NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Pfizer Registry of Outcomes in Growth Hormone RESearch (PROGRES) 2.0: A multi-country non-interventional, observational, retrospective cohort study among participants treated with human growth hormone (hGH) treatments Genotropin (somatropin) and Ngenla (somatrogon) under routine clinical care.
Protocol number	C0311028
Protocol version identifier	2.0
Date	30 January 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000705
Active substance	H01AC08 (Somatrogon), H01AC01 (Somatropin)
Medicinal product	Genotropin, Ngenla
Product reference	Genotropin: Miniquick 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0 mg powder and solvent for solution for injection PL 00057/0989, 0990-0998 Powder and solvent for solution for injection 5.3mg PL 00057/0987 Powder and solvent for solution for injection 12mg PL 00057/0988 Ngenla: EU/1/21/1617/001 for 24 mg/1.2 mL solution for injection in pre-filled pen EU/1/21/1617/002 for 60 mg/1.2 mL solution for injection in pre-filled pen
Procedure number	Genotropin: DK/H/0012/001,004,005,013-023 Ngenla: EMEA/H/C/005633
Marketing Authorization Holder(s)	Genotropin: Pfizer Limited Ramsgate Road, Sandwich, Kent CT139ND United Kingdom Ngenla: Pfizer Europe MA EEIG Boulevard de la Plaine 17, 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	The primary research question for this study is: What is the long-term effectiveness and safety of Ngenla (somatrogon), a long-acting hGH, and Genotropin (Somatropin) when used in routine clinical practice at the discretion of the treating physician?

	Primary Objective: • To describe and compare effectiveness of Ngenla (Somatrogon) and Genotropin (Somatropin) during the course of routine clinical care by measuring height, bone age, body mass index (BMI) and insulin-like-growth factor-I (IGF-I) levels Secondary Objectives: • To estimate incidence rates (IRs) of safety events of interest and medication errors among participants on Ngenla and Genotropin by conducting a descriptive analysis. • To evaluate treatment adherence and compliance of Ngenla and Genotropin.
Country(ies) of study	Armenia, Belgium, Brazil, Bulgaria, China, Czech Republic, France, Georgia, Germany, Hong Kong, Italy, Malaysia, Poland, Portugal, Saudi Arabia, Slovenia, Sri Lanka, United Kingdom, United States Additional countries will be included as the GloBE-Reg registry expands.
Author	[redacted]

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Genotropin: Pfizer Limited Ramsgate Road, Sandwich, Kent CT139ND United Kingdom Refer to Annex I document #4 for additional Genotropin MAH. Ngenla: Pfizer Europe MA EEIG Boulevard de la Plaine 17, 1050 Bruxelles Belgium Refer to Annex I document #5 for additional Ngenla MAH.
MAH contact person	[redacted]

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMAO	Chief Medical Affairs Office
CNS	Central Nervous System
CRF	Case report form
CSV	Comma-Separated Values
DDAVP	1-deamino-8-D-arginine vasopressin
DP	Data Protection
DPIA	Data Protection Impact Assessment
EC	Ethics Committee
eCRF	Electronic case report form
EHR	Electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ENT	Ear, Nose and Throat
EU	European Union
FDA	Food and Drug Administration

FOI	Freedom of Information
GDPR	General Data Protection Regulation
GH	Growth hormone
GHD	Growth hormone deficiency
GI	Gastrointestinal
GloBE-Reg	Global Registry for Novel Therapies in Rare Bone and Endocrine Conditions
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HbA1c	Hemoglobin A1C
hGH	Human growth hormone
HMA-EMA catalogue	Heads of Medicines Agencies for European Medicines Agency catalogue
HR	Hazard Ratio
HV	Height velocity
HVSDS	Height velocity standard deviation score
I&I	Inflammation & Immunology
IAR	Information Asset Register
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
ICO	Information Commissioner's Office (UK)
ID	Identification
IGF-I	Insulin-like growth factor-1
IPTW	Inverse Probability of Treatment Weighting
IR	Incidence rate
IRB	Institutional Review Board

IRR	Incidence Rate Ratio
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISS	Idiopathic Short Stature
IT	Information Technology
KIGS	Kabi/Pfizer International Growth Database
MAH	Marketing Authorization Holder
MAR	Missing At Random
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MMRM	Mixed Model for Repeated Measures
MPH	Master of Public Health
MRI	Magnetic Resonance Imaging
NIS	Non-interventional study
ORC	Office for Rare Conditions
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PROGRES	Pfizer Registry of Outcomes in Growth Hormone RESearch
PWS	Prader-Willi Syndrome
QA	Quality Assurance
r-hGH	Recombinant-human growth hormone
RoW	Rest of the World
RWD	Real World Data

SAE	Serious adverse events
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDS	Standard deviation score
SGA	Small for Gestational Age
SHOX	Short Stature Homeobox
STAT5b	Signal Transducer and Activator of Transcription 5b
T2DM	Type 2 Diabetes Mellitus
T4	Thyroxine
TS	Turner Syndrome
TSH	Thyroid-Stimulating Hormone
UofG	University of Glasgow
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

3. ABSTRACT

Title

Pfizer Registry of Outcomes in Growth Hormone RESearch (PROGRES) 2.0: A multi-country non-interventional, observational, retrospective cohort study among participants treated with human growth hormone (hGH) treatments Genotropin (somatropin) and Ngenla (somatrogon) under routine clinical care.

Protocol version

2.0, 30 January 2026

Main author

[redacted]

Rationale and background

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates production and release of insulin-like growth factor-I (IGF-I). Growth hormone (GH) and IGF-I 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. Growth hormone deficiency (GHD) results in inadequate levels of GH and IGF-I, which subsequently results in abnormal linear growth in children. Children with GHD have been treated with daily administration of recombinant hGH replacement therapy for many years which has been proven to be safe and effective.

Recombinant hGH has also been approved in many countries around the world for other conditions associated with growth failure and/or abnormal body composition. Children with GHD, Turner Syndrome (TS), Small for Gestational Age (SGA) and Idiopathic Short Stature (ISS) have been treated with daily administration of recombinant hGH replacement therapy for many years. Children with Prader-Willi syndrome (PWS) have also been treated with hGH for both the associated growth failure and abnormal body composition.

The burden of daily administration may cause sub-optimal adherence and limit the therapeutic utility of existing formulations of recombinant hGH. Ngenla (somatrogon) is a long-acting, once-weekly subcutaneously administered form of hGH, currently approved in many countries around the world for use as a long-term treatment in children with growth failure due to an inadequate secretion of endogenous GH.

PROGRES 2.0 is a multi-country, non-interventional, observational cohort study with the objective to assess the long-term effectiveness and safety of both Genotropin (somatropin) and Ngenla (somatrogon), at the discretion of the treating physician in routine clinical practice. This study will obtain real world data as a sub-study of the Global Registry for Novel Therapies in Rare Bone and Endocrine Conditions (GloBE-Reg). GloBE-Reg is an international registry project that obtains data on effectiveness and long-term safety through the collection of real-world data on all available forms of growth hormone and supports sub-studies focusing on various aspects of interest to treating

physicians related to these growth hormone preparations. PROGRES 2.0 is a retrospective, non-interventional study (NIS) and is conducted voluntarily by Pfizer.

Research question and objectives

Research question: What is the long-term effectiveness and safety of Ngenla (somatrogon), a long-acting hGH, and Genotropin (somatropin) when used in routine clinical practice at the discretion of the treating physician?

Primary Objectives:

- To describe and compare effectiveness of Ngenla (somatrogon) and Genotropin (somatropin) during the course of routine clinical care by measuring height, bone age, body mass index (BMI) and insulin-like-growth factor-I (IGF-I) levels

Secondary Objectives:

- To estimate incidence rates (IRs) of safety events of interest and medication errors among participants on Ngenla (somatrogon) and Genotropin (somatropin) by conducting a descriptive analysis.
- To evaluate treatment adherence and compliance of Ngenla (somatrogon) and Genotropin (somatropin).

Study design

PROGRES 2.0 is a retrospective, multi-country, non-interventional, observational cohort study conducted voluntarily by Pfizer to assess the long-term effectiveness and safety of both a daily hGH Genotropin (somatropin) and a long-acting hGH Ngenla (somatrogon), at the discretion of the treating physician according to routine clinical care in a real-world setting. This study will gather the data as a sub-study of the Global Registry for Novel Therapies in Rare Bone and Endocrine Conditions (GloBE-Reg). Patient treatment with a particular therapy will be determined at the discretion of the treating physician according to routine clinical care.

The study is designed for strong generalizability and external validity. Its large sample size will allow the evaluation of key endpoints across various subgroups, while longitudinal data will assess the effectiveness and safety of Ngenla (somatrogon) and Genotropin (somatropin). Participants will be stratified by age, sex, puberty status, follow-up time, medical comorbidities, initial disease/treatment indications, peak GH levels, diagnosis, and region (Europe, Japan, North America, RoW/country). All assessments are part of normal clinical practice or standard guidelines in the countries where this non-interventional study is conducted.

Population

The source population for this study will be all patients contributing data to the GloBE-Reg registry and who are treated with either long acting Ngenla (somatrogon) or daily hGH Genotropin (somatropin) at the discretion of the prescribing physician. Participants can be located anywhere in the world. Participants will be followed for up to 10 years until the end of the study or one of the following occurs: withdrawal of consent, discontinuation of either Ngenla (somatrogon) or

Genotropin (somatropin), discontinuation from the GloBE-Reg registry, lost to follow up or death. The registry is growing and additional centers around the world are expected to be included over the course of the study period.

