -0.4		-0.9; -0.4		-1.4; -0.2		-1.7; -0.4		-1.5; -0.2		-1.9; -0.4		-1.7; -0.4	
	Min; Max	-5.0; 2.8		-2.8; 1.1		-2.9; 1.7		-4.6; 1.7		-4.6; 1.7		-10.4; 1.9		-10.4; 2.8	
	Missing	20		0		1		5		6		14		40	
Month 12	n	108	98	2	2	11	11	7	6	20	19	3	3	131	120
	Mean (SD)	-0.2 (1.03)	1.0 (0.26)	0.9 (0.70)	0.8 (0.03)	0.2 (1.10)	0.8 (0.28)	0.8 (1.14)	1.1 (0.47)	0.5 (1.09)	0.9 (0.35)	-0.5 (0.08)	1.1 (0.27)	-0.1 (1.06)	1.0 (0.28)
	Median	-0.3	1.0	0.9	0.8	-0.5	0.8	0.8	1.0	0.4	0.8	-0.5	1.0	-0.3	0.9
	Q1; Q3	-0.9; 0.2	0.8; 1.2	0.4; 1.4	0.8; 0.8	-0.6; 1.1	0.7; 0.9	0.3; 1.6	0.8; 1.3	-0.5; 1.3	0.7; 1.0	-0.6; -0.4	0.8; 1.3	-0.8; 0.4	0.8; 1.2
	Min; Max	-2.2; 3.4	0.5; 1.7	0.4; 1.4	0.8; 0.8	-0.9; 2.0	0.3; 1.5	-1.0; 2.6	0.5; 1.9	-1.0; 2.6	0.3; 1.9	-0.6; -0.4	0.8; 1.3	-2.2; 3.4	0.3; 1.9
	Missing	269	279	9	9	60	60	66	67	135	136	142	142	546	557
Month 24	n	0	0	1	1	2	2	3	3	6	6	0	0	6	6
	Mean (SD)	- (-)	- (-)	2.1 (-)	1.5 (-)	1.0 (1.31)	1.9 (0.70)	2.1 (0.99)	1.7 (0.36)	1.8 (1.03)	1.7 (0.41)	- (-)	- (-)	1.8 (1.03)	1.7 (0.41)

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Puberty Status Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Median	-	-	2.1	1.5	1.0	1.9	2.1	1.6	2.0	1.5	-	-	2.0	1.5
	Q1; Q3	-; -	-; -	2.1; 2.1	1.5; 1.5	0.1; 2.0	1.4; 2.4	1.2; 3.1	1.4; 2.1	1.2; 2.1	1.4; 2.1	-; -	-; -	1.2; 2.1	1.4; 2.1
	Min; Max	-; -	-; -	2.1; 2.1	1.5; 1.5	0.1; 2.0	1.4; 2.4	1.2; 3.1	1.4; 2.1	0.1; 3.1	1.4; 2.4	-; -	-; -	0.1; 3.1	1.4; 2.4
	Missing	377	377	10	10	69	69	70	70	149	149	145	145	671	671
Patient not in puberty (N=825)															
Baseline	n	310		15		73		101		189		277		776	
	Mean (SD)	-1.4 (1.15)		-1.3 (1.14)		-1.3 (1.19)		-1.5 (1.20)		-1.4 (1.19)		-1.6 (1.21)		-1.5 (1.19)	
	Median	-1.4		-0.9		-1.4		-1.4		-1.4		-1.8		-1.5	
	Q1; Q3	-2.1; -0.7		-2.1; -0.4		-1.9; -0.8		-2.3; -0.8		-2.1; -0.8		-2.3; -1.0		-2.2; -0.8	
	Min; Max	-5.2; 4.5		-4.1; 0.1		-4.5; 2.8		-7.9; 1.7		-7.9; 2.8		-8.8; 2.3		-8.8; 4.5	
	Missing	25		2		3		3		8		16		49	
Month 12	n	67	56	5	5	12	10	11	11	28	26	5	5	100	87
	Mean (SD)	0.2 (1.14)	1.1 (0.28)	0.4 (0.56)	1.0 (0.24)	0.5 (1.05)	1.3 (0.25)	0.2 (0.57)	1.1 (0.25)	0.4 (0.80)	1.1 (0.28)	-1.0 (0.52)	1.3 (0.36)	0.2 (1.06)	1.1 (0.29)
	Median	0.2	1.1	0.4	1.0	0.5	1.4	0.1	1.0	0.3	1.1	-1.0	1.4	0.2	1.1
	Q1; Q3	-0.8; 1.1	0.9; 1.2	0.4; 0.8	0.8; 1.1	0.1; 0.8	1.2; 1.4	-0.3; 0.6	0.8; 1.3	-0.1; 0.7	0.9; 1.4	-1.4; -0.9	1.2; 1.5	-0.6; 0.8	0.9; 1.3
	Min; Max	-1.9; 3.3	0.6; 2.2	-0.4; 1.0	0.7; 1.3	-1.6; 2.9	0.8; 1.8	-0.6; 1.4	0.7; 1.5	-1.6; 2.9	0.7; 1.8	-1.6; -0.2	0.7; 1.5	-1.9; 3.3	0.6; 2.2
	Missing	268	279	12	12	64	66	93	93	169	171	288	288	725	738

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Puberty Status Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Month 24	n	5	5	2	2	2	2	1	1	5	5	0	0	10	10
	Mean (SD)	0.9 (0.60)	2.2 (0.26)	1.5 (0.04)	1.9 (0.63)	1.0 (0.77)	1.8 (0.07)	1.4 (-)	2.4 (-)	1.3 (0.48)	2.0 (0.41)	- (-)	- (-)	1.1 (0.55)	2.1 (0.35)
	Median	1.2	2.2	1.5	1.9	1.0	1.8	1.4	2.4	1.5	1.8	-	-	1.3	2.1
	Q1; Q3	0.6; 1.3	2.0; 2.5	1.5; 1.6	1.5; 2.4	0.4; 1.5	1.7; 1.8	1.4; 1.4	2.4; 2.4	1.4; 1.5	1.7; 2.4	-; -	-; -	0.6; 1.5	1.8; 2.4
	Min; Max	-0.0; 1.4	2.0; 2.5	1.5; 1.6	1.5; 2.4	0.4; 1.5	1.7; 1.8	1.4; 1.4	2.4; 2.4	0.4; 1.6	1.5; 2.4	-; -	-; -	-0.0; 1.6	1.5; 2.5
	Missing	330	330	15	15	74	74	103	103	192	192	293	293	815	815

eCRF: electronic Case Report Form; hGH: Human Growth Hormone; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum; SDS: Standard Deviation Score; WHO: World Health Organization.
Reference population from Growth Analyzer for Height SDS: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined).
Note: Puberty status as collected in eCRF.
Source: Table 15.2.1.3.7, Appendix 8: Additional documents

Table 18 Primary Effectiveness Outcome - Change in Height SDS by Primary Diagnosis

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Idiopathic GHD (N=1118)															
Baseline	n	509		17		88		109		214		328		1051	
	Mean (SD)	-1.2 (1.08)		-1.2 (1.25)		-1.0 (1.11)		-1.3 (1.26)		-1.2 (1.20)		-1.5 (1.12)		-1.3 (1.13)	
	Median	-1.2		-0.9		-1.1		-1.1		-1.1		-1.6		-1.3	
	Q1; Q3	-1.9; -0.6		-1.6; -0.6		-1.5; -0.5		-2.0; -0.6		-1.9; -0.6		-2.1; -0.8		-2.0; -0.7	
	Min; Max	-5.2; 4.5		-4.1; 1.1		-3.7; 2.8		-7.9; 1.7		-7.9; 2.8		-8.8; 2.3		-8.8; 4.5	
	Missing	32		2		2		6		10		25		67	
Month 12	n	161	145	4	4	17	16	14	14	35	34	7	7	203	186
	Mean (SD)	-0.1 (1.05)	1.0 (0.26)	0.4 (0.65)	0.9 (0.19)	0.2 (0.90)	1.0 (0.33)	0.5 (0.94)	1.1 (0.26)	0.4 (0.88)	1.0 (0.29)	-0.9 (0.42)	1.1 (0.32)	-0.1 (1.03)	1.0 (0.27)
	Median	-0.2	1.0	0.6	0.9	0.2	0.9	0.4	1.0	0.3	1.0	-0.9	1.2	-0.2	1.0
	Q1; Q3	-0.9; 0.4	0.8; 1.2	-0.0; 0.9	0.7; 1.0	-0.5; 0.7	0.8; 1.3	-0.2; 1.3	0.9; 1.3	-0.4; 0.8	0.8; 1.2	-1.4; -0.5	0.8; 1.4	-0.8; 0.5	0.8; 1.2
	Min; Max	-2.2; 3.4	0.5; 2.2	-0.4; 1.0	0.7; 1.1	-0.9; 2.0	0.3; 1.5	-1.0; 2.6	0.5; 1.5	-1.0; 2.6	0.3; 1.5	-1.6; -0.4	0.7; 1.5	-2.2; 3.4	0.3; 2.2
	Missing	380	396	15	15	73	74	101	101	189	190	346	346	915	932
Month 24	n	4	4	1	1	4	4	4	4	9	9	0	0	13	13

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Mean (SD)	1.0 (0.66)	2.3 (0.25)	1.6 (-)	1.5 (-)	1.0 (0.88)	1.8 (0.41)	1.9 (0.88)	1.9 (0.47)	1.5 (0.90)	1.8 (0.40)	- (-)	- (-)	1.3 (0.84)	2.0 (0.42)
	Median	1.3	2.3	1.6	1.5	1.0	1.8	1.8	1.8	1.5	1.7	-	-	1.4	2.0
	Q1; Q3	0.6; 1.3	2.1; 2.5	1.6; 1.6	1.5; 1.5	0.3; 1.7	1.5; 2.1	1.3; 2.6	1.5; 2.2	1.2; 2.0	1.5; 2.1	-; -	-; -	1.2; 1.6	1.6; 2.4
	Min; Max	-0.0; 1.4	2.0; 2.5	1.6; 1.6	1.5; 1.5	0.1; 2.0	1.4; 2.4	1.2; 3.1	1.4; 2.4	0.1; 3.1	1.4; 2.4	-; -	-; -	-0.0; 3.1	1.4; 2.5
	Missing	537	537	18	18	86	86	111	111	215	215	353	353	1105	1105
Turner syndrome (N=15)															
Baseline	n	8		1		1		5		7		0		15	
	Mean (SD)	-1.6 (1.06)		-2.1 (-)		-3.2 (-)		-1.9 (0.71)		-2.1 (0.74)		- (-)		-1.9 (0.93)	
	Median	-1.6		-2.1		-3.2		-2.0		-2.1		-		-2.0	
	Q1; Q3	-2.4; -0.8		-2.1; -2.1		-3.2; -3.2		-2.4; -1.8		-2.7; -1.8		-; -		-2.5; -1.1	
	Min; Max	-3.2; -0.1		-2.1; -2.1		-3.2; -3.2		-2.7; -0.8		-3.2; -0.8		-; -		-3.2; -0.1	
	Missing	0		0		0		0		0		0		0	
Month 12	n	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	8	8	1	1	1	1	5	5	7	7	0	0	15	15
Month 24	n	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	8	8	1	1	1	1	5	5	7	7	0	0	15	15
SGA/IUGR (N=67)															
Baseline	n	32		0		10		16		26		6		64	
	Mean (SD)	-1.8 (0.93)		- (-)		-1.6 (1.27)		-1.5 (0.82)		-1.6 (1.00)		-1.4 (0.63)		-1.7 (0.93)	
	Median	-1.8		-		-1.8		-1.5		-1.7		-1.5		-1.7	
	Q1; Q3	-2.3; -1.4		-; -		-2.5; -1.4		-2.1; -0.9		-2.2; -1.2		-2.0; -1.0		-2.2; -1.2	
	Min; Max	-3.9; 0.5		-; -		-3.6; 1.0		-3.2; -0.3		-3.6; 1.0		-2.2; -0.5		-3.9; 1.0	

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Missing	2		0		1		0		1		0		3	
Month 12	n	1	0	0	0	1	1	2	2	3	3	0	0	4	3
	Mean (SD)	-1.9 (-)	- (-)	- (-)	- (-)	-1.6 (-)	1.0 (-)	-0.3 (0.50)	0.8 (0.04)	-0.7 (0.86)	0.8 (0.12)	- (-)	- (-)	-1.0 (0.92)	0.8 (0.12)
	Median	-1.9	-	-	-	-1.6	1.0	-0.3	0.8	-0.6	0.8	-	-	-1.1	0.8
	Q1; Q3	-1.9; -1.9	-; -	-; -	-; -	-1.6; -1.6	1.0; 1.0	-0.6; 0.1	0.7; 0.8	-1.6; 0.1	0.7; 1.0	-; -	-; -	-1.8; -0.3	0.7; 1.0
	Min; Max	-1.9; -1.9	-; -	-; -	-; -	-1.6; -1.6	1.0; 1.0	-0.6; 0.1	0.7; 0.8	-1.6; 0.1	0.7; 1.0	-; -	-; -	-1.9; 0.1	0.7; 1.0
	Missing	33	34	0	0	10	10	14	14	24	24	6	6	63	64
Month 24	n	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	34	34	0	0	11	11	16	16	27	27	6	6	67	67
ISS (N=23)															

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline	n	13		1		2		3		6		2		21	
	Mean (SD)	-1.3 (1.50)		-0.4 (-)		-2.1 (0.58)		-1.8 (0.82)		-1.7 (0.85)		-2.8 (0.12)		-1.6 (1.31)	
	Median	-1.3		-0.4		-2.1		-1.4		-1.5		-2.8		-1.4	
	Q1; Q3	-2.6; -0.5		-0.4; -0.4		-2.5; -1.7		-2.8; -1.3		-2.5; -1.3		-2.8; -2.7		-2.7; -1.0	
	Min; Max	-3.5; 0.9		-0.4; -0.4		-2.5; -1.7		-2.8; -1.3		-2.8; -0.4		-2.8; -2.7		-3.5; 0.9	
	Missing	2		0		0		0		0		0		2	
Month 12	n	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	15	15	1	1	2	2	3	3	6	6	2	2	23	23
Month 24	n	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	15	15	1	1	2	2	3	3	6	6	2	2	23	23
Prader-Labhart-Willi / Prader-Willi Syndrome (N=29)															
Baseline	n	18		1		1		4		6		0		24	
	Mean (SD)	-0.4 (1.26)		-0.4 (-)		-2.9 (-)		-0.3 (0.94)		-0.8 (1.27)		- (-)		-0.5 (1.24)	
	Median	-0.7		-0.4		-2.9		-0.0		-0.3		-		-0.5	
	Q1; Q3	-1.2; 0.6		-0.4; -0.4		-2.9; -2.9		-1.0; 0.3		-1.7; 0.2		-; -		-1.3; 0.3	
	Min; Max	-2.6; 1.7		-0.4; -0.4		-2.9; -2.9		-1.7; 0.4		-2.9; 0.4		-; -		-2.9; 1.7	
	Missing	5		0		0		0		0		0		5	
Month 12	n	6	2	0	0	0	0	0	0	0	0	0	0	6	2
	Mean (SD)	1.5 (1.12)	1.4 (0.02)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	1.5 (1.12)	1.4 (0.02)
	Median	1.4	1.4	-	-	-	-	-	-	-	-	-	-	1.4	1.4
	Q1; Q3	0.6; 2.1	1.4; 1.5	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	0.6; 2.1	1.4; 1.5
	Min; Max	0.3; 3.3	1.4; 1.5	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	0.3; 3.3	1.4; 1.5

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Missing	17	21	1	1	1	1	4	4	6	6	0	0	23	27
Month 24	n	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Mean (SD)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Q1; Q3	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Min; Max	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -	-; -
	Missing	23	23	1	1	1	1	4	4	6	6	0	0	29	29
Other (N=248)															
Baseline	n	81		6		41		34		81		72		234	
	Mean (SD)	-1.0 (1.34)		-0.7 (0.86)		-0.8 (1.09)		-1.2 (1.12)		-1.0 (1.10)		-1.5 (1.95)		-1.1 (1.50)	
	Median	-1.0		-0.9		-0.9		-1.1		-0.9		-1.5		-1.0	
	Q1; Q3	-1.7; -0.1		-0.9; -0.3		-1.4; -0.2		-2.0; -0.5		-1.7; -0.3		-2.4; -0.3		-1.9; -0.2	
	Min; Max	-4.3; 2.8		-2.0; 0.6		-4.5; 1.5		-3.5; 1.7		-4.5; 1.7		-10.4; 1.9		-10.4; 2.8	
	Missing	5		0		2		2		4		5		14	