Variables

Exposure: Treatment with Ngnela (somatrogon) or Genotropin (somatropin) during the study period
Outcomes: The primary outcomes of interest are height, IGF-I, BMI, and bone age. The secondary outcomes of interest are injection site reactions, immunogenicity and adherence.
Key Co-variates: will include data resulting from routine clinical care on variables pertaining to participant demographics, clinical characteristics, birth history, medical history, diagnosis of growth hormone deficiency, therapy including prior and current GH treatment and concomitant medications, effectiveness outcomes, clinician reported outcomes and adverse events.

Data sources

The study will obtain the existing data collected in the GloBE-Reg database. GloBE-Reg is an international, non-interventional registry of bone and endocrine agents, conducted by the project team based at the Office for Rare Conditions at the University of Glasgow, Glasgow, Scotland, United Kingdom. GloBE-Reg, through its expert working group on Childhood GHD, developed a minimium data set for monitoring effectiveness and safety of rhGH for both daily and long-acting preparations in childhood GHD. The registry collects both efficacy and safety data through the routine collection of real-world data and allows for sub-studies that can be of interest to any of its stakeholders. To date, GloBE-Reg has collected data on over 3500 participants from across 32 centres from 20 countries.

Study size

The study is descriptive in nature without *a priori* hypothesis testing, therefore, a formal sample size estimate is not required. All eligible participants treated will be included. It is expected that at least 2000 Genotropin (somatropin) treated and 700 Ngenla (somatrogon) treated participants will be included in final analysis. The study will be conducted for a total of 10 years.

As of June 30, 2025, the GloBE-Reg registry includes data on 365 participants on treatment with Genotropin (Somatropin) and 157 participants on treatment with Ngenla (somatrogon). Since this is an expanding registry, participant numbers are expected to grow over the study period for both treatment groups.

Data analysis

Data from participants in the GloBE-Reg registry on treatment with Ngenla (somatrogon) or Genotropin (somatropin) will be obtained and analyzed. The data will be converted to SAS format for analysis and reporting and will be processed by Pfizer to create analytical variables and datasets for all analysis specified in the study protocol. All study data will exist as structured data by the start of the study. Data obtained from GloBE-Reg will not undergo any additional cleaning or error checks, and there will be no imputation of missing data, all data received from GloBE-Reg will be analyzed.

The study is descriptive in nature without *a priori* hypothesis testing. The primary analysis is to compare effectiveness of Ngenla (Somatrogon) and Genotropin (Somatropin) during the course of routine clinical care by measuring height, bone age, body mass index (BMI) and insulin-like-growth factor-I (IGF-I) levels. The primary effectiveness outcomes for height (Annual HV, HVSDS, change in height SDS) will also be presented by subgroups.

For secondary outcomes, safety events of interest, medication errors and efficacy measurements, descriptive statistics, counts and proportions, crude incidence rates (*i.e.*, number of events per person years) with associated two-sided 95% confidence intervals will be calculated. Incidence rate is calculated as the number of individual events observed during the time at risk (exposure time), divided by the total number of patient-years at risk for the event, multiplied by 100.

Overview of Effectiveness Analysis

Outcome	Primary/Secondary	Statistical Method 1	Statistical Method 2	Statistical Method 3
Annual HV	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Height standard deviation score (SDS) and change in height SDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
HVSDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in annual BMI	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in annual BMI SDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in Bone age	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats[1]
Change in IGF	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in IGF-I SDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats

[1]*Continuous variables will be summarized using descriptive statistics which will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations. Descriptive statistics for categorical/qualitative variables will be presented with number of patients (count) and percentage and this will be presented in the format 'n (%)'.*

Overview of Safety Analysis

Outcome	Primary/Secondary	Statistical Method [1]	Statistical Method 2
SAEs	Secondary	Descriptive stats[1]	IR, IRR, HR
Non-SAEs	Secondary	Descriptive stats	
Medication Errors	Secondary	Descriptive stats	IR, IRR, HR
Laboratory results	Secondary	Descriptive stats	

[1]*Continuous variables will be summarized using descriptive statistics which will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations. Descriptive statistics for categorical/qualitative variables will be presented with number of patients (count) and percentage and this will be presented in the format 'n (%)'.*

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Milestones

Milestone	Planned Date
Start of data collection	30 Sep 2025
End of data collection	31 Aug 2035
Registration in the HMA-EMA Catalogues of RWD studies	26 Sep 2025
Final study report	28 Feb 2036

4. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	30 January 2026	Substantial	Title, abstract, section 8.9, annex 2	Corrected typo by replacing “prospective” with “retrospective”.	Ensure alignment with study design.

5. MILESTONES

Milestone	Planned Date
Start of data collection	30 Sep 2025
End of data collection	31 Aug 2035
Registration in the HMA-EMA Catalogues of RWD studies	26 Sep 2025
Final study report	28 Feb 2036

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-I (IGF-I). Growth hormone (GH) and IGF-I 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-I (1, 2). Growth hormone deficiency (GHD) results in inadequate circulating IGF-I level and is manifested as abnormal growth (linear growth) in children (3, 4). 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. 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 (5).

Data on the incidence and prevalence of GHD are limited. A population-based (nationwide) study in Denmark reported average incidence rate (IR) of 2.58 males, and 1.7 females per 100,000 for childhood onset of GHD (6). 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 participants, congenital in 20%, acquired in 7% and 4% of the participants had a defined syndrome accompanying GHD; there was male predominance in all the categories (7). In the US study, the prevalence of GHD in the 1990's was at least 1:3480, with male predominance (8). The incidence has remained fairly constant over the last 2 decades. Most morbidity in children with GHD relates to short stature and abnormal metabolism. The inability to reach normal height can lead to early onset of severe psychosocial problems, along 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 an increased risk of cardiovascular morbidity and mortality (3).

Genotropin, which contains the active ingredient somatropin, is a potent hormone of importance for the metabolism of lipids, carbohydrates, and proteins and is a recombinant-human growth hormone (r-hGH) replacement therapy that has been used for decades in thousands of participants (primarily children) and has proved to be safe and effective (9, 10). Genotropin was compared with placebo in 6 randomized clinical trials totaling 172 adult GHD participants. At 6 months, beneficial changes in body composition were observed in participants receiving Genotropin when compared to placebo. In children with inadequate endogenous GH, somatropin stimulates linear growth and increases growth rate which enables short children 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 such as Prader-Willi Syndrome, Noonan syndrome, Turner syndrome, idiopathic short stature, and short stature homeobox containing gene (Shox) deficiency (11).

Treatment response is most often assessed by measurement of height and growth velocity and hGH treatment is usually continued until adult 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 (e.g., transient edema, injection site discomfort and arthralgia) may cause a reduction in compliance (12) and limit the therapeutic utility of existing formulations.

Ngenla (somatrogon) is a long-acting once-weekly, endogenous GH and daily somatropin, Ngenla binding leads to activation of the STAT5b signaling pathway and increases the serum concentration of IGF-I. IGF-I was found to increase in a dose-dependent manner during treatment with Ngenla partially mediating the clinical effect. As a result, GH and IGF-I stimulate metabolic changes, linear growth, and enhance growth velocity in pediatric participants with GHD.

The sub-optimal adherence with daily hGH is well established, as is the burden of daily injections for both participants and caregivers. Long-acting hGH may obviate the need for the majority of 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 daily injections of hGH. In the pivotal global Phase III clinical trial, the primary objective of non-inferiority (clinical comparability) 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 participants.

The purpose of the Pfizer Registry of Outcomes in Growth hormone RESearch (PROGRES) 2.0 study will be to address the identified need for long-term effectiveness and safety data on the use of Ngenla (somatrogon) and Genotropin to reflect outcomes that occur in real-world clinical practice.

This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

Research question: What is the long-term effectiveness and safety of Ngenla (somatrogon), a long-acting hGH, and Genotropin (somatropin) when used in routine clinical practice at the discretion of the treating physician?

Primary Objectives:

- To describe and compare effectiveness of Ngenla (somatrogon) and Genotropin (somatropin) during the course of routine clinical care by measuring height, bone age, body mass index (BMI) and insulin-like growth factor-I (IGF-I) levels.

Secondary Objectives:

- To estimate incidence rates (IRs) of safety events of interest and medication errors among participants on Ngenla (somatrogon) and Genotropin (somatropin) by conducting a descriptive analysis.
- To evaluate treatment adherence and compliance of Ngenla (somatrogon) and Genotropin (somatropin).

8. RESEARCH METHODS

8.1. Study Design

This is a multi-country, non-interventional, observational cohort study to assess the long-term effectiveness and safety of both a daily hGH Genotropin (somatropin) and a long-acting hGH Ngenla (somatrogon), at the discretion of the treating physician according to routine clinical care in a real-world setting.

The study will obtain data collected by the GloBE-Reg registry via a minimum data set, which was developed by an expert working group for monitoring the effectiveness and safety of both daily and long-acting GH in childhood GHD.

This study will have a broad geographic reach, including and participating centers are typically underrepresented in global studies. This will enable the evaluation of key primary and secondary endpoints, including the primary outcomes of interest: height, IGF-I, BMI, and bone age and secondary outcomes of interest: injection site reactions, immunogenicity and adherence. The longitudinal nature of the data will allow the evaluation of effectiveness and safety of Ngenla (somatrogon) and Genotropin (somatropin) and the endpoints will be evaluated within numerous prespecified strata or subgroups.

To evaluate the effectiveness and safety of Ngenla and Genotropin within the study population, participants will be stratified by select *a priori* subgroups, including but not limited to: age, sex, puberty status, follow-up time, medical comorbidities, initial disease/treatment indications, peak GH levels, diagnosis for GH disorder, and study region (Europe, Japan, North America, and Rest of the World [RoW]/country).

Strengths of this study design include the strong generalizability and external validity due to the large sample size from an international cohort of participants and the real-world clinical data that will be obtained.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the participant's population and healthcare provider specialty in the countries where this non-interventional study is being conducted.

8.2. Setting

The source population for this study will be the subset of patients contributing data to the GloBE-Reg registry who are treated with either long acting Ngenla (somatrogon) or daily hGH Genotropin (somatropin) at the discretion of the prescribing physician. This population is thought to be a representative sample of children treated with Ngenla (somatrogon) and Genotropin (somatrogon) across the world. Data will be included from eligible participants of any age who meet the study criteria and who receive care at centers enrolled in GloBE-Reg that have agreed to share their data with Pfizer during the data collection period. The registry is growing and additional centers around the world are expected to be included over the course of the study period.

The data collection period is from September 30, 2025 to August 31, 2035. No sampling will be performed. Participants can be located anywhere in the world and will be followed up to 10 years until the end of the study or one of the following occurs: withdrawal of consent, discontinuation of

either Ngenla (somatrogon) or Genotropin (somatropin), discontinuation from the GloBE-Reg registry, lost to follow up or death.

The treating physician will follow patients treated with Genotropin (somatropin) or Ngenla (somatrogon) as per routine clinical practice and will collect and enter relevant patient data as part of the defined minimum data set collected by the GloBE-Reg registry.

During the study, duration of treatment exposed will be defined as:

Genotropin/Ngenla: (last dose date – baseline date + 1)/365.25,

where baseline date is the initial visit date on the Reported Outcomes eCRF form.

The data collected via GloBE-Reg will be de-identified and sent to Pfizer for analysis. Pfizer will analyze the data to evaluate treatment effectiveness, safety, adherence and compliance.

8.2.1. Inclusion Criteria

Participants must meet all the following inclusion criteria to be eligible for inclusion in the study:

1. Receiving treatment with either Ngenla (somatrogon), or Genotropin (somatropin), at the discretion of the prescribing physician.
2. Confirmation of consent to participate in the GloBE-Reg registry and consent to have data shared with Pfizer as part of the PROGRES 2.0 sub-study.

8.2.2. Exclusion Criteria

Participants meeting any of the following criteria will not be included in the study:

1. Participation in any interventional clinical trial during the study period
2. Data fails to pass GloBE-Reg quality checks

8.3. Variables

The operational definitions will be included and detailed in the statistical analysis plan (SAP).

Variable	*Role*	*Data Source(s)*	*Operational Definition*
Core			
Study Site ID	Baseline	GloBE-Reg data base	Assessed at baseline
Demographics			
Date of birth	Baseline demographic	GloBE-Reg data base	Categorical month, day, year
Participant follow-up status	exposure	GloBE-Reg data base	Categorical Patient active, inactive, care suspended, care

			terminated, deceased, unknown
Date of death	outcome	GloBE-Reg data base	Categorical Month, day, year
Primary cause of death	outcome	GloBE-Reg data base	Categorical: See SAP
Sex at birth	Baseline characteristic	GloBE-Reg data base	Categorical male, female, other, unknown
Current gender	Baseline characteristic	GloBE-Reg data base	Categorical Male, female, non-binary, other, asked but unknown, unknown, same as sex at birth
Country at birth	Baseline demographic	GloBE-Reg data base	Categorical Select from any country in the world
Country of usual residence	Baseline demographic	GloBE-Reg data base	Categorical Select from any country in the world
Other			
Consent for PRO collection	Baseline	GloBE-Reg database	Categorical Yes, no, unknown
Participation in other registries (PROGRES 1.0)	Baseline demographic	GloBE-Reg data base	Categorical Yes, no, unknown
Name of registries (PROGRES 1.0 only)	Baseline demographic	GloBE-Reg data base	Free text box
Registry participant ID(s) (PROGRES 1.0 only)	Baseline demographic	GloBE-Reg data base	Free text box

Treatments			
Drug group and sub-group	exposure	GloBE-Reg data base	Categorical drug
Commercial name of drug used	Treatment characteristic	GloBE-Reg data base	Categorical LAGH,dGH, Somatrogon, Genotropin
Drug Indication			
Drug indication type	Treatment characteristic	GloBE-Reg data base	Categorical
Drug indication:	Treatment characteristic	GloBE-Reg data base	Categorical Drop down menu – select from indication options listed Drug indication: - Chronic Kidney Disease - Growth Hormone Deficiency (GHD)-type-Idiopathic short stature - Noonan syndrome - Prader Willi Syndrome - Skeletal Dysplasia – type - Small for Gestational Age (SGA) - type - Turner Syndrome - Other Disorder - type
hGH exposure			
visit date	exposure	GloBE-Reg data base	Categorical day, month, year

assessment date	exposure	GloBE-Reg data base	Categorical day, month, year
start date of first rhGH therapy	exposure	GloBE-Reg data base	Categorical day, month, year
start date of current rhGH therapy	exposure	GloBE-Reg data base	Categorical day, month, year
Total weekly dose	exposure	GloBE-Reg data base	numerical variable numerical input (1-100)
change in dose since last visit	exposure	GloBE-Reg data base	Categorical yes, no, unknown
Reason for change	exposure	GloBE-Reg data base	Categorical drop down menu or free text – dose adjustment for size, to optimise growth, low IGF-1, high IGF-1, adverse events, other (free text)
Reported missed doses in an average month	exposure	GloBE-Reg data base	Categorical drop down menu – unknown, 1, 2, 3, 4 or 5
Reported missed doses in an average week	exposure	GloBE-Reg data base	Categorical drop down menu – unknown, 1, 2, 3, 4, 5, 6, 7
Therapy stopped	exposure	GloBE-Reg data base	Categorical drop down menu – unknown, not applicable, yes, no

Date of therapy stop	exposure	GloBE-Reg data base	Categorical day, month, year
Reason for therapy stop	exposure	GloBE-Reg data base	Categorical drop down menu – not applicable, unknown, patient choice, poor efficacy, adverse events, final height achieved, other
Reinitiation of rhGH after final adult height	exposure	GloBE-Reg data base	Categorical drop down menu – unknown, not applicable,
Diagnosis			
Visit date	Treatment characteristic	GloBE-Reg database	Categorical Day-month-year
Date of assessment	Treatment characteristic	GloBE-Reg database	Day-month-year
Primary condition			
Primary condition:	Baseline clinical characteristic	GloBE-Reg database	Categorical Drop down menu - Chronic Kidney Disease - type GHD - Non-specific – type Acquired - CNS infection - Extracranial tumor - Intracranial tumor - Granulomatous disease - Other - Radiation therapy - Trauma - Vascular anomaly Congenital

			- Genetic - Idiopathic - Other - Prenatal infection - Structural malformation - Syndromic Idiopathic short stature Noonan Syndrome Prader-Willi Syndrome and Prader-Willi like syndrome Skeletal dysplasia Achondroplasia Hypochondroplasia SHOX gene defect Other skeletal dysplasia Small for Gestational Age (SGA) Silver-Russell Syndrome IGF-I deficiency IGF-I resistance Prenatal infection Drugs, alcohol or smoking related Idiopathic Turner Syndrome Precocious puberty Other disorder

Clinical Characteristics			
History of birth	Baseline characteristic	Globe Reg database	Categorical
Gestational age			Drop down menu: select unknown or week between 23-43
Delivery mode			Drop down menu: unknown, spontaneous vaginal delivery, forceps delivery, ventouse delivery, elective cesarean section, emergency cesarean section, other (text input)
Birth weight			Not known or whole number input (grams)
Relevant family history	Baseline characteristic	Globe Reg database	Categorical
Paternal height			Not known or whole number input (cm)
Maternal height			Not known or whole number input (cm)
Mid parental height			Calculated from paternal and maternal height (cm
Puberty	Clinical characteristic	Globe Reg database	Categorical
Date			Day, month, year
Age at assessment			Calculated from date of birth
Genitalia (Tanner stage)			Drop down: unknown, not applicable, 1, 2, 3, 4, 5
Right testicular volume (mL)			Drop down: unknown, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, more than 15 mL
Left testicular volume (mL)			Drop down: unknown, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, more than 15 mL
Breast (Tanner stage)			Drop down: unknown, not applicable, 1, 2, 3, 4, 5

Pubic hair (Tanner stage)			Drop down: unknown, not applicable, 1, 2, 3, 4, 5
Menarche attained (only for female patients)			Drop down: unknown, not applicable, yes, no
Menarche attained only for female patients (date)			Day, month, year
Auxological measures			
Age	Clinical characteristic	Globe-Reg Database	Automatic calculation from DOB
Height (primary effectiveness)	Baseline Clinical characteristic/outcome	Globe-Reg database	Numerical input
Weight	Baseline clinical characteristic/ outcome	GloBE-Reg database	Numerical input
BMI (primary effectiveness)	Baseline clinical characteristic/outcome	GloBE-Reg database	Automatic calculation from height and weight
Bone age (primary effectiveness)	Baseline clinical characteristic/outcome	GloBE-REg database	Categorical Drop down menu: unknown, not performed, performed
Bone age date performed	Baseline clinical characteristic/outcome	GloBE-REg database	Day, month, year
Bone age method	Baseline clinical characteristic/outcome	GloBE-REg database	Drop down: unknown, not applicable, Greulich-Pyle (GP), Tanner Whitehouse 2, Tanner Whitehouse 3, Radius-ulna-short bone, other
Value	Baseline clinical characteristic/outcome	GloBE-REg database	Text box
Further details	Baseline clinical characteristic/outcome	GloBE-REg database	Text box