				Other daily hGH											
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points/ Primary Diagnosis Categories		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Month 12	n	6	6	3	3	5	4	3	2	11	9	2	2	19	17
	Mean (SD)	-0.0 (1.00)	1.3 (0.41)	0.7 (0.58)	0.9 (0.28)	1.2 (1.03)	1.5 (0.19)	0.1 (0.94)	1.4 (0.64)	0.8 (0.94)	1.3 (0.39)	0.1 (0.43)	1.4 (0.27)	0.4 (0.96)	1.3 (0.37)
	Median	-0.2	1.2	0.4	0.8	0.9	1.4	0.4	1.4	0.6	1.4	0.1	1.4	0.4	1.3
	Q1; Q3	-0.6; 0.1	1.2; 1.5	0.4; 1.4	0.8; 1.3	0.6; 1.2	1.4; 1.6	-1.0; 0.8	1.0; 1.9	0.4; 1.2	1.0; 1.4	-0.2; 0.4	1.2; 1.5	-0.2; 0.9	1.2; 1.5
	Min; Max	-1.0; 1.9	0.7; 2.0	0.4; 1.4	0.8; 1.3	0.3; 2.9	1.4; 1.8	-1.0; 0.8	1.0; 1.9	-1.0; 2.9	0.8; 1.9	-0.2; 0.4	1.2; 1.5	-1.0; 2.9	0.7; 2.0
	Missing	80	80	3	3	38	39	33	34	74	76	75	75	229	231
Month 24	n	1	1	2	2	0	0	0	0	2	2	0	0	3	3
	Mean (SD)	0.6 (-)	2.0 (-)	1.8 (0.42)	1.9 (0.66)	- (-)	- (-)	- (-)	- (-)	1.8 (0.42)	1.9 (0.66)	- (-)	- (-)	1.4 (0.74)	1.9 (0.47)
	Median	0.6	2.0	1.8	1.9	-	-	-	-	1.8	1.9	-	-	1.5	2.0
	Q1; Q3	0.6; 0.6	2.0; 2.0	1.5; 2.1	1.5; 2.4	-; -	-; -	-; -	-; -	1.5; 2.1	1.5; 2.4	-; -	-; -	0.6; 2.1	1.5; 2.4
	Min; Max	0.6; 0.6	2.0; 2.0	1.5; 2.1	1.5; 2.4	-; -	-; -	-; -	-; -	1.5; 2.1	1.5; 2.4	-; -	-; -	0.6; 2.1	1.5; 2.4
	Missing	85	85	4	4	43	43	36	36	83	83	77	77	245	245

hGH: Human Growth Hormone; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum; SDS: Standard Deviation Score; WHO: World Health Organization.
Reference population from Growth Analyzer for Height SDS: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined).
Note: Other Diagnosis includes Disturbed GH Secretory Pattern/Neurosecretory dysfunction, Familial Short Stature, Medulloblastoma, Empty sella syndrome/Pituitary aplasia, Septo-Optic Dysplasia/Optic Nerve Hypoplasia, Silver-Russell / Russell-Silver Syndrome, Renal disease, Noonan syndrome, Tumor of the pituitary/hypothalamic area, Skeletal dysplasias, Astrocytoma, Neurofibromatosis / von Recklinghausen syndrome, Bio-inactive GH syndromes / Kowarski Syndrome, Histiocytosis and Other.
Source: Table 15.2.1.3.12, Appendix 8: Additional documents

Among all patients, the overall mean (SD) BMI at baseline was 18.1 (3.73) and was similar in the Genotropin group and the Other daily hGH group (18.3 [3.86], 18.2 [3.72], 0.3 (0.43), respectively) but lower in the Ngenla group (17.7 [3.50]). Data for annual BMI was missing for 93 patients. At Month 12, the overall mean (SD) change from baseline in annual BMI was 0.7 (0.94) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (0.7 [0.96], 0.7 [0.88], and 0.8 [0.93], respectively). Data were missing for 1307 patients. At Month 24, the overall mean (SD) change from baseline in annual BMI was 1.7 (1.10) overall, 1.4 (1.00) in the Genotropin group, and 1.8 (1.17) in the Other daily hGH group. There were no patient details available for the Ngenla group at Month 24. Data were missing for 1500 patients (Table 19).

Table 19 Summary of Primary Effectiveness Outcome - Change in Annual BMI (Full Analysis Set)

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline	n	670		26		144		172		342		411		1423	
	Mean (SD)	18.3 (3.86)		19.1 (4.44)		18.0 (2.95)		18.2 (4.16)		18.2 (3.72)		17.7 (3.50)		18.1 (3.73)	
	Median	17.5		17.8		17.6		17.5		17.6		17.0		17.3	
	Q1; Q3	15.8; 19.9		15.7; 20.8		16.0; 19.6		15.3; 19.5		15.6; 19.7		15.4; 19.0		15.7; 19.7	
	Min; Max	12.8; 42.7		14.2; 32.9		11.9; 31.7		11.7; 36.2		11.7; 36.2		12.0; 35.7		11.7; 42.7	
	Missing	46		2		6		9		17		30		93	
Month 12	n	175	154	7	7	23	21	19	18	49	46	9	9	233	209
	Mean (SD)	18.5 (3.24)	0.7 (0.96)	16.2 (1.41)	0.3 (0.42)	18.1 (2.92)	1.0 (0.95)	18.5 (3.92)	0.4 (0.83)	18.0 (3.24)	0.7 (0.88)	18.8 (4.47)	0.8 (0.93)	18.4 (3.28)	0.7 (0.94)
	Median	18.3	0.7	15.6	0.3	17.9	0.8	17.4	0.5	17.4	0.6	17.7	0.7	18.1	0.7
	Q1; Q3	16.3; 20.2	0.1; 1.2	15.1; 17.8	0.2; 0.8	15.3; 20.7	0.3; 1.4	15.8; 19.6	-0.1; 1.0	15.5; 19.6	0.1; 1.1	16.6; 19.5	0.4; 1.3	16.2; 20.1	0.1; 1.2
	Min; Max	13.0; 39.7	-2.2; 4.0	15.0; 18.4	-0.4; 0.8	13.9; 24.5	-0.0; 4.0	12.8; 28.1	-1.3; 2.0	12.8; 28.1	-1.3; 4.0	13.9; 29.7	-0.9; 2.1	12.8; 39.7	-2.2; 4.0
	Missing	541	562	21	21	127	129	162	163	310	313	432	432	1283	1307
Month 24	n	5	5	3	3	4	4	4	4	11	11	0	0	16	16

		Other daily hGH													
		Genotropin (N=716)		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Mean (SD)	16.5 (1.95)	1.4 (1.00)	16.1 (0.42)	1.2 (0.94)	20.2 (4.52)	2.1 (1.81)	19.6 (2.18)	1.9 (0.40)	18.8 (3.29)	1.8 (1.17)	-(-)	-(-)	18.1 (3.08)	1.7 (1.10)
	Median	16.1	1.4	16.2	1.3	18.6	1.8	19.3	1.9	17.8	1.8	-	-	17.3	1.6
	Q1; Q3	15.1; 17.1	0.6; 1.4	15.6; 16.4	0.2; 2.1	17.3; 23.1	1.0; 3.2	17.8; 21.4	1.6; 2.2	16.4; 20.5	1.3; 2.1	-; -	-; -	16.1; 19.5	0.9; 2.0
	Min; Max	14.7; 19.6	0.5; 3.0	15.6; 16.4	0.2; 2.1	16.7; 26.7	0.3; 4.6	17.6; 22.2	1.5; 2.4	15.6; 26.7	0.2; 4.6	-; -	-; -	14.7; 26.7	0.2; 4.6
	Missing	711	711	25	25	146	146	177	177	348	348	441	441	1500	1500

BMI: Body Mass Index; hGH: Human Growth Hormone; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.
Source: Table 15.2.1.5, Appendix 8: Additional documents

Among all patients, the overall mean (SD) baseline BMI SDS at baseline was 0.0 (1.19) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (-0.0 [1.17], 0.1 [1.17], 0.0 [1.22], respectively). Data for baseline BMI SDS was missing for 93 patients. At Month 12, the overall mean (SD) change from baseline in annual BMI SDS was 0.3 (0.43) and was similar in the Genotropin group, the Other daily hGH group, and the other Ngenla group (0.3 [0.42], 0.3 [0.43], and 0.4 [0.46], respectively). Data were missing for 1307 patients. At Month 24, the overall mean (SD) change from baseline in annual BMI SDS was 0.8 (0.36) and was similar in the Genotropin group and the Other daily hGH group (0.8 [0.45] and 0.7 [0.33], respectively). There were no patient details available for the Ngenla group at Month 24. Data were missing for 1500 patients (Table 20).

Table 20 Summary of Primary Effectiveness Outcome - Change in Annual BMI SDS (Full Analysis Set)

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline	n	670		26		144		172		342		411		1423	
	Mean (SD)	-0.0 (1.17)		0.2 (1.20)		0.0 (1.10)		0.1 (1.23)		0.1 (1.17)		0.0 (1.22)		0.0 (1.19)	
	Median	-0.0		0.2		0.0		0.0		0.0		-0.1		-0.0	
	Q1; Q3	-0.8; 0.6		-0.5; 1.2		-0.7; 0.9		-0.8; 0.8		-0.8; 0.9		-0.8; 0.8		-0.8; 0.7	
	Min; Max	-3.7; 4.3		-2.4; 2.9		-3.2; 3.4		-3.0; 3.7		-3.2; 3.7		-3.9; 3.7		-3.9; 4.3	
	Missing	46		2		6		9		17		30		93	
Month 12	n	175	154	7	7	23	21	19	18	49	46	9	9	233	209
	Mean (SD)	0.2 (1.03)	0.3 (0.42)	-0.5 (0.87)	0.2 (0.24)	0.4 (1.37)	0.4 (0.47)	0.3 (1.14)	0.2 (0.41)	0.3 (1.24)	0.3 (0.43)	0.6 (1.39)	0.4 (0.46)	0.2 (1.09)	0.3 (0.43)
	Median	0.2	0.3	-0.7	0.2	0.2	0.4	0.5	0.3	0.2	0.3	0.5	0.3	0.2	0.3
	Q1; Q3	-0.6; 0.7	0.0; 0.6	-1.2; 0.1	0.1; 0.3	-0.6; 1.2	0.2; 0.5	-0.4; 1.1	-0.0; 0.5	-0.6; 1.1	0.1; 0.5	-0.1; 0.8	0.2; 0.6	-0.6; 0.8	0.1; 0.6
	Min; Max	-2.5; 3.4	-1.4; 1.9	-1.9; 0.8	-0.2; 0.5	-1.7; 3.9	-0.0; 2.2	-2.4; 2.1	-0.7; 0.7	-2.4; 3.9	-0.7; 2.2	-1.1; 3.6	-0.3; 1.3	-2.5; 3.9	-1.4; 2.2
	Missing	541	562	21	21	127	129	162	163	310	313	432	432	1283	1307
Month 24	n	5	5	3	3	4	4	4	4	11	11	0	0	16	16

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
	Mean (SD)	-0.3 (0.71)	0.8 (0.45)	-0.6 (0.47)	0.7 (0.59)	0.5 (1.67)	0.7 (0.35)	0.8 (0.51)	0.8 (0.09)	0.3 (1.16)	0.7 (0.33)	-(-)	-(-)	0.1 (1.06)	0.8 (0.36)
	Median	-0.3	0.9	-0.5	0.8	0.4	0.8	0.7	0.8	0.3	0.8	-	-	-0.1	0.8
	Q1; Q3	-0.7; -0.2	0.4; 1.1	-1.1; -0.2	0.1; 1.3	-0.6; 1.7	0.5; 0.9	0.5; 1.2	0.8; 0.9	-0.5; 0.9	0.8; 0.9	-; -	-; -	-0.6; 0.7	0.6; 0.9
	Min; Max	-1.2; 0.7	0.3; 1.4	-1.1; -0.2	0.1; 1.3	-1.3; 2.7	0.2; 0.9	0.3; 1.5	0.8; 0.9	-1.3; 2.7	0.1; 1.3	-; -	-; -	-1.3; 2.7	0.1; 1.4
	Missing	711	711	25	25	146	146	177	177	348	348	441	441	1500	1500

BMI: Body Mass Index; hGH: Human Growth Hormone; BMISDS: Body Mass Index Standard Deviation Scores; Min: Minimum; Max: Maximum; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; WHO: World Health Organization.
Reference population from Growth Analyzer for BMI: Age (0-19y) / World 2007 (Brazil, Ghana, India, Oman, Norway, United States of America) / WHO (2006/2007 Combined).
Source: Table 15.2.1.5a, Appendix 8: Additional documents

Among all patients, the overall median (min, max) IGF-1 at baseline was 32.7 (0.0, 469000.0) nmol/L. The median (min, max) IGF-1 at baseline was 36.9 (0.0, 372000.0) nmol/L, 33.9 (0.0, 469000.0) nmol/L, and 25.7 (0.0, 427.0) nmol/L in the Genotropin, Other daily hGH group, and the Ngenla group, respectively (Table 21).

At Month 12, the overall IGF-1 data were available for 150 patients with median (min, max) 50.3 (0.3, 619.0) nmol/L and data were missing for 1366 patients. The IGF-1 data was highest in the Genotropin group (52.7 [0.3, 619.0] nmol/L), followed by the Other daily hGH group (41.2 [0.1, 121.0] nmol/L) and was lowest in the Ngenla group (39.2 [24.3, 55.5] nmol/L). The overall IGF-1 change from baseline data were available for 62 patients with median (min, max) 4.8 (-126.2, 552.7) nmol/L and data were missing for 1454 patients. The IGF-1 data was highest in the Genotropin group (5.6 [-41.0, 552.7] nmol/L), followed by the Other daily hGH group (3.9 [-126.2, 119.9] nmol/L) and was lowest in the Ngenla group (3.6 [-2.6, 20.3] nmol/L) (Table 21).

At Month 24, the overall IGF-1 data were available for 8 patients with median (min, max) 58.7 (0.3, 136.3) nmol/L and data were missing for 1508 patients. The IGF-1 data was similar in the Other daily hGH group (58.7 [0.3, 136.3] nmol/L) and highest in the Genotropin group (66.1 [41.0; 91.2] nmol/L). There were no patient details available for the Ngenla group at Month 24. The overall IGF-1 change from baseline data was available for only 1 Other daily hGH patient with (135.2 nmol/L and data were missing for 1515 patients. There were no patient details available for the Genotropin group and the Ngenla group at Month 24 (Table 21).

Among all patients, the overall median (min, max) IGFBP-3 at baseline was 5.8 (0.0, 7180000.0) mg/L. The median (min, max) IGFBP-3 at baseline was 5.7 (0.0, 6810000.0) mg/L, 6.1 (0.0, 7180000.0) mg/L, and 4.8 (0.0, 5528.0) mg/L in the Genotropin, Other daily hGH group, and the Ngenla group, respectively (Table 21).

At Month 12, the overall IGFBP-3 data were available for 30 patients with median (min, max) 7.2 (2.1, 10.2) mg/L and data were missing for 1486 patients. The IGFBP-3 data was similar in the Genotropin group and the Other daily hGH group (7.3 [2.1, 9.8] mg/L and 7.2 [5.4, 10.2] mg/L, respectively) and lower in the Ngenla group (3.6 [3.6, 3.6] mg/L). The overall IGFBP-3 change from baseline data were available for 7 patients with median (min, max) 1.4 (-1.2, 5.6) mg/L and data were missing for 1509 patients. The IGFBP-3 data was highest in the Genotropin group (3.6 [0.0, 5.6] mg/L), followed by the Ngenla group (2.0 [2.0, 2.0] mg/L) and was lowest in the Other daily hGH group (0.2 [-1.2, 1.4] mg/L) (Table 21).

At Month 24, the overall IGFBP-3 data were available for 4 patients with median (min, max) 9.1 (4.7, 10.9) mg/L and data were missing for 1512 patients. The IGFBP-3 data was (9.1 [4.7, 10.9] mg/L) in the Other daily hGH group. There were no patient details available for the Genotropin group and the Ngenla group at Month 24. The overall IGFBP-3 change from baseline data was available for only 1 patient (-0.5 mg/L) and data were missing for 1515 patients. There were no patient details available for the Genotropin group and the Ngenla group at Month 24 (Table 21).