Comorbidities/ **Medical history**			
Other health conditions	Baseline clinical characteristics	GloBE-Reg database	Categorical Drop down: unknown, not applicable, yes, no, text input
Date of assessment	Baseline characteristic	GloBE-Reg database	Day-month-year
Other health conditions:	Baseline characteristic	Globe-Reg database	Categorical
Neoplasia or cranial tumor	Baseline characteristic	Globe-Reg database	Unknown, Yes, no, text box
Cranial or total body irradiation	Baseline characteristic	Globe-Reg database	Unknown, Yes, no, text box
Chemotherapy	Baseline characteristic	Globe-Reg database	Unknown, Yes, no, text box
Traumatic brain injury	Baseline characteristic	Globe-Reg database	Unknown, Yes, no, text box
Pituitary or cranial surgery	Baseline characteristic	Globe-Reg database	Unknown, Yes, no, text box
Concomitant medication			
Assessment date	Clinical characteristic/exposure	GloBE-Reg database	Categorical Day, month, year
Thyroid hormone - Dose - Date started - Date stopped Glucocorticoid - Total daily dose	Clinical characteristics/exposure	GloBE-Reg database	Categorical Medication: yes, no, unknown Dose: numerical input

- Date started - Date stopped Oestrogen - Type/route/dose - Date started - Date stopped Gonadotrophins - Type/route/dose - Date started - Date stopped Testosterone - Type/route/dose - Date started - Date stopped DDAVP - Type/route/dose - Date started - Date stopped Other medication(s)			Date started/date stopped: day, month, year Prior medications will be defined as medications that are utilized prior to baseline. Concomitant medications will be defined as medications that are utilized on or after baseline.
Laboratory measures			
IGF-I (primary effectiveness) - Date performed -Time performed to the nearest hour -Date of last rhGH injection -Time of last injection to the nearest hour - Result - Value and units - Assay - Other details (if available)	Baseline clinical characteristic/outcome	GloBE-Reg database	Categorical or numerical value drop down menu – unknown, not performed, performed see SAP
GH stimulation test(s) - Date performed - Type - GH peak level	Baseline Clinical characteristic/outcome	GloBE-Reg database	Categorical or numerical value

- GH peak value and units			drop down menu – unknown, not performed, performed see SAP
TSH - Date performed - Result - Value and units	Clinical characteristic/outcome	Globe-Reg database	Categorical or numerical value drop down menu – unknown, not performed, performed see SAP
Free T4 - Date performed - Result - Value and units	Clinical characteristic/outcome	Globe-Reg database	Categorical or numerical value drop down menu – unknown, not performed, performed see SAP
HbA1c - Date performed - Result - Value and units	Clinical characteristic/outcome	Globe-Reg database	Categorical or numerical value drop down menu – unknown, not performed, performed see SAP
Imaging			
MRI pituitary	Clinical characteristic/outcome	Globe-Reg database	Categorical drop down menu – unknown, not performed, performed
Date performed	Clinical characteristic/outcome	Globe-Reg database	Categorical Day, month, year
Results	Clinical characteristic/outcome	Globe-Reg database	See SAP
Further details	Clinical characteristic/outcome	Globe-Reg database	Text input

Adverse events and exposure scenarios			
Adverse events	Outcome	GloBE-Reg database	Categorical
Date of assessment	Outcome		Categorical Day, month, year
Seriousness	Outcome		Categorical See SAP
Causality	Outcome		Categorical Drop down menu – probable, possible, unlikely
Further details	Outcome		Categorical Text box input
Blood and Lymphatics	Outcome		Categorical Tick boxes: - Anaemia - Eosinophilia - Leukaemia - Peripheral Oedema - Other
Endocrine and metabolic	Outcome		Categorical Tick boxes: - Adrenal Insufficiency - Gynaecomastia - Hyperglycaemia - Hypothyroidism - Type 2 Diabetes Mellitus (T2DM) - Other
ENT	Outcome		Categorical

			Tick boxes: -Epistaxis -Nasopharyngitis -Other
Eyes	Outcome		Categorical Tick boxes: -Conjunctivitis -Other
Gastrointestinal (GI)	Outcome		Categorical Tick boxes: -Nausea -Pancreatitis -Vomiting -Other
Immune system	Outcome		Categorical Tick boxes: -Anaphylaxis -Angioedema -Anti-GH Antibodies -Immunogenicity -Other
Injection site reaction **	Outcome		Categorical Tick boxes: -Bruising -Erythema -Haematoma -Lipoatrophy -Localised Pain -Swelling -Other
Musculoskeletal	Outcome		Categorical

			Tick boxes: -Arthralgia -Arthritis -Myalgia -Myositis -Scoliosis -Slipped upper femoral epiphyses -Other
Neoplasm *	Outcome		Categorical Tick boxes: -Primary neoplasm -Secondary Neoplasm -Other
Nervous system	Outcome		Categorical Tick boxes: -Ataxia -Dizziness -Headache -Intracranial Hypertension -Paresthesia -Other
Renal	Outcome		Categorical Tick boxes: -Hematuria -Other
Skin	Outcome		Categorical Tick boxes: Rash/urticaria/pruritus -Other

Exposure scenarios: Medication error	outcome	GloBE-Reg database	Categorical -Visit date - Date of assessment - Type of medication error(accidental/intentional) - Classification (wrong drug/route/frequency/dose/other) - Date when it occurred - Date when it was reported to physician - Report to authorities details - Adverse events associated with medication error - Other details See SAP

Baseline date is the initial visit date on the Reported Outcomes eCRF form.

The potential covariates and confounders that will be considered for the models in addition to treatment (Genotropin and Ngenla) are the following baseline variables, classified into different categories:

Table 8-3 Model Covariates

Priority Order*	**Model Covariates**	**Propensity Score Model Covariates - Categories**
7	Geographic region	Region (Europe, NA, Japan and RoW
1	Demographics	Age (in years), Sex
2	Clinical characteristics	Height, Weight
3	Naive to GH status	Naïve to GH/Non-Naïve to GH
4	Peak GH levels	≤3 ng/mL, >3 ng/mL to ≤7 ng/mL, >7 ng/mL to 10 ng/mL, >10 ng/mL
5	Duration of GH (time form first rhGH therapy)	
6	Time since start of the study (in months)	

*This priority order will be used to remove the least priority variables in case of non-convergence issues for the model. Additional variables and its priority order can be decided during the analysis. Relevant patient/disease characteristics, including baseline value of the variable to be analyzed, will also be included whenever applicable.

8.4. Data Sources

The study will obtain existing data collected in the GloBE-Reg registry. GloBE-Reg is an international, non-interventional registry of bone and endocrine agents, conducted by the project team based at the Office for Rare Conditions at the University of Glasgow, Glasgow, Scotland, United Kingdom. GloBE-Reg is approved by the National Research Ethics Service and Information Governance Authority in the UK.

The registry collects real-world data on both efficacy and safety and allows for sub-studies that can be of interest to any of its stakeholders. The GloBE-Reg steering committee identified an expert working group to develop a minimum data set for the registry. The minimum data set comprises items agreed upon by the expert working group and deemed by consensus to be easily measured in a routine clinical setting across the world to monitor the safety and effectiveness of hGH, both daily and long acting, in children with GHD. To date, GloBE-Reg has collected de-identified, patient-level data from an international cohort of over 3500 participants from across 32 centers in 20 countries. The collected data is comprised of demographics, clinical characteristics, birth and medical history, diagnosis of growth hormone deficiency, therapy, including prior and current GH treatment, concomitant medications, laboratory results, clinician reported outcomes and adverse events.

The registry is a web-based interface linked to a secure database at the University of Glasgow, which is managed and reviewed by the university Central IT Services in compliance with the UK Data Protection Act (2018) and General Data Protection Regulation (GDPR 2016/679). Reporters are healthcare professionals at medical institutions around the world who apply for clinical contributor role-based access accounts for their center. Once access to the registry is obtained, clinicians obtain local approvals to enroll eligible participants at their center, obtain and store each participant informed consent form and can then add routinely collected clinical information. All data are pseudonymized and when the core mandatory modules are entered into the registry and saved, a registry ID is provided. This unique patient identifier is used across all visits, enabling longitudinal follow-up of patients.

Data can also be uploaded using bulk transfer method available in the registry, after the above requirements are met.

Data entered in the GloBE-Reg database will be formally assessed for quality on an annual basis. Ten percent of cases (or a minimum of 1) included from each center shall be eligible for a remote quality assurance (QA), with cases selected using a randomization tool. For the selected cases, the center lead clinician is invited to submit evidence through the QA platform that is built into the registry, and the GloBE-Reg team arranges a meeting to discuss the process in detail.

In addition, the useability of the platform for data entry is checked through biannual user surveys. Limited internal validation protocols and required mandatory completion checks are performed. During subsequent processing and analysis, outliers and missing values are identified and reviewed.

8.5. Study Size

The study is descriptive in nature without any *a priori* hypothesis testing; therefore, a formal sample size estimate is not required. All eligible participants treated will be included. It is expected that at least 2000 Genotropin (somatropin) treated and 700 Ngenla (somatrogon) treated participants will be included in the final analysis.

8.6. Data Management

All data for this study will be collected through the routine data collection practices of the GloBE-Reg registry. Investigators in each country will independently generate the data needed for the registry. The investigators will check the data for consistency in terms of range of values, units of measurement, and relevance of clinical information.
The registry is a web-based interface linked to a secure database at the University of Glasgow, and investigators at centers around the world add pseudonymized, routinely collected clinical data on patients who provide consent to participate in the registry. Data contained in other databases and registries can also be uploaded using a bulk transfer method, which avoids manual double entry through bulk upload of core and longitudinal data.

All participant data is stored by GloBE-Reg on a secure physical server at the University of Glasgow, which is managed and reviewed by Central IT Services. Additional details can be found in University of Glasgow's Data Protection Impact Assessment (DPIA) document (Annex 1).