Table 21 Primary Effectiveness Outcome, IGF-1 and IGFBP-3 – Full Analysis Set

					Other daily hGH											
Laboratory Parameter (Unit)	**Time Points**		**Genotropin (N=716)**		**Humatrope (N=28)**		**Norditropin (N=150)**		**Omnitrope (N=181)**		**Total (N=359)**		**Ngenla (N=441)**		**Overall (N=1516)**	
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
IGF-I (nmol/L)	Baseline	n	389		10		80		114		204		250		843	
		Mean (SD)	2399.6 (26090.97)		31.7 (19.41)		3194.3 (28169.52)		7343.4 (53583.33)		5357.9 (43732.19)		37.8 (52.37)		2415.1 (27902.64)	
		Median	36.9		39.2		34.5		31.4		33.9		25.7		32.7	
		Q1; Q3	19.7; 54.4		22.5; 45.7		17.0; 54.9		16.7; 54.9		17.0; 54.1		11.4; 49.1		15.9; 53.0	
		Min; Max	0.0; 372000.0		0.0; 54.1		0.0; 252000.0		0.1; 469000.0		0.0; 469000.0		0.0; 427.0		0.0; 469000.0	
		Missing	327		18		70		67		155		191		673	
	Month 12	n	117	46	4	3	11	3	10	7	25	13	8	3	150	62
		Mean (SD)	59.2 (57.00)	19.3 (82.07)	38.8 (8.26)	0.0 (3.57)	47.0 (35.78)	-0.2 (123.15)	48.9 (20.77)	6.6 (11.55)	46.4 (26.76)	3.5 (51.07)	40.2 (11.03)	7.1 (11.84)	56.1 (51.84)	15.4 (74.37)
		Median	52.7	5.6	40.8	0.8	35.7	5.6	47.8	4.9	41.2	3.9	39.2	3.6	50.3	4.8
		Q1; Q3	38.7; 66.8	-1.0; 20.2	33.8; 43.9	-3.9; 3.1	13.5; 67.2	-126.2; 119.9	34.8; 63.0	-3.4; 8.9	34.8; 61.0	-3.4; 7.9	31.8; 49.8	-2.6; 20.3	36.6; 65.2	-2.6; 17.8
		Min; Max	0.3; 619.0	-41.0; 552.7	27.1; 46.5	-3.9; 3.1	0.7; 121.0	-126.2; 119.9	16.3; 82.3	-5.8; 29.6	0.7; 121.0	-126.2; 119.9	24.3; 55.5	-2.6; 20.3	0.3; 619.0	-126.2; 552.7
		Missing	599	670	24	25	139	147	171	174	334	346	433	438	1366	1454
	Month 24	n	2	0	2	0	2	1	2	0	6	1	0	0	8	1
		Mean (SD)	66.1 (35.50)	- (-)	28.9 (40.38)	- (-)	98.2 (53.95)	135.2 (-)	64.0 (38.18)	- (-)	63.7 (46.48)	135.2 (-)	- (-)	- (-)	64.3 (41.53)	135.2 (-)
		Median	66.1	-	28.9	-	98.2	135.2	64.0	-	58.7	135.2	-	-	58.7	135.2
		Q1; Q3	41.0; 91.2	-;-	0.3; 57.4	-;-	60.0; 136.3	135.2; 135.2	37.0; 91.0	-;-	37.0; 91.0	135.2; 135.2	-;-	-;-	39.0; 91.1	135.2; 135.2
		Min; Max	41.0; 91.2	-;-	0.3; 57.4	-;-	60.0; 136.3	135.2; 135.2	37.0; 91.0	-;-	0.3; 136.3	135.2; 135.2	-;-	-;-	0.3; 136.3	135.2; 135.2
		Missing	714	716	26	28	148	149	179	181	353	358	441	441	1508	1515
IGFBP-3 (mg/L)	Baseline	n	125		6		32		59		97		88		310	

					Other daily hGH											
Laboratory Parameter (Unit)	Time Points		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
		Mean (SD)	191221.6 (1066200.69)		15.7 (25.32)		758803.4 (2051401.33)		179861.4 (963804.32)		359728.1 (1414634.97)		553.1 (1372.13)		189822.6 (1047463.66)	
		Median	5.7		6.2		6.5		5.8		6.1		4.8		5.8	
		Q1; Q3	4.5; 7.2		6.0; 8.6		3.9; 2262.5		3.5; 8.8		3.8; 60.0		3.3; 9.3		3.8; 8.0	
		Min; Max	0.0; 6810000.0		0.0; 67.0		0.0; 7180000.0		0.0; 5400000.0		0.0; 7180000.0		0.0; 5528.0		0.0; 7180000.0	
		Missing	591		22		118		122		262		353		1206	
	Month 12	n	19	3	2	1	4	2	4	0	10	3	1	1	30	7
		Mean (SD)	6.6 (1.90)	3.1 (2.84)	5.9 (0.64)	0.2 (-)	7.6 (2.00)	0.1 (1.84)	7.6 (1.37)	- (-)	7.2 (1.60)	0.1 (1.30)	3.6 (-)	2.0 (-)	6.7 (1.86)	1.7 (2.33)
		Median	7.3	3.6	5.9	0.2	7.5	0.1	7.7	-	7.2	0.2	3.6	2.0	7.2	1.4
		Q1; Q3	5.3; 8.0	0.0; 5.6	5.4; 6.3	0.2; 0.2	6.2; 9.1	-1.2; 1.4	6.6; 8.5	-;-	5.8; 7.9	-1.2; 1.4	3.6; 3.6	2.0; 2.0	5.4; 7.9	0.0; 3.6
		Min; Max	2.1; 9.8	0.0; 5.6	5.4; 6.3	0.2; 0.2	5.4; 10.2	-1.2; 1.4	5.8; 9.1	-;-	5.4; 10.2	-1.2; 1.4	3.6; 3.6	2.0; 2.0	2.1; 10.2	-1.2; 5.6
		Missing	697	713	26	27	146	148	177	181	349	356	440	440	1486	1509
	Month 24	n	0	0	2	0	1	1	1	0	4	1	0	0	4	1
		Mean (SD)	- (-)	- (-)	7.3 (3.61)	- (-)	10.9 (-)	-0.5 (-)	8.4 (-)	- (-)	8.5 (2.70)	-0.5 (-)	- (-)	- (-)	8.5 (2.70)	-0.5 (-)
		Median	-	-	7.3	-	10.9	-0.5	8.4	-	9.1	-0.5	-	-	9.1	-0.5
		Q1; Q3	-;-	-;-	4.7; 9.8	-;-	10.9; 10.9	-0.5; -0.5	8.4; 8.4	-;-	6.6; 10.4	-0.5; -0.5	-;-	-;-	6.6; 10.4	-0.5; -0.5
		Min; Max	-;-	-;-	4.7; 9.8	-;-	10.9; 10.9	-0.5; -0.5	8.4; 8.4	-;-	4.7; 10.9	-0.5; -0.5	-;-	-;-	4.7; 10.9	-0.5; -0.5
		Missing	716	716	26	28	149	149	180	181	355	358	441	441	1512	1515

ALS: Amyotrophic lateral sclerosis; FSH: Follicle-stimulating hormone; GH, Growth hormone; HDL: High-density lipoprotein; HbA1c: glycated hemoglobin; hGH: Human growth hormone; IGF-1: Insulin-like growth factor-1; IGFBP-3: Insulin-like growth factor-1 binding protein-3; LDLc: Low-density lipoprotein; LH, luteinizing hormone; Lp: Lipoprotein; Max: Maximum. Min: Minimum; Q1: First quartile; Q3: Third quartile; SD: Standard deviation; TSH: Thyroid stimulating hormone.
The baseline is the results measured at baseline visit prior to informed consent.
For 'Blood Glucose', outlier values were removed for 16 patients where the values were less than 1 mmol/L or greater than 14 mmol/L.
For 'TSH', outlier values were removed for 4 patients where the values exceeded 1000 µIU/mL.
Source: Table 15.3.17.1, Appendix 8: Additional documents

10.4.3. Secondary Safety Results

There were no secondary AESIs reported at the time of the database lock. For full reporting of safety results, see Section 10.5 for details.

10.4.4. Secondary Effectiveness Results

Secondary effectiveness results available include bone age, treatment adherence, QoLISSY, and treatment experience. Body composition was not routinely conducted per standard of care. Data that were available are presented in Source Table 16.2.6.9 (Appendix 8.1).

Bone age results measured by the Tanner-Whitehouse method by treatment groups are compiled together below in Table 22 and were reported previously in Table 6 (bone age). A full description of bone age measured by the Tanner-Whitehouse method appears above in Section 10.2.1.

Bone age results measured by the G&P method at baseline and 12 months are reported in Table 22 below. Overall mean (SD) baseline bone age was 9.4 (3.88) years (10.0 [3.56] years in the Genotropin group, 9.4 [4.02] years in the Other daily hGH group, and 8.2 [4.02] years in the Ngenla group) (Table 22).

At Month 12, the overall mean (SD) bone age change from baseline was 2.0 (1.50) years and the data were missing for 1492 patients. Data were sparse within treatment groups and no data were available at Month 24 (Table 22).

The overall mean (SD) bone relative age change from baseline (i.e., change in bone age relation to the change in chronological age) was 1.4 (1.28) years. Data were sparse within treatment groups and no data were available at Month 24 (Table 22).

Table 22 Secondary Effectiveness Endpoints: Bone age by Treatment Groups

					Other daily hGH																	
		Genotropin (N=716)			Humatrope (N=28)			Norditropin (N=150)			Omnitrope (N=181)			Total (N=359)			Ngenla (N=441)			Overall (N=1516)		
Time Points/ Age Categories		Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change
Bone age at Baseline, Tanner-Whitehouse (years)	n	213			7			51			65			123			117			453		
	Mean (SD)	10.6 (3.71)			12.1 (4.00)			10.9 (3.65)			9.6 (3.69)			10.2 (3.74)			8.6 (4.07)			10.0 (3.90)		
	Median	11.6			13.0			11.6			10.0			11.0			8.6			10.9		
	Q1; Q3	8.5; 13.0			10.5; 15.0			8.3; 14.0			7.6; 12.5			8.0; 13.5			5.4; 12.0			7.5; 13.0		
	Min; Max	1.5; 18.0			4.3; 16.5			1.0; 17.0			2.0; 16.3			1.0; 17.0			0.0; 17.0			0.0; 18.0		
	Missing	503			21			99			116			236			324			1063		
Bone age at Baseline, G&P Method (years)	n	476			12			94			133			239			271			986		
	Mean (SD)	10.0 (3.56)			11.0 (3.30)			9.6 (4.08)			9.1 (4.01)			9.4 (4.02)			8.2 (4.02)			9.4 (3.88)		
	Median	11.0			11.5			10.0			9.0			10.0			8.0			10.0		
	Q1; Q3	8.0 ; 13.0			9.0 ; 13.5			7.0 ; 13.0			6.0 ; 12.0			6.0 ; 13.0			5.0 ; 11.0			6.0 ; 13.0		
	Min; Max	1.0 ; 18.0			5.0 ; 15.0			2.0 ; 18.0			2.0 ; 17.0			2.0 ; 18.0			0.0 ; 17.0			0.0 ; 18.0		
	Missing	240			16			56			48			120			170			530		
Bone age at 12 months, G&P Method (years)	n	27	15	11	0	0	0	6	4	2	6	4	1	12	8	3	3	1	1	42	24	15
	Mean (SD)	12.3 (3.33)	2.3 (1.76)	1.4 (1.48)	- (-)	- (-)	- (-)	11.2 (4.92)	1.5 (0.58)	1.5 (0.71)	11.2 (2.48)	1.3 (0.96)	1.0 (-)	11.2 (3.71)	1.4 (0.74)	1.3 (0.58)	8.7 (4.73)	2.0 (-)	2.0 (-)	11.7 (3.58)	2.0 (1.50)	1.4 (1.28)
	Median	13.0	2.0	1.0	-	-	-	12.0	1.5	1.5	11.5	1.5	1.0	11.5	1.5	1.0	7.0	2.0	2.0	13.0	2.0	1.0

					Other daily hGH															
		Genotropin (N=716)			Humatrope (N=28)			Norditropin (N=150)			Omnitrope (N=181)			Total (N=359)			Ngenla (N=441)			Overall (N=1516)		
Time Points/ Age Categories		Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change	Observed Value	Change from Baseline	Relative age change
	Q1; Q3	10.0 ; 14.0	1.0 ; 3.0	0.7 ; 2.0	- ;-	- ;-	- ;-	7.0 ; 15.0	1.0 ; 2.0	1.0 ; 2.0	10.0 ; 13.0	0.5 ; 2.0	1.0 ; 1.0	8.5 ; 13.5	1.0 ; 2.0	1.0 ; 2.0	5.0 ; 14.0	2.0 ; 2.0	2.0 ; 2.0	10.0 ; 14.0	1.0 ; 2.5	0.7 ; 2.0
	Min; Max	3.0 ; 17.0	-1.0 ; 6.0	-0.5 ; 5.0	- ;-	- ;-	- ;-	4.0 ; 17.0	1.0 ; 2.0	1.0 ; 2.0	7.0 ; 14.0	0.0 ; 2.0	1.0 ; 1.0	4.0 ; 17.0	0.0 ; 2.0	1.0 ; 2.0	5.0 ; 14.0	2.0 ; 2.0	2.0 ; 2.0	3.0 ; 17.0	-1.0 ; 6.0	-0.5 ; 5.0
	Missing	689	701	705	28	28	28	144	146	148	175	177	180	347	351	356	438	440	440	1474	1492	1501

G&P: Greulich & Pyle; hGH: Human Growth Hormone; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum;
Relative age change: Change in bone age (BA) relative to the change in chronologic age (CA) = BA in Time point X – BA in baseline/ CA at Time point X – CA at baseline
Source: Table 15.1.2 and Table 15.2.2.1, Appendix 8: Additional documents.

Among all patients, the mean (SD) duration of treatment was 655.3 (860.74) (798.9 [917.24] days, 818.2 [1003.17] days, and 289.6 [419.16] days in the Genotropin, Other daily hGH, and the Ngenla groups, respectively) (Table 23).

Overall, 333 (22.0%) patients reported a change in hGH treatment (175 [24.4%], 81 [22.6%], and 77 [17.5%] in the Genotropin, Other daily hGH group, and the Ngenla group, respectively). The most common reason for the change in treatment was other reasons (n=192, 57.7%), followed by increased targeted IGF-1 response (n=93, 27.9%), and switching to a daily treatment (n=72, 21.6%). “Other” reasons included dose changes, drug shortages or supply issues requiring treatment switch, reaching desired height, and storage inconvenience. Full details are provided in Source Table 16.2.6.1a (Appendix 8.1). A total of 32 (2.1%) patients discontinued the treatment and the most common reason for treatment discontinuation was ‘other reason’ (n=11, 34.4%) (Table 23). Full details are provided in Source Table 16.2.6.1a (Appendix 8.1).

Overall, 18 (1.2%) patients reported missed injections over the last 4-week period in Year 1 and the most common reason for missing injections was “patient was too tired / just wanted to go to bed”. Data were missing for 1498 patients. Only 1 patient-reported missed injections over the last 4 weeks period in Year 2, however the reason was not listed. Data were missing for 1515 patients (Table 23).