Data for participants treated with Ngenla (somatrogon) and Genotropin (somatropin) will be provided to Pfizer only after centers provide consent to share their data. Data transferred to Pfizer will be in CSV format every 6 months using CONFORM 4.0.10 or later via secure file transfer protocol and stored internally on a secured dedicated server. The data will be converted to SAS format for analysis and reporting and will be processed by Pfizer to create analytical variables and datasets for all analyses specified in the study protocol. All study data will exist as structured data by the start of the study. The data analysis and results generation will strictly follow the approved SAP. If for any reason any statistical method needs to be carried out differently than described in the SAP, an amendment to the SAP with required documentation and new approval will be done. All computations and generation of Tables, Listings and Data for figures will be performed using SAS Version 9.4 or higher.

8.7 Data Analysis

Data on the subset of participants in the GloBE-Reg registry who are treated with Ngenla (somatrogon) or Genotropin (somatropin) will be obtained and analyzed. The data will be converted to SAS format for analysis and reporting and will be processed by Pfizer to create analytical variables and datasets for all analysis specified in the study protocol. All study data will exist as structured data by the start of the study. Data obtained from GloBE-Reg will not undergo any additional cleaning or error checks, and there will be no imputation of missing data. All data received from GloBE-Reg will be analyzed. The study is descriptive in nature without *a priori* hypothesis testing.

Analysis of Primary Endpoint:

The primary analysis is to compare effectiveness of Ngenla (Somatrogon) and Genotropin (Somatropin) during the course of routine clinical care. The primary endpoints are height, bone age, body mass index (BMI) and insulin-like-growth factor-I (IGF-I) levels.

The primary effectiveness outcomes for height (Annual HV, HVSDS, change in height SDS) will also be presented by subgroups. The following subgroups will be defined, as categorized at baseline.

- Age group (0 to 2, 3 to 8, 9 to 18, ≥19 years)
- Sex (Male, Female)
- Naïve/Non-naïve to rhGH therapy.
- Puberty Status (Yes, No)
- Medical co-morbidities (Yes, No)
- Initial disease/treatment indications (Yes, No)
- Peak growth hormone (GH) levels ≤3 ng/mL, >3 ng/mL to ≤7 ng/mL, >7 ng/mL to 10 ng/mL, > 10 ng/mL
- Primary Condition/Diagnosis (CKD, GHD (Non-specific, Acquired, Congenital, Idiopathic), Idiopathic Short Stature, Noonan Syndrome, Prader-Willi Syndrome, SGA, *etc*.)
- Study region (Europe, Japan, North America, Rest of the World)

Table 8-7 Overview of Effectiveness Analysis

Outcome	**Primary/Secondary**	**Statistical Method 1**	**Statistical Method 2**	**Statistical Method 3**
Annual HV	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Height standard deviation score (SDS) and change in height SDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
HVSDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in annual BMI	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in annual BMI SDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in Bone age	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in IGF	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats
Change in IGF-I SDS	Primary	MMRM, 95% CI	MMRM + IPTW, 95% CI	Descriptive stats

[1] Continuous variables will be summarized using descriptive statistics which will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations. Descriptive statistics for categorical/qualitative variables will be presented with number of patients (count) and percentage and this will be presented in the format 'n (%)'.

Analysis of the Secondary Endpoints:
For secondary endpoints, safety events of interest, medication errors and efficacy measurements, descriptive statistics, counts and proportions, crude incidence rates (*i.e.*, number of events per person years) with associated two-sided 95% confidence intervals will be calculated. Incidence rate is calculated as the number of individual events observed during the time at risk (exposure time), divided by the total number of patient-years at risk for the event, multiplied by 100.

Table 8-7 Overview of Safety Analysis

Outcome	Primary/Secondary	Statistical Method [1]	Statistical Method 2
SAEs	Secondary	Descriptive stats	IR, IRR, HR
Non-SAEs	Secondary	Descriptive stats	
Medication Errors	Secondary	Descriptive stats	IR, IRR, HR
Laboratory results	Secondary	Descriptive stats	

[1] Continuous variables will be summarized using descriptive statistics which will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations. Descriptive statistics for categorical/qualitative variables will be presented with number of patients (count) and percentage and this will be presented in the format 'n (%)'.

Repeated Measures
This model will only be performed with those patients without treatment switch until a given time point. Continuous variables will be analyzed by a Mixed Model for Repeated Measures (MMRM) under the MAR framework, including all post baseline timepoints data as outcome variables and baseline data as a covariate including the relevant patient/disease characteristics. Repeated time variable will be modeled as a continuous variable and treatment (Genotropin versus Ngenla) as a class variable with an unstructured covariance and least square means along with 95% CI will be presented.
The adjusted mean changes from Baseline at Month 6, 12, 18, 24, *etc*., for each treatment group will be estimated in the framework of this model, as well as the between group differences and the 95% CIs for the adjusted mean, when applicable.

The MMRM model will be implemented using SAS® (version 9.4 or higher) generalized linear mixed procedure (PROC MIXED) with an unstructured correlation matrix to model the within-patient errors. If this model does not converge, a heterogeneous Toeplitz covariance structure followed by the

heterogeneous first-order autoregressive covariance structure will be considered. Parameters will be estimated using the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using the Kenward-Roger approximation.

Count outcomes or Incidence Rate Ratio

Poisson regression (or negative binomial regression if data presents overdispersion) will be used to estimate the incidence rate ratio (IRR) along with 95% Wald CI between Ngenla-treated patients and Genotropin-treated patients.

Longitudinal Model/Sensitivity Analysis

To assess the longitudinal association between outcomes and time-varying treatment (*i.e.* patients switch treatment from Genotropin to Ngenla or vice versa at any time-point), a propensity model approach will be applied to calculate the inverse probability of treatment weights (IPTW). This model is assumed to control for time-varying confounding when time-varying treatments are used in longitudinal analyses.

The IPTW will be calculated using propensity score model in which the choice of the treatment at each visit will be considered as the outcome (Genotropin vs Ngenla) and the pre-specified baseline characteristics (See Table 9-3 Model Covariates) as independent variables. Once IPTWs per patient are derived, the models described in the Repeated Measure model will be applied with the weights. The models will include treatment group (time-varying covariate), time (in years) and IPTW. This approach will be considered as a sensitivity analysis *to assess the impact of treatment switching*.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8 Quality Control

GloBE-Reg has a formalized process for quality/assurance of data. Data entered in the GloBE-Reg database will be formally assessed for quality on an annual basis; there is no hand-written data entry, therefore legibility is not a concern. Ten percent of cases (or a minimum of 1) included from each center shall be eligible for a remote quality assurance (QA), with cases selected using a randomization tool. For selected cases, the center lead clinician is invited to submit evidence through the QA platform that is built into the registry, and GloBE-Reg arranges a QC-specific meeting to discuss the process in detail. At a site level, investigators in respective countries are responsible for following their standard institutional procedures to ensure data quality and integrity.

In addition, the useability of the platform for data entry is checked through biannual user surveys. Internal validation protocols and required mandatory completion checks are performed. During subsequent processing and analysis, outliers and missing values are identified and reviewed. Data quality will be maximized through a range of other mechanisms, including data validation, data cleansing, data profiling and internal audits:

- Data Validation - Selected data fields have internal validation mechanisms and mandatory completion and outliers and missing values commonly become apparent and checked during

data processing and analysis. The data dictionary is automated, and the codes for specific data fields can be downloaded directly from the registry.

- Data Cleaning – The data is processed to check for duplicate records, inconsistencies, and inaccuracies at regular intervals.
- Data Profiling - Data is processed to understand its structure, patterns and relationships at regular intervals.

GloBE-Reg was developed based on the EMA Guideline on registry-based studies EMA/426390/2021 released on 22 October 2021 and follows Good Pharmacoepidemiology Practices and is approved by the National Research Ethics Service and Infromation Governance authorities in the UK.

The steering committee of GloBE-Reg established a working group of experts to create a minimum dataset for the registry. The group determined that this set consists of items that can be readily measured in a standard clinical setting worldwide to track the efficacy and safety of hGH, both long-acting and daily, in children with GHD.

Additionally, all information is stored on a secure server at the University of Glasgow in compliance with UK Data Protection Act (2018) and General Data Protection Regulation (GDPR 2016/679).

8.9 Limitations of the Research Methods

This is a non-interventional observational study, therefore, there are several potential limitations which are well-described in the literature for comparable studies, such as Kabi/Pfizer International Growth Database (KIGS) (13,14). As a retrospectivecohort study, without randomization, there is a potential for variable quality and completeness of data. In addition, confounding and biases cannot be excluded, and determination of causation is limited. Enrollment or selection bias is possible since it is affected by the willingness or ability of physicians and patients to participate in GloBE-Reg. However, centers are expected to enroll all eligible patients treated with Ngenla (somatrogon) and Genotropin (somatropin). Follow-up bias is a potential limitation as well, especially if patients with AEs are less likely to return to the treating physician or center for follow-up.

Regarding the secondary endpoints on safety and adverse events, there is a potential risk of underestimating the safety outcomes due to underreporting, misreporting or missing data from the eCRFs, and/or EHR. The clinician entering data in the registry is responsible for evaluation of seriousness and causality of the safety and adverse events and due to the secondary collection of this data further investigation is limited.

Additional potential limitations specific to our study include:

- Data collection will reflect routine clinical practice rather than mandatory assessments at specified time points thereby increasing heterogeneity of the data. For this reason, visit windows (defined in the SAP) will be applied to the statistical analysis.
- The data source for this study is the subset of participants treated with either Ngenla (somatrogon) or Genotropin (somatropin) from the GloBE-Reg registry, which collects routine data from across the world and is reflective of different routine clinical practices according to region. This may lead to heterogeneity of the data and result in information bias. For this reason, subgroup analysis will be carried out for the primary efficacy

endpoints and pre-identified confounders will be included in the statistical models as presnted in Table 9.3.

- Information bias may also occur related to risk of loss to follow up due to the long duration of this study or adverse event occurrence.

8.10 Other Aspects

Not applicable.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1 Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no participant personal information.

9.2 Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from participants by Pfizer is not required.