Table 23 Treatment Adherence and Compliance Outcomes – Full Analysis Set

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Duration of treatment (in days)[1]							
n	716	28	150	181	359	441	1516
Mean (SD)	798.9 (917.24)	945.5 (1105.11)	922.6 (1136.38)	712.0 (852.30)	818.2 (1003.17)	289.6 (419.16)	655.3 (860.74)
Median	407.5	565.0	571.5	395.0	449.0	194.0	327.0
Q1; Q3	260.0; 951.0	199.5; 1154.0	203.0; 1164.0	191.0; 849.0	195.0; 1085.0	96.0; 291.0	174.5; 775.5
Min; Max	7.0; 6203.0	97.0; 4328.0	7.0; 7131.0	1.0; 5335.0	1.0; 7131.0	1.0; 2582.0	1.0; 7131.0
Missing	0	0	0	0	0	0	0
Change in hGH treatment, n (%)							
Yes	175 (24.4)	8 (28.6)	37 (24.7)	36 (19.9)	81 (22.6)	77 (17.5)	333 (22.0)
No	541 (75.6)	20 (71.4)	113 (75.3)	145 (80.1)	278 (77.4)	364 (82.5)	1183 (78.0)
Reason for change in treatment, n (%)[2]							
Adverse Event	1 (0.6)	1 (12.5)	0	0	1 (1.2)	1 (1.3)	3 (0.9)
Cost	3 (1.7)	0	0	1 (2.8)	1 (1.2)	0	4 (1.2)
Drug-drug interaction	0	0	0	0	0	0	0
Increase targeted IGF-1 response	77 (44.0)	2 (25.0)	6 (16.2)	3 (8.3)	11 (13.6)	5 (6.5)	93 (27.9)
Decrease targeted IGF-1 response	38 (21.7)	2 (25.0)	5 (13.5)	6 (16.7)	13 (16.0)	4 (5.2)	55 (16.5)
Switching to a daily treatment	67 (38.3)	2 (25.0)	2 (5.4)	0	4 (4.9)	1 (1.3)	72 (21.6)
Unknown	7 (4.0)	0	1 (2.7)	4 (11.1)	5 (6.2)	8 (10.4)	20 (6.0)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Other	69 (39.4)	5 (62.5)	30 (81.1)	26 (72.2)	61 (75.3)	62 (80.5)	192 (57.7)
Treatment discontinuation, n (%)							
Yes	12 (1.7)	3 (10.7)	5 (3.3)	4 (2.2)	12 (3.3)	8 (1.8)	32 (2.1)
No	171 (23.9)	7 (25.0)	33 (22.0)	26 (14.4)	66 (18.4)	45 (10.2)	282 (18.6)
Reason for discontinuation, n (%)[3]							
Normal height reached	2 (16.7)	1 (33.3)	0	1 (25.0)	2 (16.7)	1 (12.5)	5 (15.6)
Growth plate fusion	1 (8.3)	0	0	1 (25.0)	1 (8.3)	2 (25.0)	4 (12.5)
Insufficient height velocity	0	0	0	0	0	0	0
Patient/parent decision	1 (8.3)	0	0	0	0	1 (12.5)	2 (6.3)
Non-compliance	1 (8.3)	0	0	0	0	0	1 (3.1)
No funds for GH	1 (8.3)	0	0	0	0	1 (12.5)	2 (6.3)
Change of diagnosis	0	0	0	0	0	0	0
Adverse Event	3 (25.0)	1 (33.3)	1 (20.0)	1 (25.0)	3 (25.0)	1 (12.5)	7 (21.9)
Unknown	0	0	0	0	0	0	0
Other reason	3 (25.0)	1 (33.3)	4 (80.0)	1 (25.0)	6 (50.0)	2 (25.0)	11 (34.4)
Year 1: Number of patients who Missed injections over the last 4 weeks, n (%)	4 (0.6)	2 (7.1)	7 (4.7)	5 (2.8)	14 (3.9)	0	18 (1.2)
n	4	2	7	5	14	0	18
Mean (SD)	1.3 (2.50)	1.5 (2.12)	4.4 (8.75)	0.2 (0.45)	2.5 (6.32)	- (-)	2.2 (5.65)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Median	0.0	1.5	1.0	0.0	0.0	-	0.0
Q1; Q3	0.0; 2.5	0.0; 3.0	0.0; 4.0	0.0; 0.0	0.0; 2.0	-; -	0.0; 2.0
Min; Max	0.0; 5.0	0.0; 3.0	0.0; 24.0	0.0; 1.0	0.0; 24.0	-; -	0.0; 24.0
Missing	712	26	143	176	345	441	1498
Reasons for missing injections							
Was too tired / just wanted to go to bed	1 (0.1)	1 (3.6)	2 (1.3)	1 (0.6)	4 (1.1)	0	5 (0.3)
Ran out of medication	0	0	1 (0.7)	0	1 (0.3)	0	1 (0.1)
Forgot to take the injection	1 (0.1)	0	0	0	0	0	1 (0.1)
Was busy with daily activities (such as chores or school)	1 (0.1)	0	0	0	0	0	1 (0.1)
Was busy with social activities (such as spending time with family and friends)	1 (0.1)	1 (3.6)	0	0	1 (0.3)	0	2 (0.1)
Was busy with recreational/ leisure activities (such as playing games, sports, or watching TV)	0	0	1 (0.7)	0	1 (0.3)	0	1 (0.1)
Spent the night away from home	0	0	2 (1.3)	0	2 (0.6)	0	2 (0.1)
Was traveling/ on vacation	0	1 (3.6)	0	0	1 (0.3)	0	1 (0.1)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Was afraid of or refused injection	0	0	0	0	0	0	0
Other	0	0	0	1 (0.6)	1 (0.3)	0	1 (0.1)
Missing	3	1	3	4	8	0	11
Year 2: Number of patients who Missed injections over the last 4 weeks, n (%)	1 (0.1)	0	0	0	0	0	1 (0.1)
n	1	0	0	0	0	0	1
Mean (SD)	0.0 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	0.0 (-)
Median	0.0	-	-	-	-	-	0.0
Q1; Q3	0.0; 0.0	-; -	-; -	-; -	-; -	-; -	0.0; 0.0
Min; Max	0.0; 0.0	-; -	-; -	-; -	-; -	-; -	0.0; 0.0
Missing	715	28	150	181	359	441	1515
Reasons for missing injections							

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Was too tired / just wanted to go to bed	0	0	0	0	0	0	0
Ran out of medication	0	0	0	0	0	0	0
Forgot to take the injection	0	0	0	0	0	0	0
Was busy with daily activities (such as chores or school)	0	0	0	0	0	0	0
Was busy with social activities (such as spending time with family and friends)	0	0	0	0	0	0	0
Was busy with recreational/leisure activities (such as playing games, sports, or watching TV)	0	0	0	0	0	0	0
Spent the night away from home	0	0	0	0	0	0	0
Was traveling/ on vacation	0	0	0	0	0	0	0
Was afraid of or refused injection	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Missing	1	0	0	0	0	0	1

CRF: Case Report Form; Min: Minimum; Max: Maximum; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile.
Percentages are calculated using non-missing values as denominator.
[1] The duration is calculated by: last dose date – first dose date +1.
[2] Percentages calculated based on the number of patients who changed the hGH treatment.

[3] Percentages calculated based on the number of patients who discontinued the treatment.
For patients, 16001016 and 22013021, records where the treatment end date is after the clinical cut-off date have been updated to 30-Apr-2024 and excluded the records where the treatment start date is after the clinical cut-off date.
Note: For Reasons for missing injections, multiple options can be selected per CRF.
Source: Table 15.4.1, Appendix 8: Additional documents

A summary of QoLISSY-Child (Core and Additional Domains) for the FAS is provided in Source Table 15.5.2, Appendix 8 and results for QoLISSY-CHILD core total scores are presented in Table 24.

Higher scores indicate better QoL. Overall, the mean (SD) QoLISSY core total score (Child) at baseline was 76.0 (19.36) and was similar in all treatment groups (74.1 [20.13], 75.8 [21.87], and 78.8 [16.66] in the Genotropin, Other daily hGH group, and the Ngenla group, respectively). At Month 12, data for QoLISSY core total score for Child were available for 29 patients with a mean (SD) of 74.7 (19.73). Overall, the mean (SD) QoLISSY core total score (Child) change from baseline was 11.7 (17.52) and was higher in the Genotropin group (13.6 [19.84]) and lower in the Other daily hGH group and the Ngenla group (10.7 [16.69] and 4.0 [5.65], respectively). There were no details available for Month 24 (Table 24).

A summary of QoLISSY-Parent (Core, Additional, and Supplementary Domains) for FAS is provided in Source Table 15.5.2.3, Appendix 8 and results for QoLISSY core total scores are presented in Table 25.

Overall, the mean (SD) QoLISSY core total score (Parent) at baseline was 72.2 (19.25) and was similar in all treatment groups (69.5 [20.84], 73.8 [18.81], and 75.6 [16.44] in the Genotropin, Other daily hGH group, and the Ngenla group, respectively). At Month 12, data for QoLISSY core total score for Parent were available for 13 patients with a mean (SD) 75.2 (12.44).

Overall, the mean (SD) QoLISSY core total score (Parent) change from baseline was 2.7 (6.34) and was similar in the Genotropin group (2.6 [10.56]) and higher in the Ngenla group (3.5 [6.18]). Only 1 parent in the Other daily hGH group had data for QoLISSY core total score (Parent) change from baseline at Month 12 (score=-1.0). At Month 24, data for QoLISSY core total score for Parent was available for only 1 parent whose child was in the Genotropin group (score=78.1) (Table 25).

Table 24 Summary of QoLISSY – CHILD Core Total Score – Full Analysis Set

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline	n	162		5		23		24		52		113		327	
	Mean (SD)	74.1 (20.13)		59.8 (27.79)		85.9 (12.95)		69.5 (23.79)		75.8 (21.87)		78.8 (16.66)		76.0 (19.36)	
	Median	77.4		60.1		91.3		78.3		83.9		83.3		80.9	
	Q1; Q3	64.6 ; 89.6		59.7 ; 71.2		79.5 ; 93.8		52.1 ; 89.2		63.9 ; 92.4		71.2 ; 90.3		66.0 ; 90.6	
	Min; Max	2.1 ; 100.0		16.0 ; 92.0		45.5 ; 99.0		18.4 ; 95.8		16.0 ; 99.0		12.5 ; 100.0		2.1 ; 100.0	
	Missing	554		23		127		157		307		328		1189	
Month 12	n	17	11	0	0	4	2	6	4	10	6	2	2	29	19
	Mean (SD)	77.9 (17.02)	13.6 (19.84)	- (-)	- (-)	65.6 (20.24)	-4.3 (8.59)	66.2 (26.68)	18.2 (14.60)	66.0 (23.07)	10.7 (16.69)	91.1 (1.72)	4.0 (5.65)	74.7 (19.73)	11.7 (17.52)
	Median	83.0	9.7	-	-	71.4	-4.3	72.7	24.0	72.7	11.3	91.1	4.0	75.3	8.0
	Q1; Q3	64.6 ; 88.2	-4.5 ; 33.3	- ; -	- ; -	52.1 ; 79.2	-10.4 ; 1.7	67.7 ; 74.0	8.9 ; 27.6	67.4 ; 75.3	-3.1 ; 27.1	89.9 ; 92.4	0.0 ; 8.0	67.4 ; 88.2	-3.1 ; 27.1
	Min; Max	41.0 ; 97.9	14.9 ; 47.6	- ; -	- ; -	36.8 ; 83.0	-10.4 ; 1.7	15.3 ; 94.8	-3.1 ; 28.1	15.3 ; 94.8	10.4 ; 28.1	89.9 ; 92.4	0.0 ; 8.0	15.3 ; 97.9	14.9 ; 47.6
	Missing	699	705	28	28	146	148	175	177	349	353	439	439	1487	1497

hGH: Human Growth Hormone; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; QoLISSY: Quality of Life in Short Stature Youth; SD: Standard Deviation.
The baseline is the results measured at baseline visit prior to informed consent.
The QoLISSY core total score is calculated by the sum of the means of the 3 core domains (Physical, Social, and Emotional) and divided by 3.
All scores have been transformed from raw scores to 0 to 100 scores with higher values representing higher quality of life.
Source: Table 15.5.2, Appendix 8: Additional documents.

Table 25 Summary of QoLISSY – PARENT Core Total Score – Full Analysis Set

				Other daily hGH											
		Genotropin (N=716)		Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)		Ngenla (N=441)		Overall (N=1516)	
Time Points		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline	n	154		7		12		17		36		110		300	
	Mean (SD)	69.5 (20.84)		70.2 (25.15)		73.8 (18.36)		75.3 (17.24)		73.8 (18.81)		75.6 (16.44)		72.2 (19.25)	
	Median	71.5		81.9		78.0		78.8		78.6		78.8		76.0	
	Q1; Q3	58.0 ; 86.5		56.3 ; 87.5		60.4 ; 88.0		65.6 ; 86.5		60.4 ; 87.2		64.2 ; 87.5		60.9 ; 87.2	
	Min; Max	8.0 ; 99.0		20.5 ; 91.3		36.5 ; 97.9		44.1 ; 100.0		20.5 ; 100.0		26.7 ; 100.0		8.0 ; 100.0	
	Missing	562		21		138		164		323		331		1216	
Month 12	n	4	2	1	0	2	1	1	0	4	1	5	5	13	8
	Mean (SD)	69.6 (6.66)	2.6 (10.56)	74.7 (-)	- (-)	78.8 (25.53)	-1.0 (-)	73.3 (-)	- (-)	76.4 (15.02)	-1.0 (-)	78.8 (14.62)	3.5 (6.18)	75.2 (12.44)	2.7 (6.34)
	Median	70.1	2.6	74.7	-	78.8	-1.0	73.3	-	74.0	-1.0	79.9	4.2	74.7	3.6
	Q1; Q3	64.4 ; 74.8	-4.9 ; 10.1	74.7 ; 74.7	- ; -	60.8 ; 96.9	-1.0 ; -1.0	73.3 ; 73.3	- ; -	67.0 ; 85.8	-1.0 ; -1.0	76.0 ; 90.6	3.1 ; 5.6	67.4 ; 79.9	-3.0 ; 7.8
	Min; Max	61.5 ; 76.7	-4.9 ; 10.1	74.7 ; 74.7	- ; -	60.8 ; 96.9	-1.0 ; -1.0	73.3 ; 73.3	- ; -	60.8 ; 96.9	-1.0 ; -1.0	55.6 ; 91.7	-6.3 ; 10.8	55.6 ; 96.9	-6.3 ; 10.8
	Missing	712	714	27	28	148	149	180	181	355	358	436	436	1503	1508
Month 24	n	1	0	0	0	0	0	0	0	0	0	0	0	1	0
	Mean (SD)	78.1 (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	78.1 (-)	- (-)
	Median	78.1	-	-	-	-	-	-	-	-	-	-	-	78.1	-
	Q1; Q3	78.1 ; 78.1	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	78.1 ; 78.1	- ; -
	Min; Max	78.1 ; 78.1	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	- ; -	78.1 ; 78.1	- ; -
	Missing	715	716	28	28	150	150	181	181	359	359	441	441	1515	1516

hGh: Human Growth Hormone; Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile; QoLISSY: Quality of Life in Short Stature Youth; Max SD: Standard Deviation.

The baseline is the results measured at baseline visit prior to informed consent.
The QoLISSY core total score is calculated by the sum of the means of the 3 core domains (Physical, Social, and Emotional) and divided by 3.
All scores have been transformed from raw scores to 0 to 100 scores with higher values representing higher quality of life.
Source: Table 15.5.2.3, Appendix 8: Additional documents.

Data from the DCOA I (treatment experience) are detailed in Table 26. A summary of the individual item scores is available in Source Table 15.5.5 (Appendix 8.1). Higher scores indicate greater life interference. Data were sparse (n=1) for DCOA I at the Month 24 timepoint and are presented in (Source Table 15.5.3, Appendix 8).

Baseline data for missed injections module were available for overall 167 patients and data were missing for 1349 patients, of which 593 were in the Genotropin group, 322 were in the Other daily hGH group, and 434 were in the Ngenla group. Overall, the mean (SD) number of missed injections in the prior 4-week period was 3.0 (4.59) at baseline. For patients in the Genotropin group, the Other daily hGH group, and the Ngenla group, the mean (SD) number of missed injections was 3.2 (5.11), 2.7 (2.78), and 1.1 (0.38) at baseline, respectively. At Month 12, data for missed injections modules were available for overall 7 patients with a mean (SD) of 5.7 (8.20). For patients in the Genotropin group and the Other daily hGH group, the mean (SD) scores of missed injections module were 5.0 (-) and 5.8 (8.98), respectively. No patient data were available for the Ngenla group at Month 12. Data were missing for 1509 patients, of which 715 patients were in the Genotropin group, 353 patients were in the Other daily hGH group, and 441 were in the Ngenla group (Table 26).

The most common reason for missing injections in patients overall was forgot to take the injection (n=63, 36.8%). For patients in the Genotropin group, 34.1% (n=42) of patients reported forgot to take the injection as the most common reason for missed injection. Among patients in the Other daily hGH group, 46.3% (n=19) of patients reported forgot to take the injection as the most common reason for missed injections. Among patients in the Ngenla group, 42.9% (n=3) of patients reported spent the night away from home as the most common reason for missed injections. At Month 12, data for reasons for missing injections were available for few patients, but the most common reason reported was too tired / just wanted to go to bed (n=5, 2.9%) (Table 26).