9.4 Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (*e.g,* informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

9.5 Ethical Conduct of the Study

The study will be 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). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891(15)
- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp(16)
- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/(17)

- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies/ European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml(18)
- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf(19)
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf(20)
- European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (EMA/813938/2011 Rev 3). 2017(21)

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exists as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (*i.e.*, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (*i.e.*, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One or more abstracts may be developed and submitted to relevant scientific conference(s) and one or more manuscripts may be developed and submitted to relevant peer-reviewed medical journals. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed. Additionally, annual investigator meetings are planned to disseminate data and communicate study results.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant, is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

The final clinical study report will be submitted to EMA according to Article 46 of the **Paediatric** Regulation (EC) No. 1901/2006.

12. REFERENCES

1) Shalet SM, Toogood A, Rahim A, et al. (1998). “The diagnosis of growth hormone deficiency in children and adults.” Endocrine reviews 19(2):203-223.

2) Bach LA. (2004). "The insulin-like growth factor system: towards clinical applications." The Clinical biochemist. Reviews/Australian Association of Clinical Biochemists 25(3):155-164.

3) Krysiak R, Gdula-Dymek A, Bednarska-Czerwińska A, et al. (2007). "Growth hormone therapy in children and adults." Pharmacol Rep 59(5):500-516.

4) Thomas, JD, Monson JP. (2009). "Adult GH deficiency throughout lifetime." Eur J Endocrinol 161 Suppl 1:S97-S106.

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16) Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp

17) Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/

18) International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies/ European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

19) Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf

20) FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf

21) European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (EMA/813938/2011 Rev 3). 2017

13. LIST OF TABLES

14. LIST OF FIGURES

Not Applicable

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A multi-country, non-interventional, observational, retrospectivecohort study among participants treated with human growth hormone (hGH) treatments Genotropin (Somatropin) and Ngenla (Somatrogon) under routine clinical care

EU PAS Register® number: 1000000705
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]				6
1.1.2 End of data collection[2]				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

N/A

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				7,8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)				7,8
2.1.2 The objective(s) of the study?				8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)				9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?				
2.1.5 If applicable, that there is no *a priori* hypothesis?				

Comments:

N/A

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.4, 9.5
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)				11

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				
	4.2.3 Country of origin				
	4.2.4 Disease/indication				9.1, 9.2
	4.2.5 Duration of follow-up				9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)				9.2.1,9.2.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)				
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				
5.3	Is exposure categorised according to time windows?				
5.4	Is intensity of exposure addressed? (e.g. dose, duration)				
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				
5.6	Is (are) (an) appropriate comparator(s) identified?				

Comments:

N/A

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?				9.3
6.2	Does the protocol describe how the outcomes are defined and measured?				9.1
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.1
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

N/A

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)				9.1

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)				9.3, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3, 9.4
9.1.3 Covariates and other characteristics?				9.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)				9.3, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3, 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.8, SAP
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.8, SAP
9.3.3 Covariates and other characteristics?				9.8, SAP

9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?				SAP
10.2	Is study size and/or statistical precision estimated?				9.5, SAP
10.3	Are descriptive analyses included?				9.7, SAP
10.4	Are stratified analyses included?				9.7, SAP
10.5	Does the plan describe methods for analytic control of confounding?				9.7, SAP
10.6	Does the plan describe methods for analytic control of outcome misclassification?				
10.7	Does the plan describe methods for handling missing data?				SAP
10.8	Are relevant sensitivity analyses described?				9.7, SAP

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)				9.6
11.2	Are methods of quality assurance described?				9.8
11.3	Is there a system in place for independent review of study results?				

Comments:

N/A

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?				9.9
	12.1.2 Information bias?				9.9
	12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				9.9

12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				

Comments:

N/A

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10.3
13.2 Has any outcome of an ethical review procedure been addressed?				
13.3 Have data protection requirements been described?				10.1

Comments:

N/A

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?				

Comments:

N/A

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?				12
15.2 Are plans described for disseminating study results externally, including publication?				12

Comments:

N/A

Name of the main author of the protocol: [redacted]

Date: 12/August/2025

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

University of Glasgow

DATA PROTECTION IMPACT ASSESSMENT (DPIA)

Data Protection Impact Assessment: List of Requirements

Before submitting your DPIA template to the DP Office, please ensure that you have completed and addressed all relevant points below. **The DP Office will not review your DPIA unless you can demonstrate engagement with or reference to the checklist and its attending documents and requirements.**

Are your data anonymous?

Yes ☐

No ☒

If you are claiming that your data are anonymous, are there any potential data linkages that would allow someone to identify your data subjects? Note that simply removing a name does not constitute anonymisation. Have you considered the impact of other identifiers e.g. you are studying individuals with an uncommon medical condition and working with gender, age, and location data or other factors that narrow your population and could lead to identification (i.e. the 'mosaic' or 'jigsaw' effect)?

Are your data pseudonymous?

Yes ☒

No ☐

If you hold an identifier key(s) that would allow you or another party to identify your masked data then it is pseudonymous and therefore must be treated as personal data.

Is the University a data controller or a data processor for this project?

Data controller ☒

Data processor ☐

Will you require third parties (outwith UofG) to assist you in gathering, storing, accessing, or translating or transcribing the data?

Yes ☒

Explain: Other centres enter data into the Registry and the Registry shares data with researchers. All processes are strictly controlled as detailed in the DPIA

No ☐

Do you have a data sharing agreement in place?

Yes ☒

No ☐

If you do not have an agreement, but you require one, complete the Questionnaire for Data Processing Involving Third Parties and return to the Contracts Team.

Have you completed a privacy notice to inform data subjects on the intended use of their personal data? *(If you answer "yes", please attach for reviewed.)*

Yes ☒

No ☐

Have you completed the University's online Data Protection and/or Information Security trainings? (These trainings are mandatory for all staff; the full project team should complete both training modules)

Yes ☒

If yes, please indicate dates of completion for all colleagues: Available in one drive

and a link can be provided.

No ☐

Have you completed a research data management plan and reviewed the DMP and DPIA Workflow chart?

Yes ☒

No ☐

If no, please explain why you do not require a data management plan.

Have you applied for, or received ethical approval?

Yes ☒

If yes, when was the application submitted? Approved? Please submit a copy with this DPIA submission.

Latest approval from WoSRES date 26/07/2022 https://globe-reg.net/documents-for-institutional-approval/ **No** ☐

Consider the following ways to reduce potential risk and demonstrate practical compliance:

Project Overview	
Project Name:	GloBE-Reg Registry
Brief description of the Project:	The GloBE-Reg Registry (referred to as the Registry) is a registry platform launched in 2022 supporting the development of studies with a focus on effectiveness and long-term safety through routine collection of real-world data on specific drugs. The project is managed by the Registries Project Management Group (PMG) in the Office for Rare Conditions (referred to as ORC Registries) at the University of Glasgow.
Project Owner: **Name, designation and email address**	[redacted]
Project Manager: **Name, designation and email address**	[redacted]
External project partners, if any:	
Summarise identified need for DPIA:	The project collects, stores and shares health data and the number of cases is expected to increase over time. A Registry DPIA would also be helpful when the project is next reviewed by the UK National Research Ethics Service in 2027.
Timing of the Project: **Start/end dates, duration as applicable**	2022 onwards. There is no end date although the project has 5 yearly ethics renewals by NRES and that will next be undertaken in 2027. The data are held for a period of 30 years from the date of the last ethics renewal.

Date template completed:	07/02/2025
Date submitted to the Data Protection Office:	07/02/2025

Describe the processing activities

Describe the nature and purpose of the processing:
You might find it useful to refer to a flow diagram or another way of describing data flows

- **What is the source of the data?**

The data subjects include the reporters and the patients. The source of the data for the reporters, are the reporters themselves. The source of the data on cases are the reporters and the cases themselves.

- **How will you collect data?**

The Registry is a web-based interface linked to a secure database at the University of Glasgow which is managed and reviewed by Central IT Services. Reporters who are usually the health care professional at centres around the world apply for clinical contributor role-based access account for their centre and once approved they and their approved team members obtain local approvals to approach eligible cases at their own centre and add pseudonymised routinely-collected data on clinical cases who provide consent. Data can also be uploaded using Bulk Transfer method available in the registry

- **How will you use the data?**

The data on reporters is used to check their suitability to use the Registry, to maintain contact with them, provide them with an update of Registry activities and involve them in studies undertaken by the Registry.
The data on cases is used to undertake research studies. At the point of consent, cases also have options to view their data in the Registry, receive newsletters or complete patient reported outcomes. For these actions they need to provide an email.

- **How will you store the data?**

The data on reporters and cases are stored in a database on a secure physical server at the University of Glasgow which is managed and reviewed by Central IT Services.

- **How will you delete the data?**

On request from the reporters or the cases, the data can be deleted from the database. There are back up copies of the database that are held in IT Services and deletion of these will also be requested from IT Services. Data from the Registry that have been processed for a specific study by a researcher are kept on a secure University drive to allow for reuse or cross-checking for research integrity. In those cases that are deleted from the Registry, the processed datasets are retained but annotated to state that the source data in the Registry have been deleted and they cannot be re-used for a study.

- **Will you be sharing data with anyone (within the University or external to the University)?**

The data are shared with researchers following a review of the data request by the Data Access Committee and completion of a Data Sharing Agreement. The data are extracted from the Registry database using queries and deposited in a secure University local drive folder and then shared via the University File Transfer Service, which provides limited-time access to the

researcher. A data flow diagram is available in the Data Access Policy which can be downloaded from https://globe-reg.net/documents-for-institutional-approval/ (https://globe-reg.net/wp-content/uploads/2025/02/ORCRegistries-Dataflow-Feb2025.pdf).