Baseline data for life interference total score were available for overall 331 patients and data were missing for 1185 patients, of which 543 patients were in the Genotropin group, 310 patients were in the Other daily hGH group, and 332 patients were in the Ngenla group. For patients overall the mean (SD) score of life interference total score was 16.3 (18.61) at baseline. For patients in the Genotropin group, the Other daily hGH group, and the Ngenla group, the mean (SD) scores of life interference total score were 18.9 (20.37), 17.5 (18.74), and 11.7 (14.48) at baseline, respectively. At Month 12, data for life interference total score were available for 14 patients with a mean (SD) of 10.9 (15.56). For patients in the Genotropin group, the Other daily hGH group and the Ngenla group, the mean (SD) scores of life interference total score were 19.2 (4.97), 13.1 (23.96), and 1.9 (4.30), respectively. Data were missing for 1502 patients, of which 712 patients were in the Genotropin group, 354 patients were in the Other daily hGH group, and 436 were in the Ngenla group (Table 26).

Baseline data for caregiver life interference score were available for overall 331 patients and data were missing for 1185 patients, of which 543 patients were in the Genotropin group, 310 patients were in the Other daily hGH group, and 332 patients were in the Ngenla group. For patients overall the mean (SD) score of caregiver life interference score was 18.7 (20.12) at baseline. For patients in the Genotropin group, the Other daily hGH group, and the Ngenla group, the mean (SD) scores of caregiver life interference score were 21.4

(21.55), 21.2 (21.43), and 13.4 (15.81) at baseline, respectively. At Month 12, data for caregiver life interference score were available for 14 patients with a mean (SD) of 12.8 (18.16). For patients in the Genotropin group, the Other daily hGH group and the Ngenla group, the mean (SD) scores of caregiver life interference score were 19.8 (8.59), 17.5 (27.86), and 2.5 (5.59), respectively. Data were missing for 1502 patients, of which 712 patients were in the Genotropin group, 354 patients were in the Other daily hGH group, and 436 were in the Ngenla group (Table 26).

Baseline data for family life interference score were available for overall 331 patients and data were missing for 1185 patients, of which 543 patients were in the Genotropin group, 310 patients were in the Other daily hGH group, and 332 patients were in the Ngenla group. For patients overall the mean (SD) score of family life interference score was 14.2 (18.58) at baseline. For patients in the Genotropin group, the Other daily hGH group, and the Ngenla group, the mean (SD) scores of family life interference score were 16.7 (20.54), 14.3 (17.83), and 10.3 (14.71) at baseline, respectively. At Month 12, data for family life interference scores were available for 14 patients with a mean (SD) of 9.2 (13.78). For patients in the Genotropin group, the Other daily hGH group and the Ngenla group, the mean (SD) scores of family life interference score were 18.8 (3.42), 9.3 (20.76), and 1.4 (3.19), respectively. Data were missing for 1502 patients, of which 712 patients were in the Genotropin group, 354 patients were in the Other daily hGH group, and 436 were in the Ngenla group (Table 26).

No participants had responded to the DCOA II at the time of study termination and database lock (Source Table 15.5.4, Appendix 8.1).

Table 26 Summary of DCOA 1 (Treatment experience) at Baseline by Treatment Groups

	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
			Observed Value	Change from baseline	Observed Value	Change from baseline	Observed Value	Change from baseline	Observed Value	Change from baseline	Observed Value	Change from baseline	Observed Value	Change from baseline	Observed Value	Change from baseline
Missed Injections	Baseline	n	123		4		15		18		37		7		167	
		Mean (SD)	3.2 (5.11)		2.8 (2.36)		2.7 (2.40)		2.6 (3.26)		2.7 (2.78)		1.1 (0.38)		3.0 (4.59)	
		Median	2.0		2.0		2.0		2.0		2.0		1.0		2.0	
		Q1; Q3	1.0; 3.0		1.0; 4.5		1.0; 4.0		1.0; 2.0		1.0; 3.0		1.0; 1.0		1.0; 3.0	
		Min; Max	1.0; 30.0		1.0; 6.0		1.0; 10.0		1.0; 15.0		1.0; 15.0		1.0; 2.0		1.0; 30.0	
		Missing	593		24		135		163		322		434		1349	
	Month 12	n	1	1	1	1	4	3	1	0	6	4	0	0	7	5
		Mean (SD)	5.0 (-)	3.0 (-)	3.0 (-)	2.0 (-)	7.8 (10.90)	8.3 (13.58)	1.0 (-)	- (-)	5.8 (8.98)	6.8 (11.53)	- (-)	- (-)	5.7 (8.20)	6.0 (10.12)
		Median	5.0	3.0	3.0	2.0	3.0	1.0	1.0	-	2.5	1.5	-	-	3.0	2.0
		Q1; Q3	5.0; 5.0	3.0; 3.0	3.0; 3.0	2.0; 2.0	1.5; 14.0	0.0; 24.0	1.0; 1.0	-; -	1.0; 4.0	0.5; 13.0	-; -	-; -	1.0; 5.0	1.0; 3.0
		Min; Max	5.0; 5.0	3.0; 3.0	3.0; 3.0	2.0; 2.0	1.0; 24.0	0.0; 24.0	1.0; 1.0	-; -	1.0; 24.0	0.0; 24.0	-; -	-; -	1.0; 24.0	0.0; 24.0

	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
		Missing	715	715	27	27	146	147	180	181	353	355	441	441	1509	1511
Reasons for Missed Injections, n (%)[1]	Baseline															
Too Tired / Just Wanted to go to Bed			34 (27.6)		1 (25.0)		4 (22.2)		5 (26.3)		10 (24.4)		2 (28.6)		46 (26.9)	
Ran Out of Medication			13 (10.6)		0 (0.0)		2 (11.1)		2 (10.5)		4 (9.8)		0 (0.0)		17 (9.9)	
Forgot to Take the Injection			42 (34.1)		1 (25.0)		8 (44.4)		10 (52.6)		19 (46.3)		2 (28.6)		63 (36.8)	
Busy with Daily Activities			17 (13.8)		0 (0.0)		1 (5.6)		1 (5.3)		2 (4.9)		0 (0.0)		19 (11.1)	
Busy with Social Activities			17 (13.8)		1 (25.0)		4 (22.2)		3 (15.8)		8 (19.5)		0 (0.0)		25 (14.6)	
Busy with Recreational/Leisure Activities			10 (8.1)		1 (25.0)		3 (16.7)		1 (5.3)		5 (12.2)		0 (0.0)		15 (8.8)	
Spent the Night Away from Home			31 (25.2)		1 (25.0)		5 (27.8)		9 (47.4)		15 (36.6)		3 (42.9)		49 (28.7)	

	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
Traveling/On Vacation			20 (16.3)		1 (25.0)		2 (11.1)		5 (26.3)		8 (19.5)		1 (14.3)		29 (17.0)	
Afraid of or Refused Injection			6 (4.9)		0 (0.0)		1 (5.6)		0 (0.0)		1 (2.4)		1 (14.3)		8 (4.7)	
Other			7 (5.7)		0 (0.0)		2 (11.1)		2 (10.5)		4 (9.8)		0 (0.0)		11 (6.4)	
Missing			0		0		0		0		0		0		0	
Reasons for Missed Injections, n (%)[1]	Month 12															
Too Tired / Just Wanted to go to Bed			1 (0.8)		1 (25.0)		2 (11.1)		1 (5.3)		4 (9.8)		0 (0.0)		5 (2.9)	
Ran Out of Medication			0 (0.0)		0 (0.0)		1 (5.6)		0 (0.0)		1 (2.4)		0 (0.0)		1 (0.6)	
Forgot to Take the Injection			1 (0.8)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		1 (0.6)	
Busy with Daily Activities			1 (0.8)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		1 (0.6)	
Busy with Social Activities			1 (0.8)		1 (25.0)		0 (0.0)		0 (0.0)		1 (2.4)		0 (0.0)		2 (1.2)	

	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
Busy with Recreational/Leisure Activities			0 (0.0)		0 (0.0)		1 (5.6)		0 (0.0)		1 (2.4)		0 (0.0)		1 (0.6)	
Spent the Night Away from Home			0 (0.0)		0 (0.0)		2 (11.1)		0 (0.0)		2 (4.9)		0 (0.0)		2 (1.2)	
Traveling/On Vacation			0 (0.0)		1 (25.0)		0 (0.0)		0 (0.0)		1 (2.4)		0 (0.0)		1 (0.6)	
Afraid of or Refused Injection			0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Other			0 (0.0)		0 (0.0)		0 (0.0)		1 (5.3)		1 (2.4)		0 (0.0)		1 (0.6)	
Missing			0		0		0		0		0		0		0	
Life Interference Total Score	Baseline	n	173		8		20		21		49		109		331	
		Mean (SD)	18.9 (20.37)		8.2 (9.68)		18.1 (15.78)		20.4 (23.02)		17.5 (18.74)		11.7 (14.48)		16.3 (18.61)	
		Median	13.5		4.8		15.4		11.5		11.5		5.8		9.6	
		Q1; Q3	3.8; 28.8		0.0; 15.4		5.8; 27.9		5.8; 26.9		3.8; 25.0		0.0; 17.3		0.0; 25.0	
		Min; Max	0.0; 90.4		0.0; 25.0		0.0; 57.7		0.0; 71.2		0.0; 71.2		0.0; 59.6		0.0; 90.4	

	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
		Missing	543		20		130		160		310		332		1185	
	Month 12	n	4	2	1	0	2	2	2	0	5	2	5	4	14	8
		Mean (SD)	19.2 (4.97)	11.5 (2.72)	0.0 (-)	- (-)	28.8 (38.07)	-2.9 (34.00)	3.8 (2.72)	- (-)	13.1 (23.96)	-2.9 (34.00)	1.9 (4.30)	-9.6 (19.23)	10.9 (15.56)	-2.6 (20.25)
		Median	19.2	11.5	0.0	-	28.8	-2.9	3.8	-	1.9	-2.9	0.0	0.0	3.8	0.0
		Q1; Q3	15.4; 23.1	9.6; 13.5	0.0; 0.0	-; -	1.9; 55.8	-26.9; 21.2	1.9; 5.8	-; -	1.9; 5.8	-26.9; 21.2	0.0; 0.0	-19.2; 0.0	0.0; 17.3	-13.5; 11.5
		Min; Max	13.5; 25.0	9.6; 13.5	0.0; 0.0	-; -	1.9; 55.8	-26.9; 21.2	1.9; 5.8	-; -	0.0; 55.8	-26.9; 21.2	0.0; 9.6	-38.5; 0.0	0.0; 55.8	-38.5; 21.2
		Missing	712	714	27	28	148	148	179	181	354	357	436	437	1502	1508
Caregiver Life Interference Score	Baseline	n	173		8		20		21		49		109		331	
		Mean (SD)	21.4 (21.55)		8.3 (11.79)		24.6 (19.91)		22.8 (24.42)		21.2 (21.43)		13.4 (15.81)		18.7 (20.12)	
		Median	16.7		0.0		22.9		12.5		16.7		8.3		12.5	
		Q1; Q3	4.2; 33.3		0.0; 20.8		8.3; 33.3		4.2; 37.5		0.0; 33.3		0.0; 20.8		0.0; 29.2	

	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
		Min; Max	0.0; 100.0		0.0; 25.0		0.0; 62.5		0.0; 79.2		0.0; 79.2		0.0; 62.5		0.0; 100.0	
		Missing	543		20		130		160		310		332		1185	
	Month 12	n	4	2	1	0	2	2	2	0	5	2	5	4	14	8
		Mean (SD)	19.8 (8.59)	14.6 (2.95)	0.0 (-)	- (-)	35.4 (44.19)	-12.5 (23.57)	8.3 (5.89)	- (-)	17.5 (27.86)	-12.5 (23.57)	2.5 (5.59)	-8.3 (16.67)	12.8 (18.16)	-3.6 (18.15)
		Median	20.8	14.6	0.0	-	35.4	-12.5	8.3	-	4.2	-12.5	0.0	0.0	6.3	0.0
		Q1; Q3	14.6; 25.0	12.5; 16.7	0.0; 0.0	-; -	4.2; 66.7	-29.2; 4.2	4.2; 12.5	-; -	4.2; 12.5	-29.2; 4.2	0.0; 0.0	-16.7; 0.0	0.0; 20.8	-14.6; 8.3
		Min; Max	8.3; 29.2	12.5; 16.7	0.0; 0.0	-; -	4.2; 66.7	-29.2; 4.2	4.2; 12.5	-; -	0.0; 66.7	-29.2; 4.2	0.0; 12.5	-33.3; 0.0	0.0; 66.7	-33.3; 16.7
		Missing	712	714	27	28	148	148	179	181	354	357	436	437	1502	1508
Family Life Interference Score	Baseline	n	173		8		20		21		49		109		331	
		Mean (SD)	16.7 (20.54)		8.0 (9.11)		12.5 (14.26)		18.4 (22.45)		14.3 (17.83)		10.3 (14.71)		14.2 (18.58)	
		Median	7.1		5.4		7.1		7.1		7.1		3.6		7.1	
		Q1; Q3	0.0; 25.0		0.0; 14.3		0.0; 25.0		3.6; 17.9		0.0; 17.9		0.0; 14.3		0.0; 25.0	

	Time Points		Genotropin (N=716)		Other daily hGH								Ngenla (N=441)		Overall (N=1516)	
					Humatrope (N=28)		Norditropin (N=150)		Omnitrope (N=181)		Total (N=359)					
		Min; Max	0.0; 92.9		0.0; 25.0		0.0; 53.6		0.0; 67.9		0.0; 67.9		0.0; 57.1		0.0; 92.9	
		Missing	543		20		130		160		310		332		1185	
	Month 12	n	4	2	1	0	2	2	2	0	5	2	5	4	14	8
		Mean (SD)	18.8 (3.42)	8.9 (7.58)	0.0 (-)	- (-)	23.2 (32.83)	5.4 (42.93)	0.0 (0.00)	- (-)	9.3 (20.76)	5.4 (42.93)	1.4 (3.19)	-10.7 (21.43)	9.2 (13.78)	-1.8 (23.69)
		Median	19.6	8.9	0.0	-	23.2	5.4	0.0	-	0.0	5.4	0.0	0.0	0.0	0.0
		Q1; Q3	16.1; 21.4	3.6; 14.3	0.0; 0.0	-; -	0.0; 46.4	-25.0; 35.7	0.0; 0.0	-; -	0.0; 0.0	-25.0; 35.7	0.0; 0.0	-21.4; 0.0	0.0; 17.9	-12.5; 8.9
		Min; Max	14.3; 21.4	3.6; 14.3	0.0; 0.0	-; -	0.0; 46.4	-25.0; 35.7	0.0; 0.0	-; -	0.0; 46.4	-25.0; 35.7	0.0; 7.1	-42.9; 0.0	0.0; 46.4	-42.9; 35.7
		Missing	712	714	27	28	148	148	179	181	354	357	436	437	1502	1508

DCOA: Dyad Clinical Outcomes Assessment; hGH: Human Growth Hormone; Max: Maximum; Min: Minimum Q1: First quartile; Q3: Third quartile; SD: Standard Deviation.
The baseline is the results measured at baseline visit prior to treatment.
1. Percentages are calculated using number of patients who missed injections. The added up percentage can be >100 as multiple reasons can be selected.
Note: All the raw scores (Likert scale values) were transformed into 0-100 scale (refer SAP section 6.4 for more details).
Source: Table 15.5.3, Appendix 8: Additional documents.

10.5. Other Analyses

None.

10.6. Adverse Events/Adverse Reactions

A summary of TEAEs is presented in Table 27. Overall, 98 (6.5%) patients had 195 TEAEs reported (53 [7.4%] patients had 86 TEAEs, 22 [6.1%] patients had 45 TEAEs, and 23 [5.2%] patients had 64 TEAEs in the Genotropin group, the Other daily hGH group, and the Ngenla group, respectively). Five (0.3%) patients (1 patient each in the Genotropin group and the Ngenla group and 3 patients in the Other daily hGH group) had any SAEs during the study. Patient safety narratives describe these events in full. Sixteen (1.1%) patients (6 patients in the Genotropin group and 5 patients each in the Other daily hGH group and the Ngenla group) had any AESI during the study. Sixteen (1.1%) patients (6 patients in the Genotropin group and 5 patients each in the Other daily hGH group and the Ngenla group) had primary AESIs and no patients had secondary AESIs reported as such in the EDC. However, 13 patients had 14 events that, upon MedDRA coding, were classified as arthralgia (Appendix 8, Source Table 15.3.2). This discrepancy in the counting of arthralgia events was due to investigators entering a free-text AE term indicating arthralgia, as opposed to selecting the prespecified secondary AESI option of arthralgia. Five (0.3%) patients (3 patients in the Other daily hGH group and 1 patient each in the Genotropin and the Ngenla group) had severe AE during the study. Twelve (0.8%) patients (2 patients in the Genotropin group, 6 patients in the Other daily hGH group, and 4 patients in the Ngenla group) had TEAEs that were considered related to the study drug. Five (0.3%) patients (2 patients in the Genotropin group and the Ngenla group, 1 patient in the Other daily hGH group) had a TEAE that led to study drug withdrawal. Four (0.3%) patients (2 patients each in the Other daily hGH group and the Ngenla group) had TEAEs that led to study drug reduction or interruption. Four (0.3%) patients (2 patients in the Genotropin group and 1 patient each in the Other daily hGH and the Ngenla group) had at least one TEAE that led to study discontinuation (Table 27).

Table 27 Summary of Treatment-Emergent Adverse Events – Full Analysis Set

Treatment-Emergent Adverse Events (TEAE)	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Patients with at least one TEAE, n (%)	53 (7.4)	2 (7.1)	13 (8.7)	7 (3.9)	22 (6.1)	23 (5.2)	98 (6.5)
Number of TEAEs	86	3	31	11	45	64	195
Patients with, n (%)							
Any SAE	1 (0.1)	1 (3.6)	0	2 (1.1)	3 (0.8)	1 (0.2)	5 (0.3)
AESI	6 (0.8)	1 (3.6)	2 (1.3)	2 (1.1)	5 (1.4)	5 (1.1)	16 (1.1)
Primary AESIs	6 (0.8)	1 (3.6)	2 (1.3)	2 (1.1)	5 (1.4)	5 (1.1)	16 (1.1)

Treatment-Emergent Adverse Events (TEAE)	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Secondary AESIs	0	0	0	0	0	0	0
Severe AE	1 (0.1)	0	1 (0.7)	2 (1.1)	3 (0.8)	1 (0.2)	5 (0.3)
TEAE related to study drug	2 (0.3)	2 (7.1)	2 (1.3)	2 (1.1)	6 (1.7)	4 (0.9)	12 (0.8)
TEAE leading to study drug withdrawal	2 (0.3)	1 (3.6)	0	0	1 (0.3)	2 (0.5)	5 (0.3)
TEAE leading to study drug reduction or interruption	0	0	2 (1.3)	0	2 (0.6)	2 (0.5)	4 (0.3)
TEAE leading to study discontinuation	2 (0.3)	1 (3.6)	0	0	1 (0.3)	1 (0.2)	4 (0.3)

AE: Adverse Event; AESI: Adverse Events of Special Interest; hGh: Human Growth Hormone; MedDRA: Medical Dictionary for Regulatory Activities; SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event.
All adverse events are coded using MedDRA Version 27.0 - Mar 2024.
Percentages are based on total number of patients N.
Source: Table 15.3.1, Appendix 8: Additional documents.

Treatment-Emergent AEs are presented in Table 28. Full data with SOCs and PTs are located in Source Table 15.3.2 (Appendix 8).

Overall, 98 (6.5%) patients had 195 TEAEs reported with 816.1 person-years of exposure. The IR (95% confidence interval [CI]) was 23.9 (20.8, 27.5) events per 100 person-years. The most frequently reported TEAEs were reported in SOCs of infections and infestations (n=27, 1.8% patients), general disorders and administration site conditions (n=21, 1.4% patients), musculoskeletal and connective tissue disorders (n=21, 1.4% patients), and nervous system disorders (n=15, 1.0% patients). The most frequently reported TEAEs by PT included arthralgia (n=13 patients, 0.9% patients), headache (n=13 patients, 0.9% patients), and injection site pain (n=7 patients, 0.5% patients).

Table 28 Treatment-Emergent Adverse Events – Full Analysis Set

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Any TEAE							
Number of patients, n (%)[1]	53 (7.4)	2 (7.1)	13 (8.7)	7 (3.9)	22 (6.1)	23 (5.2)	98 (6.5)
Number of events, n	86	3	31	11	45	64	195

Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	18.8 [15.3 - 23.3]	14.6 [4.7 - 45.2]	35.6 [25.0 - 50.6]	12.9 [7.2 - 23.4]	23.3 [17.4 - 31.3]	38.3 [30.0 - 48.9]	23.9 [20.8 - 27.5]

CI: Confidence Interval; hGh: Human Growth Hormone; TEAE: Treatment-Emergent Adverse Event.
[1] The denominator for calculating the percentage is the N shown in the table header.
[2] Incidence rate is calculated as 100 x (number of events / number of person-years). The total number of person-years is computed (Date of last known Follow-up visit-Date of baseline visit+1)/365.25.
MedDRA dictionary Version MedDRA v27.0 - Mar 2024.
Number (%) of subjects who experienced each specific SOC and PT are sorted by descending order of overall incidence.
Within each SOC or PT, subjects experiencing multiple occurrences of the same event is counted only once.
Percentages are calculated using the non-missing values as denominator.
Source: Table 15.3.2, Appendix 8: Additional documents.

Treatment-Emergent AEs related to study drugs are presented in Table 29 below. Full data with SOCs and PTs are located in Source Table 15.3.9 (Appendix 8).

Twelve (0.8%) patients (2 patients in the Genotropin group, 6 patients in the Other daily hGH group, and 4 patients in the Ngenla group) had 30 any TEAEs that were considered related to the study drug. The IR (95% CI) was 3.7 (2.6, 5.3) events per 100 person-years. Nine (0.6%) patients (1 patient in the Genotropin group and 4 patients each in the Other daily hGH group and the Ngenla group) had general disorders and administration site conditions related to the study drug. The PTs under the general disorders and administration site conditions SOC included 5 (0.3%) patients (3 patients in the Other daily hGH group and 2 patients in the Ngenla group) with injection site pain that was considered related to the study drug. One (0.1%) patient from the Ngenla group had injection site erythema, injection site pruritus, injection site swelling, and puncture site pain, one (0.1%) patient from the Genotropin group had injection site reaction, and one (0.1%) patient from the Other daily hGH group had localized oedema.

Table 29 Treatment-Emergent Adverse Events Related to Study Drug -- Full Analysis Set

	Genotropin (N=716)	**Other daily hGH**				**Ngenla (N=441)**	**Overall (N=1516)**
		Humatrope (N=28)	**Norditropin (N=150)**	**Omnitrope (N=181)**	**Total (N=359)**		
Any TEAE related to study drug							
Number of patients, n (%)[1]	2 (0.3)	2 (7.1)	2 (1.3)	2 (1.1)	6 (1.7)	4 (0.9)	12 (0.8)
Number of events, n	2	3	3	2	8	20	30

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	0.4 [0.1 - 1.8]	14.6 [4.7 - 45.2]	3.4 [1.1 - 10.7]	2.4 [0.6 - 9.4]	4.2 [2.1 - 8.3]	12.0 [7.7 - 18.6]	3.7 [2.6 - 5.3]

CI: Confidence Interval; hGh: Human Growth Hormone; TEAE: Treatment-Emergent Adverse Event.
[1] The denominator for calculating the percentage is the N shown in the table header.
[2] Incidence rate is calculated as 100 x (number of events / number of person-years). The total number of person-years is computed (Date of last known Follow-up visit-Date of baseline visit+1)/365.25.
MedDRA dictionary Version MedDRA v27.0 - Mar 2024.
Number (%) of subjects who experienced each specific SOC and PT are sorted by descending order of overall incidence.
Within each SOC or PT, subjects experiencing multiple occurrences of the same event is counted only once.
Percentages are calculated using the non-missing values as denominator.
Source: Table 15.3.9, Appendix 8: Additional documents.

Treatment-Emergent SAEs are presented in Table 30 below. Full data with SOCs and PTs are located in Source Table 15.3.3 (Appendix 8).

Five (0.3%) patients (1 patient in the Genotropin group, 3 patients in the Other daily hGH group, and 1 patient in the Ngenla group) had 5 treatment-emergent SAEs. The incidence rate (95% CI) was 0.6 (0.3, 1.5) events per 100 person-years (Table 30). Two (0.1%) patients (1 patient each in the Other daily hGH group and the Ngenla group) had infections and infestations, which included 1 (0.1%) patient with appendicitis and 1 (0.1%) patient with gastroenteritis. One (0.1%) patient in the Other daily hGH group had an endocrine disorders (adrenal insufficiency). One (0.1%) patient in the Other daily hGH group had a nervous system disorder (idiopathic intracranial hypertension). One (0.1%) patient from the Genotropin group had a psychiatric disorder (affective disorder). Details on these events are available in the safety narratives.

Table 30 Treatment-Emergent Serious Adverse Events – Full Analysis Set

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Any Treatment-Emergent SAEs,							
Number of patients, n (%)[1]	1 (0.1)	1 (3.6)	0	2 (1.1)	3 (0.8)	1 (0.2)	5 (0.3)
Number of events, n	1	1	0	2	3	1	5
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Incidence rate (per 100 person-years) [95% CI][2]	0.2 (0.0 ; 1.6)	4.9 (0.7 ; 34.5)	- (-;-)	2.4 (0.6 ; 9.4)	1.6 (0.5 ; 4.8)	0.6 (0.1 ; 4.2)	0.6 (0.3 ; 1.5)
Incidence rate ratio [95% CI][3]	0.1 [0.0 - 1.4]					0.4 [0.0 - 3.7]	

CI: Confidence Interval; hGh: Human Growth Hormone; IRR: Incidence Rate Ratio; SAE: Serious Adverse Event; SOC: System Organ Class.
MedDRA dictionary Version MedDRA dictionary Version MedDRA v27.0 - Mar 2024.
Percentages are based on total number of patients N.
[1] The denominator for calculating the percentage is the N shown in the table header.
[2] Incidence rate is calculated as 100 x (number of events / number of person-years). The total number of person-years is computed (Date of last known Follow-up visit-Date of baseline visit+1)/365.25.
SOC terms will be sorted alphabetically and then Preferred Term will be sorted in order of frequency within each SOC.
[3] The IRR is calculated based on the IRs of given treatment compared to Other daily hGH treatments. The 95% CIs are calculated using Wald approach.
Source: Table 15.3.3, Appendix 8: Additional documents.

10.6.1. Primary Safety

Overall, 16 (1.1%) patients (6 patients in the Genotropin group, 5 patients each in the Other daily hGH group, and the Ngenla group) had 32 primary AESIs (Table 31). The overall IR (95% CI) for any primary AESI was 3.9 (2.8, 5.5) events per 100 person-years. The IR was highest in the Ngenla group (12.0 (7.7, 18.6) events per 100 person-years), followed by Other daily hGH (3.1 (1.4, 6.9) events per 100 person-years), and Genotropin (1.3 (0.6, 2.9) events per 100 person-years). The incidence rate ratio (IRR) (95% CI) was 0.4 (0.1, 1.3) comparing Genotropin to Other daily hGH and 3.8 (1.5, 9.6) comparing Ngenla to the Other daily hGH group.

Two serious primary AESIs, one acute critical illness event and 1 intracranial hypertension event, were each reported in Other daily hGH patients. The IR (95% CI) was 0.5 (0.1, 3.7) events per 100 person-years for each event type (Table 31).

Two adrenal cortical hypofunction events were reported, one each in the Other daily hGH group and the Ngenla group. The IR (95% CI) was 0.2 (0.1, 1.0) events per 100 person-years overall and the IRR (95% CI) was 1.2 (0.1-18.4) comparing the Ngenla IR to the Other daily hGH IR (Table 31).

Four bone fracture events were reported in 3 Genotropin patients and 1 Other daily hGH patient. The IR (95% CI) was 0.5 (0.2, 1.3) events per 100 person-years overall and the IRR (95%) CI was 1.3 (0.1, 12.2) comparing the Genotropin IR to the Other daily hGH IR (Table 31).

Nine injection site reaction events, as defined by the PT, were reported among 3 Genotropin, 2 Other daily hGH and 4 Ngenla patients. The IR (95% CI) was 2.9 (2.0, 4.4) events per 100 person-years. The IRR (95% CI) was 0.6 (0.1, 3.8) comparing Genotropin to Other daily hGH and 11.0 (2.6, 47.1) comparing Ngenla to Other daily hGH) (Table 31). When considering the High-Level Term of injection site reactions, 26 events were reported

in 11 patients (hematoma injection site=1, injections site burning=3, injection site itching=6, injection site pain=1, injection site reaction=2, injection site redness=8, injection site swelling=1, pain during injection=2, pain injection site=1, and rash injection site=1) (data on file).

Three patients experienced non-serious AESIs of injection site reactions that led to permanent discontinuation: 1 in the Genotropin group (injection site rash) and 2 in the Ngenla group (2 application site pain/erythema in the same patient and one lipodystrophy) (Source Table 16.2.7.1, Appendix 8). Additionally, 1 SAE event of intracranial hypertension leading to permanent discontinuation was reported in a patient in the Other daily hGH group and 1 non-serious AE of eczema leading to permanent discontinuation was reported in a patient in the Genotropin group (Source Table 16.2.7.1, Appendix 8).

Table 31 Summary of Primary AESIs – Full Analysis Set

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Any Primary AESIs							
Number of patients, n (%)[1]	6 (0.8)	1 (3.6)	2 (1.3)	2 (1.1)	5 (1.4)	5 (1.1)	16 (1.1)
Number of events, n	6	1	2	3	6	20	32
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	1.3 (0.6 ; 2.9)	4.9 (0.7 ; 34.5)	2.3 (0.6 ; 9.2)	3.5 (1.1 ; 10.9)	3.1 (1.4 ; 6.9)	12.0 (7.7 ; 18.6)	3.9 (2.8 ; 5.5)
Incidence rate ratio [95% CI][3]	0.4 [0.1 - 1.3]					3.8 [1.5 - 9.6]	
Acute critical illness							
Number of patients, n (%) [1]	0	0	0	1 (0.6)	1 (0.3)	0	1 (0.1)
Number of events, n	0	0	0	1	1	0	1

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	-(-;-)	-(-;-)	-(-;-)	1.2 (0.2 ; 8.4)	0.5 (0.1 ; 3.7)	-(-;-)	0.1 (0.0 ; 0.9)
Incidence rate ratio [95% CI] [3]	NA					NA	
Intracranial hypertension							
Number of patients, n (%) [1]	0	1 (3.6)	0	0	1 (0.3)	0	1 (0.1)
Number of events, n	0	1	0	0	1	0	1
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	-(-;-)	4.9 (0.7 ; 34.5)	-(-;-)	-(-;-)	0.5 (0.1 ; 3.7)	-(-;-)	0.1 (0.0 ; 0.9)
Incidence rate ratio [95% CI] [3]	NA					NA	
Adrenal cortical hypofunction							
Number of patients, n (%) [1]	0	0	0	1 (0.6)	1 (0.3)	1 (0.2)	2 (0.1)
Number of events, n	0	0	0	1	1	1	2
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100	-(-;-)	-(-;-)	-(-;-)	1.2 (0.2 ; 8.4)	0.5 (0.1 ; 3.7)	0.6 (0.1 ; 4.2)	0.2 (0.1 ; 1.0)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
person-years) [95% CI][2]							
Incidence rate ratio [95% CI] [3]	NA					1.2 [0.1 - 18.4]	
Bone fractures							
Number of patients, n (%) [1]	3 (0.4)	0	1 (0.7)	0	1 (0.3)	0	4 (0.3)
Number of events, n	3	0	1	0	1	0	4
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	0.7 (0.2 ; 2.0)	-(-;-)	1.1 (0.2 ; 8.1)	-(-;-)	0.5 (0.1 ; 3.7)	-(-;-)	0.5 (0.2 ; 1.3)
Incidence rate ratio [95% CI] [3]	1.3 [0.1 - 12.2]					NA	
Injection site reactions							
Number of patients, n (%)[1]	3 (0.4)	0	1 (0.7)	1 (0.6)	2 (0.6)	4 (0.9)	9 (0.6)
Number of events, n	3	0	1	1	2	19	24
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Incidence rate (per 100 person-years) [95% CI][2]	0.7 (0.2 ; 2.0)	- (-;-)	1.1 (0.2 ; 8.1)	1.2 (0.2 ; 8.4)	1.0 (0.3 ; 4.1)	11.4 (7.3 ; 17.8)	2.9 (2.0 ; 4.4)
Incidence rate ratio [95% CI][3]	0.6 [0.1 - 3.8]					11.0 [2.6 - 47.1]	

AESI: Adverse Event of Special Interest; CI: Confidence Interval; hGH: Human Growth Hormone; NA: Not Applicable.
MedDRA: Medical Dictionary for Regulatory Activities.
MedDRA dictionary Version MedDRA v27.0 - Mar 2024.
Percentages are based on total number of patients N.
[1] The denominator for calculating the percentage is the N shown in the table header.
[2] Incidence rate is calculated as 100 x (number of events / number of person-years). The total number of person-years is computed (Date of last known Follow-up visit-Date of baseline visit+1)/365.25.
[3] The IRR is calculated based on the IRs of given treatment compared to Other daily hGH treatments. The 95% CIs are calculated using count regression model.
Source: Table 15.3.5, Appendix 8: Additional documents.