- **What measures do you take to ensure data processors comply? Do you have a data sharing agreement drafted?**

The data are shared with researchers following a review of the data request by the Data Access Committee and completion of a Data Sharing Agreement (https://globe-reg.net/documents-for-institutional-approval/). The data are extracted from the Registry database using queries and deposited in a secure University local drive folder shared via the University File Transfer Service, which provides limited-time access to the researcher. A data flow diagram is available in the Data Access Policy https://globe-reg.net/documents-for-institutional-approval/

- **What types of processing identified as likely high risk are involved?**

Given that the Registry collects health data on people with rare conditions, it is possible that there may be circumstances when it is possible to identify one or more individuals from the data contained within the data set. An example may be a person with a very rare condition where there is only one person at one centre of a specific age or sex. All scenarios such as these are monitored closely by the PMG for any instance where a single case such as this can be identified. All publications and outputs do not mention centres when single cases or low numbers (<10) are described and data are aggregated where indicated and scientifically justifiable. The Data Sharing Agreement identifies this as a risk in Clause 5.10. https://globe-reg.net/wp-content/uploads/2025/02/GloBE-Reg-Data-Sharing-Agreement-v3-050225-Data-Receivers.docx

- **What types of processing identified as likely high risk are involved?**

Given that the Registry collects health data on people with rare conditions, it is possible that there may be circumstances when it is possible to identify one or more individuals from the data contained within the data set. An example may be a person with a very rare condition where there is only one person at one centre of a specific age or sex. All scenarios such as these are monitored closely by the PMG for any instance where a single case such as this can be identified. All publications and outputs do not mention centres when single cases or low numbers (<10) are described and data are aggregated where indicated and scientifically justifiable. The Data Sharing Agreement identifies this as a risk in Clause 5.10. https://globe-reg.net/wp-content/uploads/2025/02/GloBE-Reg-Data-Sharing-Agreement-v3-050225-Data-Receivers.docx

- **What do you want to achieve?**

The Registry achieves the following:-
- The collection of data that allows researchers internationally to design studies that can recruit large enough groups of carefully ascertained patients.
- The promotion of the use of standardised methods of collecting data and describing clinical conditions driving up standards of clinical care.
- Enable collection of data that can lead to long-term outcome studies.
- By developing a high quality process for collecting and sharing data, the registry will also promote standards of information governance.

- **Does the processing actually achieve your purpose?**

Yes. The main purpose of the Registry is to collate data in the Registry and provide pseudonymised data to researchers within a secure environment so that they can perform studies in sufficiently large cohorts.

- **Is there another way to achieve the same outcome?**

For rare conditions, it is imperative that data are collected in a standardised manner from several centres. There are no other international rare disease registries for this group of conditions.

- **What is the intended effect on participants or users?**

- Reporting centres are a part of a large collaborative research and quality improvement network
- Research into a wide range of rare conditions is more meaningful when there are greater number of participants.
- There is no direct effect on participants but their data are contributing to the improvement in the care of people with conditions like theirs.

- **What are the benefits of the processing for you or the University, and more broadly?**

There are no direct personal benefits to any member of the Office for Rare Conditions. However, the research group has a research interest in some of the rare conditions that are included in the Registry and the processing allows it to remain at the forefront in these fields. The group also has an academic interest in the use of real-world data through international registries.

Describe the scope and context of the processing:

- **What is the nature of the data, and does it include special category or criminal offence data?**

The Registry collects personal information on the reporters who are usually health care providers/clinicians from centres across the world who apply for access to the registry. Personal identifiers in these data include their name, place of work, professional website and contact details. All applicants shall be provided a link to the ORC Registries Privacy Notices by email when they register and it is included in the Clinician section of the website (https://globe-reg.net/clinician/). This also included on the registration form and they will have to check the box before completion of the registration process. These reporters recruit patients (cases) at their local centres (the Reporting Centre) for entry into the Registry. This occurs after consent is obtained from the cases by the reporter according to locally approved recruitment protocols. This also includes provision of a Participant Information Sheet and an Informed Consent Form https://globe-reg.net/information-sheets/) that has been approved by the UKNRES for a research database study (https://globe-reg.net/documents-for-institutional-approval/). In addition, the ORC Registries Privacy Notice for patients posted on the Patient section of the website (https://globe-reg.net/patients/) and included in the email which goes from the Registry to the patient for account activation. Data cannot be entered into the Registry unless consent has been obtained; the actual consent record is stored at the Reporting Centre. Data that are entered into the Registry include routinely collected clinical information with minimal personal identifiers that includes date of birth. Details of the data fields that are collected are available in the data dictionary at https://globe-reg.net/data-dictionary/. On creation of a case record, the case is provided with a unique ID which the reporting centre retains to link to local health records. Thus, the case records in the Registry are pseudonymised; only the Reporting Centre can link the Registry case record to the name of the case. The PMG or any other registry user who is not based at the Reporting Centre cannot identify the case.

At recruitment, cases also have the option of accessing the Registry themselves. This is not mandatory. However, the PIS explains to them that if they want to look at their record in the Registry they can either ask their Reporting Centre for a copy of the record or access it directly. To access it directly, they need to provide an email address. This email is entered into the Registry by the reporting centre and the email is used by the Registry to send an activation link.

This email can also be used by the Registry to send requests for Patient Reported Outcomes or Newsletters if the case approves of receiving these on the ICF. All emails stored in the registry are logically separated from the pseudonymised data using cryptographic methods i.e encrypted at rest.

- **How many individuals are affected by your planned processing?**

Currently, the Registry has almost 2770 cases from over 28 centres in 17 countries. It is anticipated that the participating centres and countries will continue to increase as the Project matures and more studies are launched. (https://globe-reg.net/activity-report/).

- **What is the nature of your relationship with the individuals whose data you will process?**

There is no relationship of the patient data subjects to the ORC Registries team. In some of the cases in the Registry, the patients attend the clinical services in Glasgow and these patients are under the care of the project lead who is also the lead for Glasgow as a Reporting Centre. The Centre Reporters have a scientific collaborative relationship with the ORC Registries team. There is no financial relationship.

- **How much control will they have over what you do with their data?**

The ownership of the data is outlined in Section 6 of the Data Access Policy (https://globe-reg.net/wp-content/uploads/2024/09/GloBE-Reg-Management-Protocol-v3.0-040924.pdf). The cases are aware that the data can be used for any secondary analysis study which is approved by the Data Access Committee. Details of all the approved studies are available on the website https://globe- reg.net/studies/. After a data request from a Researcher has been approved by the Data Access Committee, the Researcher completes a Data Sharing Agreement. Then, the Reporting Centre is provided a list of eligible cases at that Centre and is asked to approve the sharing of data from the eligible cases with the Researcher.

- **Does your processing include children or other vulnerable groups?**

The patient data subjects include children.

- **What geographical area does it cover?**

Currently, the Registry has almost 2770 cases from over 28 centres in 17 countries. It is anticipated that the participating centres and countries will continue to increase as the Project matures and more studies are launched (https://globe-reg.net/activity-report/).

- **Are there concerns over this type of processing generally or more specifically regarding information security? *If yes, have you contacted Information Security for advice?***

The Registry has been active since 2022 at the University of Glasgow and has not encountered any security flaws. Its operations have been regularly discussed in the past as well as continue to be transparently communicated to its users. The platform is managed by central IT services. The project relies on the Information Security Policies of UofG (https://www.gla.ac.uk/myglasgow/it/informationsecurity/policies/).

- **Does the project involve the use or development of new technology? *If yes, have you contacted* IT Services *for advice?***

The Registry is built using software that is commonly used for web-based databases.

- **Are there any current issues of public concern that you should factor in?**

The registry was developed in consultation with patient groups. The governance structures of the Registry have patient group representation.

- **Are you signed up to any approved code of conduct or certification scheme (once any have been approved)?**

All members of the ORC Registries team have completed the University's GDPR course and the Information Security Course. Prior to the development of this course, team members had completed the MRC's Information Governance Course as well as the NHS' Safe data Handling Course.

- **Do you have stakeholders, either within the University or external, that you must consult with regarding this intended processing?** ***If yes, who are they?***

The Registry has several stakeholders across the world. These stakeholders are present at several levels and include the Steering Committee (https://globe-reg.net/steering-committee), the Data Access Committee (https://globe-reg.net/data-access-committee/), the Study Teams (https://globe-reg.net/studies/), the Scientific Activities Committee (https://globe-reg.net/scientific- activities-committees/), the Patient Advisory Group (https://globe-reg.net/patient-advisory-group/) and the Expert Working Groups (https://globe-reg.net/expert-working-groups/).

Describe when and how you will seek these stakeholders' views – or justify why it's not appropriate to do so.

From the outset of the project in 2022, the project has sought patients' and parents' views as well as professionals. The project has a patient advisory group (https://globe-reg.net/patient-advisory-group/) and patient representatives are present in the Steering Committee, Data Access Committee and other drug specific activities.

- **Do you need to involve anyone else within your organisation?**

The project has had close involvement of the Contracts and Legal Office, IT Services, Information Security and the Data Protection Office. The project also has close links to NHS Greater Glasgow & Clyde Health Board, the National Research Ethics Service and the West of Scotland Caldicott Guardian.

- **Do you need to ask your data processors to assist with consultation?**

Data may be processed by ORC Registries team but are not provided to any other parties without the completion of a Data Sharing Agreement.

- **Do you plan to consult information security experts, or any other experts?**

The development of the platform is undertaken by an IT company with experience of developing secure systems (Honorary Affiliate). The platform is currently housed in IT Services in the University of Glasgow and undergoes the same level of checks as other databases that are held in the University.

Ensuring basic compliance
Describe how you will uphold the data protection principles:

- **What is your** lawful basis for processing**?**

The lawful basis for processing is covered under the following articles of the UK GDPR:-
Article 6(1)(e) - research is a component of the University's public tasks and processing personal data for research purposes is likely to be considered necessary for the performance of a task carried out in the public interest,
Article 9(2)(j) - processing of special categories of personal data is likely to be considered necessary for scientific or historical purposes, as long as appropriate safeguards are in place to protect the data

- **What information will you give to individuals about the project, *e.g. privacy notice, participant information sheet etc.***

All data subjects are provided with a Participant Information Sheet and an Informed Consent Form. In addition, a ORC Registries Privacy Notice will also be available for them as well the Reporting Centres.

- **How will you help to support their rights?**

The Participant Information Sheets explain how the data subjects can obtain more information about the project and how they can complain if necessary. The website provides further information on how they can contact the ORC Registries team in Glasgow. In addition, an ORC Registries Privacy Notice is available for them as well the Reporting Centres.

- **How will you prevent function creep?**

The operations of the Registry are closely managed by the Project Management Group which meets two-weekly, and overseen by the Steering Committee (meets 6-monthly), the Data Access Committee (meets 6-monthly) and the Patient Advisory Group (meets 6-monthly). The PMG monitors studies and also meets Study Leads at regular intervals while the studies are active to ensure that individual studies supported by the Registry are achieving their objectives.. As an additional measure, the project has to obtain a fresh ethics approval every 5 years and this allows it to review its functions.

- **How will you ensure data quality and data minimisation?**

In some cases, the data entered into GloBE-Reg will be assessed for quality on an annual basis. This exercise will only occur when an active GloBE-Reg study has specified the need to undertake regular quality assurance (QA). Only less than 10% of the cases (or a minimum of 1) that are included in any study of any clinician shall be eligible for a remote QA. For these eligible cases, the centre will be invited to submit evidence through the QA platform that is built into the Registry. The GloBE-Reg team will arrange to meet the Centre and discuss the process in more detail. https://globe-reg.net/quality-assurance/.
Furthermore, data quality will be maximised through a wide range of other mechanisms including internal audits that have been utilised in other projects run by ORC Registries. See Kourime M et al. An assessment of the quality of the I-DSD and the I-CAH registries - international registries for rare conditions affecting sex development. Orphanet J Rare Dis. 2017 Mar 20;12(1):56. doi: 10.1186/s13023-017-0603-7.

Data Validation - Some of the data fields have internal validation mechanisms and mandatory completion but usually when the data are processed and analysed, outliers and missing values become apparent and checked. The Data Dictionary is automated, and the codes for specific data fields can be downloaded directly from the registry.

Data Cleansing – This occurs at regular intervals when the data are processed to check for duplicate records and inconsistencies and inaccuracies.

Data Profiling - This occurs at regular intervals when the data are processed to understand its structure, patterns and relationships. An example of this is when the high level data are used to create a quarterly activity report (https://globe-reg.net/activity-report/)

- **How will the data be kept up to date, if necessary?**

Purpose limitation – The Registry fields (Minimum Dataset) have been designed following very wide consultation with experts, for instance see Chen et al. Development of A Minimum Dataset for the Monitoring of Recombinant Human Growth Hormone (rhGH) Therapy Use in Children with Growth Hormone Deficiency (GHD) – A GloBE-Reg Initiative. Hormone Res Peds (2023). These fields have been developed to cater for a specific set of studies looking at specific conditions and the studies are listed on the GloBE-Reg website.. Data requests by researchers have to justify the data they require for the research and this is reviewed by the Data Access Committee.
Minimise identification - All data are pseudonymised and provided to investigators with a study ID. When the core mandatory data are entered into the Registry and saved, the registry provides a Registry ID. The Reporting Centre than physically records this Registry ID in their centre records. This Registry ID links the data to local records and it is the Reporting Centre that has the sole ability to do this.
Data retention policies – An important aspect of the Registry is to look at long-term outcome and this requires retaining the data into mid to late adulthood and given that many cases are entered in infancy, the Registry has ethics approval to retain records for 30 years but this approval is extended for 5 more years with every 5 year renewal. The back-up policy for the Registry aligns with that for UofG Central IT Services.
Data deletion – The option to request data deletion by the centre reporters or by the patient or parent is available. All centre reporters of the Registry need to have an active account, ie they should have logged in at least once in a calendar year. An annual audit is performed of all accounts and all inactive account holders are sent an email. For those centres that do not have cases in the Registry and the account is not re-activated, the account is deactivated to maintain audit trail. For those centres that have cases in the Registry, the account is disabled but not deactivated as it affects the audit trail that is linked to the case datasets that are associated with the account.

- **How long will you keep the data?**

The Registry has ethics approval to retain records for 30 years and this approval is extended for 5 more years with every 5-year renewal. It is intended to keep the data indefinitely, even after the subject has deceased and this is made clear in the Participant Information Sheet.

- **How will the retention be reinforced?**

All data that are collected in the Registry are regularly backed up by IT Services according to standard UofG policies.

- **How will the data be kept securely, both during the project and after completion?** During the project all data are kept securely on physical servers in IT Services. Once the project completes and the Registry becomes inactive, all data will be returned to the Reporting Centres.

- **Will you be sharing data internationally, *e.g. sending it to or receiving it from an organisation abroad, or using an international service/platform to process your data*?**

- In the majority of cases, data for the purpose of research are supplied to centres in the UK and in the EU with whom the UK has data adequacy. In those conditions where data are supplied to non-adequacy countries, the Registry will use the UK addendum to the EU Standard Contractual Clauses.
- In addition, the Legal Office at the University of Glasgow is regularly consulted if there are any uncertainties.
- The Participant Information Sheet has also explicitly stated that non-identifiable data shall be shared with other countries.
- Data transfer between the Registry and Researchers and between Clinical Centres and the Registry uses the University of Glasgow's secure Drive facility via University File Transfer Service.

- **What measures do you take to ensure processors comply?**

When data are supplied to researchers (ie processors), several measures are undertaken.

- Researchers have to complete a Data Request Form which specifies the purpose of their data request.
- This Data Request Form is examined by the Data Access Committee and approved when queries are resolved.
- The researcher completes a Data Sharing Agreement which is a contract with the Registry that the data will be used for the purpose described in the Data Request Form.
- The ORC Registries team meets the researcher at fixed intervals over the period of the project to check progress.
- The ORC Registries team is involved in all scientific outputs and checks that the Researcher is complying.
- The Researcher provides an annual progress report to the Data Access Committee.
- The ORC Registries team maintains a log of all data breeches (to date there have not been any)

Identify and assess risks and measures to reduce risk					
Describe the source of risk and nature of potential impact on individuals. Include associated compliance and corporate risks as necessary.	**Likelihood of harm** + (Remote, possible or probable)	**Severity of harm** = (Minimal, significant or severe)	**Overall risk** (Low, medium or high)	**Options to reduce or eliminate risk**	**Residual risk** *(after reduction)* (Low, medium or high)
1. Identification of cases	Remote	Significant	Medium	Several measures are employed to eliminate the risk of identifying a case. This includes pseudonymisation of the case where the key is held by the reporting centre. Given that many conditions are very rare, any description of cases that are in single figures (<10) is undertaken carefully without reference to the actual centre.	Low
2. Data are shared with an	Remote	Significant	Medium	Data processors sign a Data Sharing Agreement and their use of the data is carefully monitored.	Low

unauthorised person					
3. Patient emails are accessible to an unauthorised person	Remote	Significant	Medium	All emails stored in the registry are logically separated from the pseudonymised data using cryptographic methods i.e encrypted at rest.	Low
4. Processing of data related to adults where consent was obtained from legal guardian when they were a minor	Possible	Significant	Medium	The Registry collects information on minors following obtaining consent from legal guardians/parents. When the patient reaches the age of consent (12-18 year depending on the country), reconsent is required from the patient. The Registry sends a reminder. This process needs further testing.	Low
5. Impossibility of exercising control over data	Possible	Significant	Medium	Data processors sign a Data Sharing Agreement and their use of the data is carefully monitored	Low
6. Third party developers may not exercise the same level of data protection as the Registry Team	Remote	Severe	High	An approved contract will be in place with all third party developers with appropriate DP clauses	Low

Data Protection & FOI Office recommendations		
DP & FOI Office advice provided:	Gemma Tougher, Deputy Head of DP & FOI Office	DP & FOI Office should advise on compliance and measures to reduce risk

Summary of DP & FOI advice:

The following advice was applied to the I-DSD Registry DPIA which was thoroughly reviewed and updated. As the GloBE Registry operates in a similar way the same advice applies:

- The legal bases for processing personal and special category have been confirmed as 6(1)(e) and 9(2)(j)– consent was not appropriate in this instance
- Privacy notices for reporters and patients have been revised and updated using the University template
- Joint controllership status confirmed between University and reporting institution and appropriate agreements drawn up by the Contracts team
- More detail has been added to the DPIA on data sharing, patient access to data, data security and pseudonymisation
- Risk table revised and updated and non-personal data related risks removed All

comments above have been incorporated 28.11.23

This DPIA will be kept under review by:	S. Faisal Ahmed, PI, Office for Rare Conditions Registries	A copy of the most recent version should be sent to the DP & FOI Office and retained in the IAR* by the PI/Project Lead.

Sign off and record outcomes **(To be completed by the PI/Project Lead)**	
Mitigation measures and residual risks approved by *(sign & date)*: [redacted] 28th November 2023	Notes: • All mitigation measures must be integrated back into the project, with a documented date and responsibility for completion. • The ICO must be consulted if high risks are identified and cannot be mitigated. • If the DP & FOI Office advice is overruled, an explanation must be provided.

*The University's Information Asset Register (IAR) is a repository for all data protection compliance documents, e.g. privacy notices, DPIAs etc. You can access the IAR (using VPN or remote staff desktop) here: https://www.gla.ac.uk/myglasgow/dpfoioffice/gdpr/onlineinformationassetregister/.

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