10.6.2. Secondary Safety

A summary of all AESIs (primary or secondary) is presented in Table 32 below. Full data with SOCs and PTs are located in Source Table 15.3.4 (Appendix 8).

Overall, 16 (1.1%) patients (6 patients in the Genotropin group, 5 patients each in the Other daily hGH group, and the Ngenla group) had 32 primary or secondary AESIs reported with 816.1 person-years of exposure. The IR (95% CI) was 3.9 (2.8, 5.5) events per 100 person-years (Table 32).

Thirteen patients had 14 events that, upon MedDRA coding, were classified as arthralgia (Appendix 8, Source Table 15.3.2) and are not counted in the secondary AESI event rate due to the data issue described in Section 10.6.

Table 32 Summary of Any Adverse Event of Special Interest (Primary and Secondary) – Full Analysis Set

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Any AESIs							
Number of patients, n (%)[1]	6 (0.8)	1 (3.6)	2 (1.3) (	2 (1.1)	5 (1.4)	5 (1.1)	16 (1.1)

	Genotropin (N=716)	Other daily hGH				Ngenla (N=441)	Overall (N=1516)
		Humatrope (N=28)	Norditropin (N=150)	Omnitrope (N=181)	Total (N=359)		
Number of events, n	6	1	2	3	6	20	32
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	1.3 (0.6 ; 2.9)	4.9 (0.7 ; 34.5)	2.3 (0.6 ; 9.2)	3.5 (1.1 ; 10.9)	3.1 (1.4 ; 6.9)	12.0 (7.7 ; 18.6)	3.9 (2.8 ; 5.5)
Incidence rate ratio [95% CI][3]	0.4 [0.1 - 1.3]					3.8 [1.5 - 9.6]	
Injection site reactions							
Number of patients, n (%)[1]	3 (0.4)	0	1 (0.7) (	1 (0.6)	2 (0.6) (	4 (0.9) (	9 (0.6) (
Number of events, n	3	0	1	1	2	19	24
Person-years of exposure	456.3	20.6	87.2	85.0	192.7	167.0	816.1
Incidence rate (per 100 person-years) [95% CI][2]	0.7 (0.2 ; 2.0)	- (-;-)	1.1 (0.2 ; 8.1)	1.2 (0.2 ; 8.4)	1.0 (0.3 ; 4.1)	11.4 (7.3 ; 17.8)	2.9 (2.0 ; 4.4)
Incidence rate ratio [95% CI][3]	0.6 [0.1 - 3.8]					11.0 [2.6 - 47.1]	

AESI: Adverse Event of Special Interest; CI: Confidence Interval; hGH: Human Growth Hormone; NA: Not Applicable.
MedDRA dictionary Version MedDRA v27.0 - Mar 2024.
Percentages are based on total number of patients N.
[1] The denominator for calculating the percentage is the N shown in the table header.
[2] Incidence rate is calculated as 100 x (number of events / number of person-years). The total number of person-years is computed (Date of last known Follow-up visit-Date of baseline visit+1)/365.25.
[3] The IRR is calculated based on the IRs of given treatment compared to Other daily hGH treatments. The 95% CIs are calculated using count regression model.
Source: Table 15.3.4, Appendix 8: Additional documents.

10.6.3. Other Safety

Five patients on Pfizer study drug reported 9 events related to drug exposure, which included 4 events of injection site reactions (2 patients in the Genotropin and 1 patent in the Ngenla group), 2 events of IGF-1 increase in the Ngenla group and one event each of headache, arthralgia and walking disability in the Ngenla group.
Among other events of interest, headache was reported as a non-serious TEAE in 13 patients (6 patients from the Genotropin group and 7 from the Ngenla group), as described in Section 10.6.

11. DISCUSSION

11.1. Key Results

Between the start of data collection (18 November 2021) and database lock (18 July 2024), 1559 patients were enrolled in the study. A total of 1516 patients had treatment details and safety or effectiveness outcomes recorded, which comprised 716 patients in the Genotropin group, 359 patients in the Other daily hGH group, and 441 patients in the Ngenla group. Males were represented in the cohort more than females (67.5% versus 32.5%), which is consistent with the known treatment patterns of GHD (Grimberg, Stewart et al. 2008).[5] Patients in Europe were represented most often (46.2%), with France (16.5%) and Spain (16.4%) comprising the majority of patients in the Europe region. Patients from the US and Canada represented 26.8% of the population, followed by Japan (15.9%) and RoW (11.1%) (Australia, Israel, Taiwan, and the United Arab Emirates). Patients were aged 11.1 years, on average, at enrollment and were diagnosed with GHD at a mean age of 7.7 years. The majority (74.5%) of patients were reported as having idiopathic GHD as their primary hGH diagnosis; however, 67 (4.5%) patients with SGA/IUGR, 29 (1.9%) patients with Prader-Labhart-Willi / Prader-Willi Syndrome, 23 (1.5%) patients with ISS, and 15 (1.0%) with Turner Syndrome were also in the FAS.

For primary safety endpoints, 32 primary AESI events were reported in 16 patients, including 9 injection site reactions, 4 bone fractures, 2 adrenal cortical hypofunction events, 1 acute critical illness, and 1 intracranial hypertension event. The overall IR (95% CI) for any primary AESI was 3.9 (2.8, 5.5) events per 100 person-years, and the IR (95% CI) was highest in the Ngenla group (12.0 (7.7, 18.6) events per 100 person-years). The overall IRR (95% CI) was 0.4 (0.1, 1.3) comparing Genotropin to Other daily hGH and 3.8 (1.5, 9.6) comparing Ngenla to Other daily hGH). No secondary AESIs were reported at the time of the database lock.

Five (0.3%) patients (1 patient in the Genotropin group, 3 patients in the Other daily hGH group, and 1 patient in the Ngenla group) had 5 treatment-emergent SAEs. The incidence rate (95% CI) was 0.6 (0.3, 1.5) events per 100 person-years. The SAEs included 1 each of appendicitis, gastroenteritis, adrenal insufficiency, idiopathic intracranial hypertension and affective disorder.

Overall, 98 (6.5%) patients reported 195 TEAEs. Most frequently reported TEAEs by PT included arthralgia (n=13, 0.9% patients), headache (n=13, 0.9% patients), and injection site pain (n=7, 0.5% patients), which are known safety concerns associated with daily hGH and Ngenla.

For primary effectiveness endpoints, the mean (SD) height at baseline was 136.5 (21.17) cm and was similar across treatment groups. At Month 12 among 209 patients, the overall mean (SD) HV was 7.3 (1.86) and was similar in the Genotropin and the Ngenla group (7.5 [1.88] and 7.6 [1.84], respectively). At Month 24 among 16 patients, no data were available for the Ngenla group, and the mean (SD) HV was greater in the Genotropin group (7.7 [1.47]) than in the Other daily hGH group (5.9 [1.28]). Data were too sparse within primary diagnosis subgroups to make any inferences. The overall mean (SD) height SDS at baseline was -1.3 (1.20) and was similar in the Genotropin, Other daily hGH group, and the Ngenla group (-1.2 [1.14], -1.2 [1.16], and -1.5 [1.29], respectively). At Month 12 among 208 patients, the overall mean (SD) HVSDS was 1.1 (2.54). The HVSDS in the Genotropin group was 1.3 (2.52), the Other daily hGH group was 0.6 2.45), and the Ngenla group was 1.5 [3.14]. At Month 12 also among 208 patients, the overall mean (SD) change from baseline in height SDS was 1.0 (0.29) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (1.0 [0.28] and 1.0 [0.32], 1.2 [0.31], respectively). At Month 24 only 16 patients had follow-up data for both HVSDS and change from baseline height SDS. The overall mean (SD) HVSDS was 0.6 (2.62). The highest mean (SD) HVSDS was seen in the Genotropin group (2.5 [2.02]) and the least mean (SD) HVSDS was seen in the Other daily hGH group (-0.3 [2.43]). the overall mean (SD) change from baseline in height SDS was 2.0 (0.41) and was similar in the Genotropin and the Other daily hGH group (2.2 [0.26], 1.8 [0.42], respectively). There were no patient details available for the Ngenla group at Month 24. Among all patients, the overall mean (SD) BMI at baseline was 18.1 (3.73) and was similar in the Genotropin group and the Other daily hGH group (18.3 [3.86], 18.2 [3.72], respectively) but slightly lower in the Ngenla group (17.7 [3.50]). The overall mean (SD) baseline BMI SDS was 0.0 (1.19) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (-0.0 [1.17], 0.1 [1.17], 0.0 [1.22], respectively). At Month 12 among 209 patients, the overall mean (SD) change from baseline in annual BMI was 0.7 (0.94) and was similar in the Genotropin group, the Other daily hGH group, and the Ngenla group (0.7 [0.96], 0.7 [0.88], and 0.8 [0.93], respectively). Likewise, the overall mean (SD) change from baseline in annual BMI SDS was 0.3 (0.43) and was similar in the Genotropin group, the Other daily hGH group, and the other Ngenla group (0.3 [0.42], 0.3 [0.43], and 0.4 [0.46], respectively). At Month 24 among 16 patients, the overall mean (SD) change from baseline in annual BMI was 1.7 (1.10) overall, 1.4 (1.00) in the Genotropin group, and 1.8 (1.17) in the Other daily hGH group. At Month 24, the overall mean (SD) change from baseline in annual BMI SDS was 0.8 (0.36) and was similar in the Genotropin group and the Other daily hGH group (0.8 [0.45] and 0.7 [0.33], respectively). There were no patient details available for the Ngenla group at Month 24.

For secondary effectiveness endpoints included in this annual report, bone age data at enrollment using the Tanner-Whitehouse approach were available for 453 of the 1516 patients in the FAS and using the G&P method were available for 986 of the 1516 patients in the FAS. The Tanner-Whitehouse bone age was similar to the chronological age for patients with results (mean bone age of 10.0 years among patients with a mean chronological age of 10.9 years). Follow-up data for bone age was sparse (42 patients at Month 12 using the G&P method). Among 24 patients with both baseline bone age using the G&P method and Month 12 data, the overall mean (SD) bone age change from baseline was 2.0 (1.50) years. Body composition data were also sparse, highlighting that body composition assessments were not routinely completed per standard of care in the real-world.

Treatment experience was captured by the LIQ-GHD; however, follow-up data was limited and change scores from enrollment were sparse. Treatment adherence was captured by the LIQ-GHD missed injections section. Among 167 patients with data at enrollment, in the Genotropin group, the Other daily hGH group, and the Ngenla group, the mean (SD) number of missed injections was 3.2 (5.11), 2.7 (2.78), and 1.1 (0.38) at baseline, respectively. Missed injection data were available for only 7 patients at Month 12. Patients most commonly reported that at baseline the reason why they missed injections was forgetting to take the injection (36.8%). For the life interference total score where higher scores indicate greater life interference, at baseline, respondents in the Ngenla group reported an overall lower mean (SD) total score (11.7 (14.48)) than the Genotropin or Other daily hGH groups (18.9 (20.37) and 17.5 (18.74), respectively). Data were too sparse at Month 12 to make further inferences (n=8).

Secondary HRQoL endpoints as reported on the QoLISSY-Child and QoLISSY-Parent ranged from total scores of approximately 70-80 (of 100, where higher scores indicate higher QoL) and did not differ appreciably across treatment groups. Follow-up data were sparse at Month 12 (n=19 for the Child questionnaire and n=8 for the Parent questionnaire).

11.2. Limitations

The results presented in this final study report are presented in aggregate and do not focus on subgroup analyses by naïve and non-naïve patients, as in prior annual reports. The interpretation of primary effectiveness endpoints such as height SDS and HVSDS rely heavily on how long a patient has been on GH treatment, therefore interpretation of effectiveness endpoints is limited. In prior annual reports, the issue of classifying patients as naïve and non-naïve has been discussed at length. Despite efforts to collect additional data from sites on GH treatment history, misclassification of naïve and non-naïve patients is probable, as evidenced by higher than expected baseline height SDS and IGF-1 in patients classified as naïve. For example, patients classified as naïve and non-naïve were observed as having a mean (SD) baseline height SDS of -1.9 (0.99) and -1.2 (1.20), respectively. In a global cohort of children treated with Genotropin, the mean height SDS at hGH start (i.e., in naïve patients) was -3.0 (1.2) (Maghnie, Ranke et al. 2022).[9] It is important to note that not all patients in the study have GHD. Prader-Willi Syndrome, for example, may be initiated on hGH treatment without a low height SDS, driving the mean height SDS above what would be clinically expected in a cohort of patients with GHD. While this may be a factor, the proportion of patients in the study with primary diagnoses other than GHD does not appear significant enough to substantially drive the baseline height SDS in the naïve group.

This is a real-world study collecting data available as per standard of care. Certain data was not available for the majority of patients (eg, Apgar scores, body composition), limiting the inferences that could be made for these endpoints. Due to early study termination, there was less follow-up time accumulated than expected per the protocol. Inferences on longitudinal outcomes such as HV and HVSDS are limited and should be interpreted with caution in cases of small sample sizes. Despite this, the registry has collected a quorum of data on baseline characteristics in the study population.

11.3. Interpretation

Of the 1516 patients included in the FAS for this final study report, 441 comprise the Ngenla group. A major emphasis of study objectives is to describe and compare safety and

effectiveness outcomes by treatment groups, including Ngenla. Per protocol design, PROGRES was initiated in many markets before Ngenla was approved, resulting in an initial imbalance of Ngenla-treated children at the beginning of enrollment. Despite this early imbalance and the early termination of the study, PROGRES has collected a substantial amount of baseline data on patients initiating Ngenla and generated evidence on patients on GH treatments for diagnoses such as Prader-Willi Syndrome and Turner Syndrome.

The primary safety objective of the study is to estimate IRs of safety events. Few primary AESIs and no secondary AESIs were reported up to the time of database lock, which is consistent with prior evidence of relatively low rates of AEs observed in this study population. Specifically, in a global cohort of children treated with Genotropin, only 14.4% of 83,803 patients had one or more AEs over a mean (SD) duration of follow-up of 3.9 (3.1) years (Maghnie, Ranke et al. 2022).[9] Overall, there were no unanticipated risks observed with the daily hGH therapy, Genotropin, or long-acting GH, Ngenla, relative to the known safety profile of somatropin-containing products.

The primary effectiveness objective of the study is to describe and compare outcomes such as height across treatment groups. Due to early study termination, a primary value of the data collected is description of the patient characteristics at baseline across hGH treatment groups.

11.4. Generalizability

This multi-country, multi-site, prospective real-world study enrolled a diverse cohort of patients from 18 countries. Due to early study termination, the study size at present represents only a percentage of the total number of patients that were planned for enrollment. The limited inclusion and exclusion criteria facilitated enrollment for a broad population of patients on Ngenla, Genotropin and Other daily hGH treatments. Despite the smaller sample size than originally planned, the study population remains globally representative due to enrollment across Europe, Asia, North America, Australia, and the Middle East. Hence, the conclusions drawn from this population may be generalizable to GHD patients and patients with growth disorders broadly on the treatments of interest.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Despite early termination of the PROGRES registry, data collected contribute to the known safety of Genotropin, Other daily hGH treatment, and Ngenla, a weekly hGH treatment. Effectiveness endpoints related to height gain were similar across treatment groups at Month 12. Sparse follow-up data for all treatment groups limits the ability to draw conclusions on effectiveness endpoints at later time points related to height gain and adult height.

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15. LIST OF SOURCE TABLES AND FIGURES

Tables

Listings

Table 16.2.7.4 Listing of Deaths
Table 16.2.8 Laboratory Results

Participant Number:	26027051
Country:	United States
Participant Details:	15 years old, Unspecified race, Male
Treatment Group:	Genotropin (Somatropin 0.23 mg/kg/week subcutaneously)
Treatment Start Date:	19 Apr 2023 (Study Day 1)
Treatment Stop Date:	30 Apr 2024 (Study Day 378)
Case Number:	PV202300161820

Narrative Reason: Serious Adverse Event	
MedDRA Preferred Term (Investigator Term)	**Event Category**
Affective disorder (Exacerbation of pre-existing mood-disorder)	Serious Adverse Event

The participant 26027051 was a 15-year-old male of an unspecified race with idiopathic diagnosis of growth hormone deficiency on 10 May 2021 of 55.7 kg weight from United States. The participant's other present medical history included attention deficit hyperactivity disorder and aggression.

The participant was enrolled in a multi-country, non-interventional, prospective cohort study with human growth hormone (hGH) treatments under routine clinical care. The participant received hGH treatment (Genotropin) within the study from 19 Apr 2023 (Study Day 1) to 30 Apr 2024 (Study Day 378).

On 13 Sep 2023 (Study Day 148), the participant experienced a serious adverse event (SAE) of affective disorder, which was moderate in severity. On the same day the participant was admitted to a mental health facility due to an exacerbation of pre-existing mood disorder.

The participant was treated with aripiprazole since an unspecified date in Sep 2023 for the event of affective disorder.

On 26 Sep 2023 (Study Day 161), the dose of somatropin was reduced to 0.22 mg/kg/week due to decreased targeted IGF-1 response.

The study drug dose was not changed due to the event of affective disorder.

The outcome of the event of affective disorder was reported as resolved on 18 Sep 2023 (Study Day 153) and the participant was discharged from the hospital on the same day.

Date	Parameter	Result	Reference range

Not reported	HbA1c	6.1%	Not reported

No other concurrent adverse events were reported. The participant received concomitant medications of methylphenidate hydrochloride, cyproheptadine, and sertraline for an unspecified medical history; metformin for glycosylated haemoglobin increased; and vitamin A NOS, and vitamin D NOS for other unspecified indication.

In the opinion of the Investigator, there was not a reasonable possibility that the event of affective disorder was related to the study drug. Based on the information provided, as per Sponsor there was not a reasonable possibility that the event of affective disorder be related to study drug. Alternatively, Sponsor suggests that the event of affective disorder was more likely related to the underlying disease of 'attention deficit hyperactivity disorder (ADHD)' and 'under-socialized conduct disorder of aggressive type' in such adolescent patients.

The participant was discontinued from the study on 30 Apr 2024 (Study Day 378) due to study was terminated by the Sponsor.

This narrative reflects information available to the Sponsor in the clinical database (as of the cutoff date 30 Apr 2024) and safety database (as of the cutoff date 03 Sep 2024).

Participant Number:	26016006
Country:	United States
Participant Details:	11 year and 6 months old, White, Male
Treatment Group:	Humatrope (Somatropin 12 mg/kg/week subcutaneously)
Treatment Start Date:	04 Jan 2024 (Study Day 1)
Treatment Stop Date:	10 Apr 2024 (Study Day 98)
Case Number:	PV202400050944

Narrative Reason: Serious adverse event	
MedDRA Preferred Term (Investigator Term)	**Event Category**
Idiopathic intracranial hypertension (Pseudotumor cerebri)	Serious adverse event

The participant 26016006 was a 11 year and 6 months old white male with diagnosis of growth hormone deficiency (panhypopituitarism on 03 Apr 2025 and hypothyroidism on 21 Jan 2016) of 34.4 kg weight from United States. The participant's other present medical history included adrenal insufficiency, attention deficit, hyperactivity disorder, sleep disorder, brain tumor, central nervous system (CNS) tumor, hypothyroidism, and scoliosis.

The participant was enrolled in a multi-country, non-interventional, prospective cohort study with human growth hormone (hGH) treatments under routine clinical care. The participant received hGH treatment (Humatope) within the study from 04 Apr 2024 (Study Day 92) to 10 Apr 2024 (Study Day 98).

On 12 Apr 2024 (Study Day 100), the participant experienced a serious adverse event (SAE) of idiopathic intracranial hypertension (pseudotumor cerebri), which was moderate in severity. On an unspecified date, the participant was hospitalized for the event of idiopathic intracranial hypertension.

On 13 Apr 2024 (Study Day 101), the participant underwent lumbar puncture which resulted in 35 (further information not reported) and magnetic resonance imaging of head revealed subtle bulging of the optic nerve heads suggestive of papilledema.

No treatment was reported for this event.

The study drug was permanently discontinued due to SAE of idiopathic intracranial hypertension with the last dose administered on 10 Apr 2024 (Study Day 98).

The outcome of the event of idiopathic intracranial hypertension was reported as resolved on 14 Apr 2024 (Study Day 102). On an unspecified date, the participant was discharged from the hospital.

No other concurrent adverse events were reported. The participant received concomitant medications of dexamfetamine sulfate for attention deficit hyperactivity disorder, clonidine for both attention deficit hyperactivity disorder and sleep disorder, hydrocortisone for adrenal insufficiency and trazodone hydrochloride for sleep disorder.

In the opinion of the Investigator, there was a reasonable possibility that the event of idiopathic intracranial hypertension was related to the study drug. Based on the information provided, the Sponsor agreed with the investigator that there was a reasonable possibility that the event was related to the study drug.

The participant was discontinued from the study on 14 APR 2024 (Study Day 102) due to the event of idiopathic intracranial hypertension.

This narrative reflects information available to the Sponsor in the clinical database (as of the cutoff date 30 Apr 2024) and safety database (as of the cutoff date 03 Sep 2024).

Participant Number:	23002001
Country:	Sweden
Participant Details:	6 years and 5 months old, White, Male
Treatment Group:	Ngenla (Somatrogon 0.58 mg/kg/week subcutaneously)
Treatment Start Date:	02 Sep 2023 (Study Day 1)
Treatment Stop Date:	30 Apr 2024 (Study Day 242)
Case Number:	PV202300203962

Narrative Reason: Serious Adverse Event	
MedDRA Preferred Term (Investigator Term)	**Event Category**
Gastroenteritis (Gastroenteritis)	Serious Adverse Event

The participant 23002001 was a 6-year and 5-month-old white male with diagnosis of empty sella syndrome/pituitary aplasia on 19 Apr 2017 of 25.8 kg weight from Sweden. The participant's other present medical history included hypopituitarism, hypothyroidism, mental impairment, and autism spectrum disorder.

The participant was enrolled in a multi-country, non-interventional, prospective cohort study with human growth hormone (hGH) treatments under routine clinical care. The participant received hGH treatment (somatrogon) within the study from 12 Sep 2023 (Study Day 11) to 30 Apr 2024 (Study Day 242).

On 15 Nov 2023 (Study Day 75), the participant experienced a serious adverse event (SAE) of gastroenteritis, which was moderate in severity. The participant was hospitalized on the same day. The participant also experienced vomiting and received intramuscular hydrocortisone sodium succinate 50 mg, but vomiting did not stop. The participant remained hospitalized for further intravenous treatment. The patient started to feel better but stayed overnight in the hospital and participant started to drink and eat by himself.

No treatment was reported for this event.

The study drug dose was not changed due to the event of gastroenteritis.

The outcome of the event of gastroenteritis was reported as recovered/resolved on 16 Nov 2023 (Study Day 76) and the participant was discharged from the hospital on this same day.

No other concurrent adverse events were reported. The participant received concomitant medications of hydrocortisone (prophylaxis) and levothyroxine (substitutive therapy, history of hypothyroidism).

In the opinion of the Investigator, there was not a reasonable possibility that the event of gastroenteritis was related to the study drug. Based on the information provided, the Sponsor considered that the event of gastroenteritis was not related to the study drug, considering the infectious etiology of the event.

The participant was discontinued from the study on 30 Apr 2024 (Study Day 242) due to study was termination by the Sponsor.

This narrative reflects information available to the Sponsor in the clinical database (as of the cutoff date 30 Apr 2024) and safety database (as of the cutoff date 03 Sep 2024).

Participant Number:	16004012
Country	France
Participant Details:	5-year and 8-month-old, Unspecified race, Female
Treatment Group:	Omnitrope (Somatropin 0.4 mg/day subcutaneously)
Treatment Start Date:	18 Jan 2023 (Study Day 1)
Treatment Stop Date	30 Apr 2024 (Study Day 469)
Case Number:	PV202400064817

Narrative Reason: Serious adverse event	
MedDRA Preferred Term (Investigator Term)	**Event Category**
Adrenal insufficiency (Acute adrenal insufficiency)	Serious adverse event

The participant 16004012 was a 5-year and 8-month-old female of unspecified race with diagnosis of idiopathic growth hormone deficiency on 23 May 2018 of 21.4 kg weight from France. The participant's other present medical history included secondary adrenocortical insufficiency, septo-optic dysplasia, strabismus since, asthma, abnormal fundus of eye, hypoglycemia, hypothyroidism, all since unspecified date.

The participant was enrolled in a multi-country, non-interventional, prospective cohort study with human growth hormone (hGH) treatments under routine clinical care. The participant received hGH treatment (Omnitrope) within the study from 14 Mar 2024 (Study Day 422) to 30 Apr 2024 (Study Day 469).

On 30 Apr 2024 (Study Day 469), at morning, the participant presented to the emergency department with the abdominal pain and vomiting (3 episodes), which made it impossible to take her regular oral Hydrocortisone. Additionally reported symptoms of asthenia and sleepiness.

The participant was pale and was diagnosed with a serious adverse event (SAE) of event adrenal insufficiency, which was moderate in severity, and was hospitalized.

The participant was treated with glucose and hydrocortisone both on 30 Apr 2024 (Study Day 469) for the event of adrenal insufficiency.

Initial blood glucose on 30 Apr 2024 revealed hypoglycemia (0.46 g/l), however, repeat tests showed improvement after clinical course of treatment with glucose levels within normal values 0.62 g/l and 0.84 g/l, 30 Apr 2024 and 01 May 2024, respectively.

The study drug dose was not changed due to the event of adrenal insufficiency.

The outcome of the event of adrenal insufficiency was reported as recovered/resolved on 01 May 2024 (Study Day 470). The participant's discharged details were not reported.

Date	Parameter	Result	Reference range
14 Mar 2024 (Study Day 422)	Free thyroxine	17 pmol/L	Not reported
14 Mar 2024 (Study Day 422)	Insulin-like growth factor-1	29 nmol/L	Not reported
14 Mar 2024 (Study Day 422)	Insulin-like growth factor binding protein 3	2.7 mg/L	Not reported
30 Apr 2024 (Study Day 469)	Blood glucose	0.46 g/L	0.6 to 1 g/L
30 Apr 2024 (Study Day 469) (repeat test)	Blood glucose	0.62 g/L	0.6 to 1 g/L
01 May 2024 (Study Day 470)	Blood glucose	0.84 g/L	0.6 to 1 g/L

No other concurrent adverse events were reported. The participant received concomitant medications of fluticasone propionate for asthma.

In the opinion of the Investigator, there was not a reasonable possibility that the event of adrenal insufficiency was related to the study drug. The suspect product is a non-Pfizer drug as per brand name mentioned; no causality assessment has been provided by the Sponsor.

The participant was discontinued from the study on 30 Apr 2024 (Study Day 469), as the study was terminated by the Sponsor.

This narrative reflects information available to the Sponsor in the clinical database (as of the cutoff date 30 Apr 2024) and safety database (as of the cutoff date03 Sep 2024).

Participant Number:	13002006
Country:	Canada
Participant Details:	7-year and 3-month-old, Unspecified race, Male
Treatment Group:	Omnitrope (Somatropin 0.5 mg, 6 times weekly subcutaneously)
Treatment Start Date:	29 Sep 2020 (Study Day 1)
Treatment Stop Date:	30 Apr 2024 (Study Day 1310)
Case Number:	PV202300157278

Narrative Reason: Serious Adverse Event	
MedDRA Preferred Term (Investigator Term)	**Event Category**
Appendicitis (Acute appendicitis)	Serious Adverse Event

The participant 13002006 was a 7-year and 3-month-old male of an unspecified race with diagnosis of small anterior pituitary gland on 15 Jun 2019 of 16.5 kg weight from Canada. The participant's other past medical history included head injury, haematoma, nasal congestion, pain in extremity, tachycardia, arthralgia, and adenoidal hypertrophy.

The participant was enrolled in a multi-country, non-interventional, prospective cohort study with human growth hormone (hGH) treatments under routine clinical care. The participant received hGH treatment (Omnitrope) within the study from 25 Oct 2022 (Study Day 757) to 30 Apr 2024 (Study Day 1310).

On 25 Oct 2022 (Study Day 757), the participant started receiving 0.6 mg subcutaneously 6 times weekly.

On 02 May 2023 (Study Day 946), the participant experienced a non-serious adverse event of abdominal pain of mild severity. The participant reported to have complaints of abdominal pain about once per week. Non-serious headaches (ongoing) occurring once-weekly were also reported as starting on 02 May 2023.

On 14 Sep 2023 (Study Day 1081), the participant presented to hospital with complaint of 1 to 2 days of abdominal pain, nausea and nonbilious (NB) emesis (1 episode). Pain started as crampy (verbatim) and caused generalized periumbilical discomfort. Over the past 48 hours the pain had migrated and was localized (as reported) to the right lower quadrant. Participant was afebrile and otherwise well. Participant's appetite had been slightly decreased from baseline. Participant reported feeling of more tired and that running increased the abdominal pain. No diarrhea (1 to 2 formed stools per day) was reported. Ultrasound of abdomen and pelvis on the same day reported uncomplicated acute appendicitis, with no appendicolith identified.

On 15 Sep 2023 (Study Day 1082), the participant had a single episode of nonbilious emesis and was started with anesthesia and taken to the operating room for a planned laparoscopic appendectomy. The participant's appendix was found to be non-perforated and there were no complications. The operative diagnosis was acute edematous appendicitis. Post-operation, the participant was discharged the same day (15 Sep 2023). At the time of discharge, participant's pain was controlled, tolerating clear fluids, voiding well, and mobilizing. Participant's abdomen was soft, non-distended and appropriately tender. The dressing was clean, dry and intact. Participant could follow-up with their General Practitioner (GP) as needed and did not require general surgery follow-up.

The participant was treated with ceftriaxone, glucose/sodium chloride, and metronidazole/sodium chloride, all from 14 Sep 2023 (Study Day 1081) to 15 Sep 2023 (Study Day 1082) and paracetamol, ondansetron, bupivacaine/epinephrine, cefoxitin, dexamethasone phosphate, dimenhydrinate, fentanyl, ketorolac, calcium chloride/potassium chloride/sodium lactate, lidocaine, morphine sulfate, propofol, and suxamethonium, all on 15 Sep 2023 (Study Day 1082) for the event of appendicitis.

The study drug dose was not changed due to the event of appendicitis.

The outcome of the event of appendicitis was reported as resolved on 15 Sep 2023 (Study Day 1082) and post-operatively, the participant was able to be discharged the same day from the hospital.

On 07 Nov 2023 (Study Day 1135), the event of abdominal pain resolved.

Date	Parameter	Result	Reference range
14 Sep 2023 (Study Day 1081)	White blood cell count	18.1×10^9/L	13.1 to 5.1×10^9/L

The participant's concurrent adverse events included headache and injection site reaction. The participant received concomitant medications of ibuprofen and paracetamol for headache.

In the opinion of the Investigator, there was not a reasonable possibility that the event of appendicitis was related to the study drug. The Investigator considered appendicitis not related to concomitant medications. The suspect product is a non-Pfizer drug as per brand name mentioned; no causality assessment has been provided by the Sponsor.

The subject was discontinued from the study on 30 Apr 2024 (Study Day 1310) due to study was terminated by the Sponsor.

This narrative reflects information available to the Sponsor in the safety database (as of the cutoff date 03 Sep 2024) and clinical database (as of the cutoff date 30 Apr 2024).

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